وزارة الصحة

قرار وزاري رقم (383) لسنة 2025
بشأن تحديد الأسس والمعايير والإجراءات
الفنية والإدارية اللازمة لتنظيم التعامل
مع مسائل الخلايا الجذعية

وزير الصحة:

- بعد الاطلاع على أحكام المادة 24 من القانون رقم 70 لسنة 2020 بشأن مزاولة مهنة الطب والمهن المساعدة لها وحقوق المرضى والمنشآت الصحية.

- وعلى القرار الوزاري رقم 57 لسنة 2022 بشأن إلزام كافة المنشآت الصحية بالقطاعين الحكومي والأهلي بتنفيذ سياسات وإجراءات الحصول على موافقة المريض المستنيرة.

- وعلى القرار الوزاري رقم 87 لسنة 2023 بشأن ضوابط ولوائح تنظيم عملية الإعلانات الطبية في القطاع الأهلي.

- وعلى القرار الوزاري رقم 287 لسنة 2025 بشأن اعتماد الهيكل التنظيمي والاختصاصات التفصيلية لوزارة الصحة.

- وعلى القرار الوزاري رقم 339 لسنة 2025 بشأن الشروط والضوابط العامة لترخيص مزاولة المهنة في القطاع الحكومي والقطاع الطبي الأهلي.

- وبناء على مقتضيات مصلحة العمل ، وما عرضه علينا السيد / وكيل الوزارة .

قرر

مادة أولى

التعاريف:

1. الوزارة: وزارة الصحة.

2. المنشأة الصحية:

كل مكان مخصص ومعد لتقديم الخدمات الطبية أو الرعاية الصحية للأفراد بقصد تشخيص الأمراض أو علاجها أو الوقاية منها أو تحسين الصحة أو إعادة التأهيل أو النقاهة، وتشمل المستشفيات والمراكز الصحية والمختبرات.

3. الإدارة المركزية للدم والعلاج الخلوي :

هي إدارة مركزية توفر كافة الخدمات المتعلقة بالدم ومشتقاته والعلاج الخلوي في وزارة الصحة.

4. مراكز معالجة وتخزين الخلايا الجذعية:

هي مختبرات مؤهلة لتجميع وتخزين ومعالجة الخلايا الجذعية وخلايا الحبل السري والمحددة في القطاع الحكومي على النحو التالي:

أ. مختبرات الخلايا الجذعية بالمستشفيات المتخصصة التي تتبع المستشفى إدارياً وتتبع الإدارة المركزية للدم والعلاج الخلوي فنياً.

ب. مركز الشيخة المرحومة سلوى صباح الأحمد الصباح للخلايا الجذعية والحبل السري: وهو مركز للخلايا الجذعية والحبل السري مجهز بمختبرات لتجميع وتخزين ومعالجة الخلايا الجذعية وخلايا الحبل السري يتبع فنياً وإدارياً الإدارة المركزية للدم والعلاج الخلوي.

5. مراكز زراعة الخلايا الجذعية:

هي الأجنحة الإكلينيكية في المنشآت الصحية المتخصصة لزراعة النخاع والخلايا الجذعية، تقع في أماكن مخصصة ومصممة لهذا الغرض وتتوافق مع الضوابط والمعايير المعتمدة من الإدارة المركزية للدم والعلاج الخلوي ويشرف عليها فريق رعاية صحية متكامل مؤهل فنياً بالخبرة والتدريب اللازمين وفقاً للضوابط والمعايير التي تصدرها الإدارة المركزية للدم والعلاج الخلوي.

6. مواقع تجميع الخلايا الجذعية:

هي الأجنحة الإكلينيكية في المنشآت الصحية التي يتم فيها أي إجراء لتجميع الخلايا الجذعية بغض النظر عن مصادرها، ويمكنها تجميع وتخزين الخلايا الجذعية بصفة مؤقتة لحين نقلها إلى مراكز المعالجة والتخزين، على أن تقع في أماكن مخصصة ومصممة لهذا الغرض ويشرف عليها فريق رعاية صحية مؤهل فنياً بالخبرة والتدريب اللازمين وفقاً للضوابط والمعايير التي تصدرها الإدارة المركزية للدم والعلاج الخلوي.

7. مختبرات معالجة الخلايا الجذعية:

هي المختبرات المجهزة في المنشآت الصحية المتخصصة لاستقبال الخلايا الجذعية والتي يتم فيها أعمال المعالجة والتصنيف والترقيم والتخزين لاستخدامها في الأغراض العلاجية والبحثية، على أن تقع في أماكن مخصصة ومصممة لهذا الغرض وتتوافق مع الضوابط والمعايير المعتمدة من الإدارة المركزية للدم والعلاج الخلوي، ويشرف عليها في القطاع الحكومي فريق رعاية صحية يتبع فنياً الإدارة المركزية للدم والعلاج الخلوي.

8. السجل الوطني لمتبرعي الخلايا الجذعية:

هو قاعدة بيانات وطنية تُعنى بتسجيل الأفراد الراغبين في التبرع بالخلايا الجذعية لإنقاذ حياة المرضى ، ويحتوي السجل على معلومات المتبرعين المحتملين وذلك لتسهيل المطابقة بين المرضى الذين يحتاجون لزراعة خلايا جذعية، ويشرف على توثيق هذه البيانات فريق رعاية صحية متكامل معني بنشر ثقافة أهمية التبرع الطوعي بالخلايا الجذعية ويتبع مركز الشيخة المرحومة سلوى صباح الأحمد للخلايا الجذعية والحبل السري.

9. الخلايا الجذعية (Stem Cells):

وهي خلايا متعددة المصادر غير متميزة ولا متخصصة تستطيع في ظروف معينة ومحددة أن توالي الانقسام وأن تتمايز إلى خلايا متخصصة تكون لبنات في بناء أنسجة وأعضاء أو أجزاء منه، يتم الحصول عليها من المصادر التالية:

- نخاع العظم (Bone Marrow) .
- الخلايا الجذعية المكوِّنة للدم (HSCs).
- دم الحبل السري المستخلص مباشرة بعد عملية الولادة (Cord Blood).
- الأسنان اللبنية (Dental Cells).
- الأنسجة المختلفة للإنسان بعد ولادته بما في ذلك الخلايا الدهنية وغيرها من الأنسجة (Other Human tissues like Adipose tissues).
- أجنة الإجهاض المشروع أو التلقائي وأنسجة الأجنة المنغرسة داخل الرحم أو الحبل السري أو المشيمة وأغشيتها والسائل الأمينوسي سواء كانت داخل الرحم أو خارجه.

10. الخلايا الجذعية الذاتي (Autologous Stem Cells):

وهي الخلايا الجذعية التي يتم أخذها من نفس المريض لاستخدامها لاحقاً في العلاج.

11. الخلايا الجذعية غير ذاتية (Allogenic stem cells):

هي الخلايا الجذعية التي يتم الحصول عليها من شخص آخر (متبرع)، وليس من المريض نفسه، وتُستخدم لعلاج أمراض مثل اللوكيميا وبعض اضطرابات الدم. (Allogenic Stem Cells)

12. الخلايا المناعية التائية (CAR-T Cells) :

يتم تعديلها في المختبر حتى تتعلم كيف تهاجم الخلايا السرطانية يعتبر من أنواع العلاج الخلوي.

13. العلاج الخلوي (Cellular Therapy):

هو نوع من العلاجات الطبية التي تُستخدم فيها خلايا حيّة (مثل الخلايا الجذعية أو الخلايا المناعية) لعلاج أمراض معينة، مثل السرطان أو اضطرابات المناعة أو أمراض الدم، أنواع العلاج الخلوي:

- العلاج بالخلايا الجذعية (Stem Cell Therapy).
- العلاج بالخلايا المناعية مثل علاج بالخلايا التائية المعدلة وراثيًا (CAR-T Cell Therapy).

14. الاستنساخ العلاجي (Therapeutic Cloning):

هو عملية تُستخدم فيها تقنية الاستنساخ لإنتاج خلايا جذعية مطابقة جينياً للمريض، بهدف علاج أمراض أو إصلاح أنسجة تالفة في جسمه.

15. زراعة الخلايا الجذعية المعروفة أيضاً باسم زراعة النخاع العظمي:

وهي عملية حقن خلايا جذعية لاستبدال الخلايا التالفة، وتضم نوعان من الزراعة:

- إما زراعة ذاتية للخلايا للشخص نفسه.
- أو زراعة الخلايا الجذعية من متبرع.

مادة ثانية:

تلتزم الجهات المعنية بأحكام هذا القرار بتوفير مخزون وطني للخلايا الجذعية والحبل السري وذلك عند التعامل مع الخلايا الجذعية سواء بمعالجتها وتجميعها وزراعتها وفقاً للضوابط والمعايير المعتمدة من الإدارة المركزية للدم والعلاج الخلوي.

مادة ثالثة

تختص الجهات المعنية بأحكام هذا القرار بما يلي:

أولاً: الإدارة المركزية للدم والعلاج الخلوي:

1. إعداد الخطة العامة لخدمات نقل الخلايا الجذعية في البلاد في ضوء الخطة الصحية واعتمادها من الجهات المختصة ومتابعة تنفيذها.
2. ضمان توفير مخزون الخلايا الجذعية لتلبية احتياجات المرضى بجودة عالية وبأحدث الطرق لجميع المستشفيات بالكويت.
3. إصدار المعايير والمواصفات والشروط الواجب توافرها للتعامل مع الخلايا الجذعية في القطاعين الحكومي والأهلي والإشراف والرقابة على تطبيقها، مع ضرورة الالتزام بها كمتطلب من متطلبات الحصول على

الترخيص للمنشآت الصحية الأهلية.

4. الإشراف على الطلبيات السنوية من الأجهزة والمحاليل الطبية الخاصة بالتعامل مع الخلايا الجذعية في وزارة الصحة.

5. إنشاء قاعدة بيانات بين الإدارة وباقي الجهات المحددة بالقرار والتي تشمل السجل الوطني للتبرع بالخلايا الجذعية وذلك وفق النظم واللوائح المتبعة في هذا الشأن.

6. التوعية المجتمعية حول الخلايا الجذعية بالوسائل المرئية والمسموعة.

7. تنسيق العمل بين الإدارة المركزية وباقي الجهات المعنية لضمان توفير الخلايا الجذعية وإيصالها للمرضى.

8. وضع الخطوات الفنية اللازمة لجمع الخلايا من المتبرعين وإجراء الفحوصات الوقائية عليها وتخزينها وفق الطرق الصحيحة المتعارف عليها بكافة عناصرها ومشتقاتها.

ثانياً: مركز الشيخة المرحومة سلوى الصباح للخلايا الجذعية والحبل السري:

1. توفير مخزون وطني من الخلايا الجذعية والحبل السري للاستخدام الإكلينيكي للمواطنين والمقيمين في الكويت بجودة ومعايير عالمية.

2. استقبال الخلايا الجذعية من مواقع التجميع ومعالجتها وتصنيفها وترقيمها وتخزينها في المختبرات المخصصة لذلك تمهيداً لصرفها للاستخدامات الإكلينيكية.

3. تقديم الرعاية الصحية والمعلومات الشاملة لمتبرعي الخلايا الجذعية بشكل يكفل لهم التوقيع على الموافقة المستنيرة تمهيداً لتجميع الخلايا الجذعية بالطرق المختلفة.

4. القيام بالأبحاث العلمية في مجالات الخلايا الجذعية حسب الإجراءات والنظم المنظمة لذلك في وزارة الصحة.

5. الإشراف على توثيق المعلومات المتعلقة بالسجل الوطني للتبرع بالخلايا الجذعية.

ثالثاً: مراكز زراعة الخلايا الجذعية ومواقع التجميع ومختبرات المعالجة، كل حسب اختصاصه:

1. تطبيق الضوابط والمعايير والبروتوكولات الإكلينيكية وبرامج التدريب للعاملين المعتمدة من الإدارة المركزية للدم والعلاج الخلوي.

2. تقديم الرعاية الصحية والمعلومات الشاملة الخاصة بالتعامل مع الخلايا الجذعية للمرضى والمتبرعين بشكل يكفل لهم التوقيع على الموافقة المستنيرة.

3. تسجيل المعلومات المتعلقة بالخلايا الجذعية بقاعدة البيانات التابعة الإدارة المركزية للدم والعلاج الخلوي.

4. تجميع الخلايا الجذعية بالطرق المختلفة من الفرق الفنية المؤهلة وفقاً للضوابط والمعايير المعتمدة من الإدارة المركزية للدم والعلاج الخلوي.

5. تقوم مختبرات معالجة الخلايا الجذعية باستقبال الخلايا الجذعية من مواقع التجميع وذلك لترقيمها وتخزينها والتعامل معها وفقاً للضوابط والمعايير المعتمدة.

مادة رابعة

تسري الأحكام والضوابط التالية على استخدام الخلايا الجذعية وفقاً لما يلي:

1- يصرح باستخدام الخلايا الجذعية الذاتية (Autologous stem cells) سواء في العلاج أو الزراعة أو الأبحاث السريرية حسب العلاجات المثبتة علمياً من المصادر المحددة على النحو التالي:

• كل ما يصنف علمياً بخلايا جذعية بشرية بالغة بأنواعها المتعددة (Stem Cells).

• الخلايا الجذعية البشرية المحفزة (Induced Stem Cells).

2- يقتصر استخدام الخلايا الجذعية من مصادر غير ذاتية (Allogenic stem cells) على حالات زراعة النخاع العظمي لعلاج أمراض الدم الوراثية والسرطانية وحالات الأمراض الأخرى المثبتة علمياً ويحظر استخدامها في ما عدا ذلك.

3- يشترط للحصول على الخلايا الجذعية واستعمالها وجود ضرورة طبية أو علاجية مبررة أو حاجة بحثية، وذلك بما يتفق مع اللوائح والنظم المعتمدة.

4- يراعي في مصادر الخلايا الجذعية واستخدامها وجميع الإجراءات المرتبطة بها الحق في الخصوصية والسرية والتقيد بمعايير الجودة والسلامة.

5- لا يجوز التعامل مع الخلايا الجذعية أو استخدام أي تقنية أخرى معتمدة عالمياً إلا بعد الحصول على الموافقة المستنيرة للمريض أوالمتبرع بالخلايا أو أحد والديه أو وليه الشرعي وذلك طبقاً للقوانين والقرارات واللوائح المنظمة لذلك.

6- يحظر على المنشآت الصحية ومزاولي المهنة والمرضى ما يلي:

• بيع وشراء الخلايا الجذعية أو أجزائها بأية وسيلة كانت أو تقاضي أي مقابل عنها.

• إجراء أي جمع، أو اختبار، أو تجهيز، أو حفظ أو تخزين أو توزيع أو منح أو استيراد أو تصدير، أو نقل أو زراعة أو حفظ الخلايا الجذعية أو أجزائها أو الأنسجة البشرية الناتجة عنها من غير الجهات المحددة بهذا القرار.

• الدعاية أو الإعلان أو الترويج أو الوساطة لأي من عمليات نقل أو زراعة أو حفظ الخلايا الجذعية أو أجزائها أو الأنسجة البشرية الناتجة عنها وفقاً للضوابط والقرارات المنظمة لذلك.

• الحصول على الخلايا الجذعية واستخدامها من مصدر مخالف للضوابط والمعايير المعتمدة.

• تمويل عمليات نقل وزراعة وحفظ الخلايا الجذعية أو أجزائها أو الأنسجة البشرية ثبت العلم بأن مصدرها تم بمقابل مادي.

مادة خامسة

يحظر على القطاع الأهلي التعامل أو العلاج بالخلايا الجذعية سواء بالزرع أو العلاج الخلوي أو التخزين أو إجراء الأبحاث دون الحصول على ترخيص بذلك من وزارة الصحة.

مادة سادسة

يُبلغ هذا القرار من يلزم لتنفيذه، ويلغى كل قرار أو نص يتعارض مع أحكامه، ويعمل به بعد ثلاثة أشهر من تاريخ صدوره، وينشر في الجريدة الرسمية.

وزير الصحة

د. أحمد عبد الوهاب العوضي

صدر في : 10 رجب 1447هـ

الموافق : 30 ديسمبر 2025م

قرار وزاري رقم (385) لسنة 2025

اعتماد الدليل الإرشادي الكويتي لليقظة الدوائية

بشأن ضوابط وممارسات اليقظة الدوائية الجيدة

وزيـر الصحة:

- بعد الإطلاع على أحكام المرسومين بقانون ونظام الخدمة المدنية وتعديلاتهما.
- وعلى أحكام القانون رقم 28 لسنة 1996 في شأن تنظيم مهنه الصيدلة وتداول الأدوية والمعدل بالقانون رقم 30 لسنة 2016
- ولائحتيهما التنفيذية.
- وعلى القرار الوزاري رقم 382 لسنة 2023 بشأن إنشاء مكتب مراقبة اليقظة الدوائية التابع للوكيل المساعد لشئون الرقابة الدوائية والغذائية.
- وعلى القرار الإداري رقم 3275 لسنة 2025 بشأن تشكيل اللجنة الفنية لليقظة الدوائية لتقييم البلاغات الواردة عن سلامة الأدوية والمنتجات الطبية.
- وعلى القرار الإداري رقم 1105 لسنة 2018 بشأن تشكيل فريق عمل اليقظ والسلامة الدوائية لمراقبة سلامة المستحضرات الصيدلانية والمستلزمات الطبية.
- وعلى التعميم رقم 108 لسنة 2018 بشأن تنظيم إجراءات السحب والتعليق والإلغاء للأدوية والمستحضرات الصيدلانية.
- وعلى المعايير والتوصيات الدولية المعتمدة في مجال اليقظة الدوائية:

WHO-UMC, GCC, ICH E2C(R2), Arab ((Pharmacovigilance Guidelines

- وبناء على مقتضيات مصلحة العمل، وما عرضه علينا السيد وكيل الوزارة.

– قـرر –

مادة أولى

يُعتمد الدليل الإرشادي الكويتي لليقظة الدوائية المرافق لهذا القرار كوثيقة رسمية ملزمة ومكملة لأحكامه.

مادة ثانية

يتضمن الدليل الإرشادي الكويتي لليقظة الدوائية القواعد والإجراءات والمعايير الفنية اللازمة لتنظيم الأنشطة المتعلقة بتطبيق ممارسات اليقظة الدوائية الجيدة في دولة الكويت Kuwait Good Pharmacovigilance Practice (Ku GVP) بما يتوافق مع الأطر المعتمدة دولياً.

مادة ثالثة

تعتمد الضوابط والممارسات الواردة بالدليل الإرشادي الكويتي لليقظة الدوائية والمبينة في هذا القرار.

مادة رابعة

يختص مركز الكويت للتيقظ الدوائي بالإشراف على ضوابط ممارسات اليقظة الدوائية الجيدة الواردة في الدليل الإرشادي الكويتي لليقظة الدوائية ومتابعة الالتزام به وفقاً لأحكام هذا القرار.

مادة خامسة: تهدف ضوابط ممارسات اليقظة الدوائية الجيدة إلى ضمان الرصد المنهجي والتقييم العلمي والمتابعة المستمرة للمخاطر المرتبطة بالاستخدام أو التعرض للأدوية والمنتجات الطبية، وذلك من خلال جمع وتحليل وتقييم بيانات السلامة وتحديد الإشارات والمخاطر المحتملة واتخاذ التدابير الوقائية والاحترازية اللازمة.

مادة سادسة

يلتزم جميع مزاولي مهنة الطب والمهن المساعدة لها ومزاولي مهنة الصيدلة وممارسي الأنشطة الخاضعة لأحكام هذا القرار في القطاعين الحكومي والأهلي بتطبيق ضوابط ممارسات اليقظة الدوائية الجيدة، كلٌ في نطاق اختصاصه، وفقًا لما يصدر من تعليمات وأدلة تنظيمية معتمدة من مركز الكويت للتيقظ الدوائي.

مادة سابعة

يتولى مركز الكويت للتيقظ الدوائي، بالتنسيق مع إدارة التفتيش والتراخيص الصيدلانية، متابعة الالتزام بتطبيق معايير ضوابط ممارسات اليقظة الدوائية الجيدة من خلال الجولات التفتيشية والتقييمات الرقابية الميدانية على الصيدليات والمستشفيات والمراكز الطبية والجهات ذات الصلة.

مادة ثامنة

استخدام أنظمة مرجعية معتمدة لجمع وتحليل وإدارة بيانات اليقظة الدوائية واستخلاص المؤشرات والتقارير المتعلقة بالأحداث السلبية والمخاطر الدوائية.

مادة تاسعة

يتولى مركز الكويت للتيقظ الدوائي إعداد تقارير دورية عن مستوى الالتزام بضوابط ممارسات اليقظة الدوائية الجيدة ونتائج التحليل والتقييم والتوصيات الفنية، وترفع هذه التقارير إلى مدير الإدارة العامة للرقابة والشؤون الصيدلانية بصفة دورية.

مادة عاشرة

يقوم مركز الكويت للتيقظ الدوائي بتنظيم البرامج التدريبية وورش العمل والأنشطة التوعوية اللازمة لرفع كفاءة الكوادر الطبية والصيدلانية وتعزيز الالتزام العملي بضوابط ممارسات اليقظة الدوائية الجيدة.

مادة حادية عشر

يكلف مركز الكويت للتيقظ الدوائي بالتنسيق والتواصل المستمر مع الجهات المحلية والإقليمية والدولية ذات الصلة بمجال اليقظة الدوائية، بما يحقق التكامل وتبادل المعلومات وفقاً للأطر المعتمدة في الدليل الإرشادي الكويتي لليقظة الدوائية.

مادة ثاني عشر

يختص مركز الكويت للتيقظ الدوائي بإصدار التوصيات المتعلقة بسحب الأدوية والمنتجات الطبية الخاضعة لأحكام هذا القرار، وذلك استناداً إلى بيانات ومعلومات وتقارير وإنذارات وإشعارات السلامة الدوائية الواردة إليه، وما يسفر عنه تحليلها وتقييمها من مخاطر على الصحة العامة.

مادة ثالثة عشر

ترفع التوصيات إلى السيد وكيل وزارة الصحة لاعتمادها من معالي وزير الصحة وتتولى إدارة التفتيش والتراخيص الصيدلانية تنفيذ قرارات السحب، وفقاً لنطاق السحب المحدد بالقرار ووفقاً للإجراءات المعتمدة في الدليل الإرشادي الكويتي لليقظة الدوائية.

مادة رابعة عشر

تُصنف قرارات السحب الصادرة عن مركز الكويت للتيقظ الدوائي وفقاً لمستوى الخطورة إلى الفئات الآتية:

1. سحب من الفئة الأولى (Class I):

عند وجود خطر جسيم أو تهديد مباشر على سلامة المريض أو الصحة العامة.

2. سحب من الفئة الثانية (Class II):

عند وجود خطر محتمل قد يؤدي إلى آثار صحية مؤقتة أو قابلة للعلاج.

3. سحب من الفئة الثالثة (Class III):

عند وجود مخالفة أو عيب لا يُتوقع أن يؤدي إلى ضرر صحي مباشر، ويكون السحب إجراءً احترازياً.

ويُحدد نطاق وآلية السحب وفقاً لهذا التصنيف.

مادة خامسة عشر

يتم التعامل مع بلاغات وإشارات السلامة الدوائية وفقاً للمسار التنظيمي الآتي:

1. رصد الإشارة أو البلاغ من خلال أنظمة اليقظة الدوائية المعتمدة في الدليل الإرشادي الكويتي لليقظة الدوائية.
2. التقييم والتحليل الفني للمخاطر من قبل مركز الكويت لليقظة الدوائية.
3. إصدار قرار السحب – عند الحاجة – وتحديد نطاقه وتصنيفه.

4. تنفيذ قرار السحب من قبل إدارة التفتيش والتراخيص الصيدلانية.

5. إحالة التقارير الفنية ونتائج السحب إلى إدارة تسجيل ورقابة الأدوية والمنتجات الطبية لاتخاذ الإجراءات الرجعية بشأن التسجيل ورفع التوصيات إلى الإدارة العامة للرقابة والشؤون الصيدلانية لاتخاذ القرار اللازم حسب السلسل الوظيفي.

مادة سادسة عشر

يُبلغ هذا القرار من يلزم لتنفيذه، ويعمل به إعتباراً من تاريخ صدور القرار، وينشر في الجريدة الرسمية.

وزير الصحة

د. أحمد عبد الوهاب العوضي

صدر في: 10 رجب 1447هـ

الموافق: 30 ديسمبر 2025م

Ministry of Health
State of Kuwait
Drug and Food Control
Kuwait Good Pharmacovigilance Practice Guidelines (KuGVP)

Version 1 (2019)
Version 2 (2020)
Version 3 (2022)
Version 4 (2024)
Version 5 (2025)
Version 6 (2026)

Ministry of Health
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PREFACE

Adverse Drug Reactions (ADRs) are an inevitable consequence of pharmacotherapy. It is well known that all medicines carry the potential to produce side effects (desirable and undesirable effects). No medicine is absolutely safe under all circumstances of use in all patients and ADRs may occur even if a medicine is correctly selected and dosed. Likewise, no medicine is absolutely harmful under all circumstances of use in all patients and, therefore, a positive balance must be established to ensure that benefits outweigh the risks of using medicine.

In Kuwait, the processes of ADR reporting and monitoring are growing and continuously becoming part of the regulatory and clinical practice. However, it is still in its development stage, and hence, serious and non-serious ADRs tend to be underreported. Many adverse effects of medicines are highly subjective and a large fraction of the total ADR burden in the country is not being recognized.

Kuwait Pharmacovigilance Taskforce (KPTF) was established in 2018 under the umbrella of the Sector of Drug and Food Control Affairs (KDFC), comprising of members from several disciplines in pharmacy, such as regulatory affairs, inspection, clinical practice, and academia. The main goal of KPTF was to build the basic infrastructure and legal framework for the Pharmacovigilance System to carry out effective ADR monitoring and reporting activities, which essentially embraces detection, assessment, understanding and prevention of ADRs. Such activities necessitate cooperation among all healthcare professionals (HCPs), regulators, pharmaceutical companies and manufacturers in the country.

The intention of these guidelines is therefore to provide guidance to all stakeholders who deal with manufacturing, production, distribution and provision of healthcare services, to monitor and report ADRs to the pharmacovigilance entity in Kuwait.

It is our sincere belief that these guidelines will be a useful guide to HCPs, regulators and pharmaceutical companies, allowing them to commit and cooperate efficiently and effectively in order to safeguard the health of the people of Kuwait. Active involvement and effective communication between the relevant stakeholders will certainly enable prompt regulatory actions to protect the people from preventable ADRs that might occur due to medication use.

Finally, the pharmacovigilance team will always be ready to receive comments, enquiries and suggestions for further improvements in the pharmacovigilance practice of Kuwait.

Kuwait Office for Pharmacovigilance Surveillance (KPVC)

DISCLAIMER

This document is intended to provide general guidance. Although we have tried to ensure that the information contained here is accurate, however, constant evaluation for further updates and developments according to the local regulatory and clinical environment is required. Kuwait Drug and Food Control (KDFC), represented by the Kuwait Office for Pharmacovigilance Surveillance (KPVC) bares no liability for any

documented previously.

12. Unexpected adverse drug reaction: An adverse reaction, the nature or severity of which is not mentioned in the summary of product characteristics or market authorization, or expected from characteristics

13. Shall: a term used to express strong obligation, legal requirements, or formal rules, often found in official documents (laws, executive regulations, decrees, ... etc), ie. "Shall" implies a requirement.

14. Should: a soft term, used for advice, recommendations, expectations, or moral duties, ie "should" suggests guidance or probability.

ACRONYMS

MOH	Ministry of Health
WHO	World Health Organization
UMC	Uppsala Monitoring Center
KDFC	Kuwait Drug and Food Control
PHILA	Pharmaceutical Inspection and Licensing Administration
KPVC	Kuwait Pharmacovigilance Center
KuPRAC	Kuwait Pharmacovigilance Risk Assessment Committee
EMA	European Medicine Agency
GCC	Gulf Cooperation Council
GVP	Good Pharmacovigilance Practice
ICH	International Conference for Harmonization
ICSR	Individual Case Safety Report
MAH	Marketing Authorisation Holder
MAA	Market Authorisation Applicant
MA	Market Authorisation
NDA	New Drug Application
MD	Medical Device
HP	Health Product
PASS	Post-Authorization Safety Study
PAES	Post-Authorization Efficacy Study
DDP	Detailed Description of Pharmacovigilance
PBRER	Periodic Benefit Risk Evaluation Report
PL	Package Leaflet
PSMF	Pharmacovigilance System Master File
PSSMF	Pharmacovigilance Sub-System Master File
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
QPPV	Qualified Person Responsible for Pharmacovigilance
LSR	Local Safety Responsible Person
QMS	Quality Management System
RMM	Risk Minimization Measures
RMP	Risk Minimization Plan
RMS	Risk Management System
SmPC	Summary of Product Characteristics
ADR	Adverse Drug Reaction / Adverse Reaction
AE	Adverse Event
AER	Adverse Event Report
CA	Competent Authority
CAPA	Corrective Action Preventive Action
CSR	Clinical Study Report
ICSR	Individual Case Safety Report
IR	Inspection Report
QA	Quality Assurance
RA	Regulatory Authority
SAE	Serious Adverse Event

misunderstandings or misinterpretations of information from this document. If you need specific legal or professional advice, you should consult relevant legal, clinical/pharmaceutical or regulatory advisers.

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GLOSSARY OF TERMINOLOGY

1. Adverse Drug Reactions (ADRs): A response to a medicinal product that is noxious or potentially harmful and unintended and which occurs at doses normally used in human for prophylaxis, diagnosis or therapy of a disease or for the modification of physiological function in which individual factors may play an important role.

2. Adverse Event or Experience (AE): Any unfavorable medical occurrence that in coincidence may present during treatment with a pharmaceutical product, but which does not necessarily have a causal relationship with the treatment.

3. An Adverse Drug Reaction (ADR) Case Report: A case report in ADR monitoring programme is a notification relating to a patient with an adverse effect or laboratory test abnormality suspected to be induced by a medicinal product.

4. Benefit/risk analysis: Examination of the favorable (benefit) and unfavorable results of undertaking a specific course of action

5. A drug or a medicinal product: Any substance or mixture of substances manufactured, sold or presented for use in: i. the diagnosis, treatment, mitigation or prevention of a disease, disorder, abnormal physical or mental state, or the symptoms thereof, in human or animal. ii. restoring, correcting or beneficial modification of organic or mental functions in human or animal.

6. Healthcare professionals: For the purposes of reporting suspected ADRs, these include specialists, medical practitioners, pathologists, dentists, pharmacists, nurses, medical assistants, pharmaceutical technicians, pharmaceutical assistants, etc.

7. Herbal drugs: Any labeled preparation in pharmaceutical dosage form that contains one or more substances of natural origin that are derived from plants as active ingredients.

8. Life-threatening reaction: A reaction in which the patient was at risk of death at the time of the event and does not refer to an event, which hypothetically might have caused death if it was more severe.

9. Serious adverse drug reaction: A noxious and unintended response to a drug that at any dose, result in death, is life-threatening (such as Stevens-Johnson Syndrome), requires patient hospitalization or prolongation of existing hospitalization, causes a congenital anomaly or birth defect, results in persistent or significantly disability or incapacity, or require intervention to prevent permanent impairment or damage.

10. Side effect: Any unintended effect of a pharmaceutical product occurring at doses used in man which is related to the pharmacological properties of the product and in which there is no deliberate overdose.

11. Signal: Reported information (at least 3 spontaneous case reports) on a possible causal relationship between an adverse event a drug, the relationship being unknown or incompletely

vaccines. Although all these products required monitoring by the pharmacovigilance team, there are, however, some differences in their guidelines due to differences in their nature and the way they are used. For those conducting clinical trials of locally registered products, it is mandatory to report all adverse events encountered to the KPVC.

All adverse events should be considered reportable according to the requirements outlined in these guidelines and key players in this activity are all pharmaceutical companies/ manufacturers and HCPs, preferably those directly associated with the care of patients/consumers.

The current Kuwaiti system of AE monitoring relies on the World Health Organization (WHO) model. This system is well known of being cost-effective and it utilizes internationally recognized methods for detecting signals and identifying previously unknown AEs to medicinal products or changes in the patterns of known AEs to ensure that patients obtain safe and effective treatments. Where necessary, epidemiological studies may be conducted in collaboration with research institutions to substantiate generated signals.

In addition, the AE monitoring system is important in detecting lack of efficacy, addressing quality concerns, which may be related to harm, and preventing counterfeits and substandard products. Therefore, knowledge and awareness of HCPs about the AE monitoring program is necessary to ensure the safety of medical and pharmaceutical products.

The impact of not reporting AEs may result in compromising patient safety as the product is left unnoticed for a long time or if an association between a product and an event becomes clear worldwide e.g., Aspirin in the Gastro-intestinal tract, amidopyrine in agranulocytosis, phocomelia with thalidomide. For the same reason it may take too long before it is recognized that prolonged abuse of a medicinal product can produce deliberate health effects e.g., phenacetin in renal papillary necrosis.

Therefore, proper implementation of these guidelines will help reduce the harmful effects resulting from the use of drugs or medicinal products by early detection of safety concerns, evaluation of signals, assessment of the benefit-risk balance for an individual and the population, application of effective risk minimization measures, selection of optimal therapies in cooperation with Health Technology Assessment (HTA) programmes, and application of rational use of drugs or medicinal products by developing effective communication methods with HCPs. The guidelines provide brief definitions related to AE monitoring and classifications based on etiology. It highlights the importance of monitoring and reporting procedures. Principles of efficient reporting by HCPs, data handling and analysis have also been covered.

Pharmacovigilance Definition

Pharmacovigilance (PV) is the science and practice of reporting, detecting, evaluating, understanding and monitoring adverse effects of drugs or medicinal products or any other related problems associated with such products.

KPVC Core Values

Professionalism- Knowledge- Shared responsibilities- Responsiveness and Reactiveness- Integrity- High quality- Reliability

KPVC Vision

New healthcare and regulatory systems empowered with the required pharmacovigilance resources and tools to make an

SAR	Serious Adverse Reaction
SSAR	Suspected Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Drug Reaction
TP	Therapeutic Product MP Medicinal Product
IP	Investigational Product
AP	Auxiliary Product
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBA	To Be Announced
HTA	Health Technology Assessment
HCP	Healthcare Professionals
KuGVP	Kuwait Good Pharmacovigilance Practice
RSI	Reference Safety Information
CCDS	Core Company Data Sheet
CSPI	Country Specific Prescribing Information
EU	Europe
US	United States
FDA	Food and Drug Administration
IB	Investigators Brochure

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MODULE ONE
INTRODUCTION TO PHARMACOVIGILANCE

MODULE ONE: INTRODUCTION TO PHARMACOVIGILANCE

Overview of Pharmacovigilance and Adverse Event Monitoring

Adverse Event (AE) Monitoring is the process of continuously monitoring undesirable effects suspected to be associated with the use of medical and pharmaceutical products. It facilitates collection of unbiased safety data observed both during clinical trials and during 'real- life' circumstances.

The guidelines have been developed to assist HCPs to understand the process of monitoring AEs. It is necessary to understand the methods used to report AEs and the four pillars of a valid AE case report. Such pillars include information about the patient, description of the adverse event, the suspected medical or pharmaceutical product and the reporter/ source of the report.

The AE reporting system in Kuwait is centralized, whereby HCPs and patients are sensitized to submit case reports of suspected AEs to the Kuwait Office for Pharmacovigilance Surveillance (KPVC). Pharmaceutical companies/ manufacturers and regulators have systems in place to monitor locally registered products and report safety concerns to KPVC. This is the department that operates under the autonomy of Kuwait Drug and Food Control (KDFC) sector, Ministry of Health.

AE reporting covers all medical and pharmaceutical products, biologicals, herbal drugs, medical cosmetics, medical devices and

often excluded from studies, such as patients in certain age groups, pregnant women, patients with diseases other than the one being treated, and patients using other drugs concomitantly. This often prevents the identification of side effects caused by the interaction of more than one product given at the same time. Statistically, reactions with an incidence of less than 1% are frequently not identified.

2. The duration of clinical trials is too short. Such studies do not allow the detection of adverse effects that appear after prolonged use or exposure, especially with chronic medications (e.g., oral contraceptives).

3. There are differences between countries, including variations in patient factors, product consumption levels, and manufacturing processes, which may influence the quality of the locally produced products compared with the imported counterparts.

The pharmacovigilance and AE monitoring is carried out in Phase IV, where monitoring of safety and effectiveness is considered a lifetime process to ensure a continuous positive benefit–risk ratio.

Post Marketing Surveillance

It is not possible to identify all safety–related problems that may exist with drugs or medicinal products during pre–marketing tests and evaluations. For this reason, it is obvious that safety monitoring is carried out through the life cycle of each product (medicine, vaccine, health product, cosmetic product, medical device and biological product). The KPVC team, regulators, inspectors, dossier reviewers, and HCPs play a vital role in the post–marketing surveillance of these products. One of the most common methods of post–marketing surveillance is AE monitoring.

Purpose of Good Pharmacovigilance Practice Guidelines in Kuwait

The main purpose of having a Good Pharmacovigilance Practice Guideline (GVP) in Kuwait is to address the requirements, tasks, responsibilities, activities, procedures, and roles necessary for implementing an effective and efficient pharmacovigilance system. These guidelines are a set of standards to be applied in order to facilitate the performance of pharmacovigilance in the State of Kuwait. Kuwait Good Pharmacovigilance Practice (KuGVP) guidelines are issued as a guide for the practice of pharmacovigilance for pharmaceutical companies, marketing authorization holders, the regulatory authority, and HCPs to guide them to the best practices for monitoring the safety of drugs or medicinal products authorized at the national level.

KuGVP guidelines are based on the Guideline On Good Pharmacovigilance Practice For Arab Countries, which is adopted from the European Good Pharmacovigilance Practicies guidlies The guidelines shall be reviewed and updated every two years. The version number will be updated and approved by the Assistant Undersecretary for Drug and Food Control.

MODULE TWO.

THE PHARMACOLOGICAL BASIS OF ADVERSE DRUG REACTIONS AND INTERACTIONS

THE PHARMACOLOGICAL BASIS OF ADVERSE DRUG REACTIONS and INTERACTIONS

This module addresses reactions that specifically occur due to the use of medications. These are called Adverse Drug Reactions (ADRs). An ADR is an unexpected consequence of drug usage and its risk of occurrence cannot be predetermined. Almost all effective drugs, no matter how safely used, may cause adverse

informed regulatory and clinical decisions about safe and effective use of drugs or medicinal products in Kuwait.

KPVC Mission Statement

Our mission is to support patient safety by applying all elements and facilities to warrant an effective pharmacovigilance system and to ensure the availability of high quality, safe and effective drugs or medicinal products in Kuwait.

Goals

1. Implementing high–standard pharmacovigilance and risk management plans.
2. Standardizing the quality of Kuwait's pharmacovigilance system to be in line with internationally recognized pharmacovigilance systems.
3. Improving patient safety through stimulating safe, effective, and rational use of drugs or medicinal products.
4. Assessing the benefit–risk balance of drugs or medicinal products and enhancing the availability of safe and effective medicines.
5. Promoting awareness and understanding of pharmacovigilance and ADR monitoring among HCPs and the public.

Objectives

1. To secure early detection of new or existing ADRs.
2. To demonstrate the safety and efficacy of the newly registered and marketed pharmaceutical products by monitoring their adverse event profile throughout their lifecycle.
3. To ensure proper safeguards for patients from all populations, particularly those with exceptional medical cases.
4. To identify risk factors and possible mechanisms underlying adverse reactions.
5. To apply risk management measures as necessary.
6. To establish effective collaborative efforts among all stakeholders involved in the safety monitoring process.
7. To promote understanding and education related to regulatory and clinical training for HCPs in Pharmacovigilance.
8. To promote education and awareness about the safety of drugs or medicinal products among patients and consumers.

Rationale for Pharmacovigilance and AE Monitoring

Once a medical or pharmaceutical product is marketed, information on its safety and efficacy is primarily based on pre–marketing evaluations, clinical trials (Phase I, II and III), animal studies and, other data from the product development process.

1. Phase I trial – Single–dose studies in healthy volunteers using low doses of the medicinal product. The pharmacological and pharmacokinetic properties of the product are evaluated in this phase.
2. Phase II trial – Efficacy is the primary objective of this phase, but safety is also continuously monitored and evaluated.
3. Phase III trial – Evaluation of safety in a group of patients with the target disease.

Each phase involves an increasing number of participants, and by the end of the full pre–marketing clinical trial, about 5,000 participants would have received the product. However, there is a problem of whether a clinical trial involving 5,000 people provides sufficient information to extrapolate the safety of a new product to millions of people.

Therefore, pre–marketing safety evaluation of pharmaceutical products at the time of registration is inherently limited due to the following three reasons:

1. The population in Phase III clinical trials is very selective and limited. Many types of patients with different characteristics are

to know the responsible drugs and mechanisms of interactions involved.

Predisposing factors of ADRs and the mechanisms of drug interaction

Many reactions occur early in the course of treatment (such as anaphylaxis after penicillin injection); some other reactions may develop over a prolonged period of treatment (such as osteoporosis with oral steroids); the other reactions may appear long after the drug is discontinued (such as vaginal adenocarcinoma due to diethylstilbestrol given to the mother). The following are predisposing factors of ADRs: Age

The incidence of ADRs appears to be highest in the very young and very old people. In these two extreme periods of life, there is poorly developed and altered physiological function, respectively. Therefore, metabolism and elimination of some drugs may be delayed.

Pathophysiological conditions

Intercurrent diseases may alter the pharmacokinetic handling of a drug, its tissue sensitivity or the response to a drug. That is, diseases can alter drug absorption, metabolism, elimination and the body's response to drugs.

Amount of drug administered

An excessive response to drug or prolonged therapy may be predisposing factors for ADRs. Over dosage is often relative rather than absolute because the individual response to a drug varies.

Sex

Several studies have shown that for some drugs women are more likely to suffer from ADRs than men. This is due to pharmacokinetic and or pharmacodynamic sex–related factors.

Previous history of allergy

Patients who have previously suffered an allergic drug reaction appear to be more susceptible than others to allergic ADRs in general. Heredity may make some people more susceptible to the toxic effects of certain drugs.

Racial or Genetic Factors

There may be racial differences in the incidence of some types of ADRs, and some individuals may have a genetically determined response to the development of ADRs. For example,an ethinopharmacological difference such as glucose 6–phosphate dehydrogenase deficiency, which predisposes to some drug induced hemolytic anemia, is more common among Africans, Kurds, Iraqi Jews, some Mediterranean people and Filipinos, and is relatively infrequent amongst other races.

Multiple Drug Therapy (Polypharmacy)

The incidence of ADRs increases with the number of drugs given due to the risk of interactions. Interaction between prescribed drugs is therefore an area, which is of concern to every healthcare professional. The followings are mechanisms of drug interactions: –

(a) Direct physical or chemical interactions of more than one drug given concomitantly.

(b) Altered gastrointestinal absorption, competition for protein binding sites or receptors.

(c) Increased or decreased metabolism of a drug by induction, activation or inhibition of drug metabolizing enzymes.

(d) Alteration of acid–base equilibrium thereby influencing drug distribution and renal clearance.

(e) Alteration of hemodynamics or renal function that influences the rates of renal excretion.

Evaluation of Adverse Drug Reactions

reactions. These reactions can also occur due to other medical or pharmaceutical products e.g. vaccines, but we will describe ADRs in the contexts of medications (or drugs). The fact that an adverse reaction has occurred does not affect in any way the credibility of the healthcare professional who prescribed, dispensed or sold the drug as long as sufficient knowledge and awareness of the medicine, its adverse effects, safety monitoring procedures, and risk minimization measures are acquired.

Classification of ADRs (etiological basis)

In many cases no specific reason can be given as to why a particular patient develops an adverse drug reaction, while another patient does not. With some relatively toxic drugs, adverse reactions are the rule rather than the exception. Four special etiological factors can, however, be defined. They comprise of inherent anomalies in the patient response (allergic or idiosyncratic), acquired patient anomalies, anomalies of drug presentation and administration, and interactions.

Inherent anomalies in patient response (allergic or idiosyncratic)

(a) Drug allergy (hypersensitivity): Reactions are due to genetic factors and physiological variables such as age, sex and pregnancy. Drug allergy is mediated by immunological mechanisms. The followings are characteristics of allergic reactions;

i. are not correlated with known pharmacological effects
ii. can be precipitated by small amounts of drugs
iii. repeated exposure will cause recurrence of reactions
iv. often include skin rash, angioneurotic oedema, serum sickness and anaphylaxis or asthma.

Factors affecting the incidence of allergic reactions are: the drug, the patient and the disease for which the drug is given.

(b) Genetically determined ADRs (idiosyncratic): The major genetically determined ADRs can be divided into two types;

i. Reactions due to altered pharmacokinetic handling of the drug in the body.
ii. Reactions due to altered tissue responsiveness.

Acquired patient anomalies

These reactions are due to the presence of intercurrent illness, which may unmask pharmacological effects that are not apparent in normal individuals. For example, hemorrhage or perforation of the peptic ulcers due to aspirin or corticosteroids. In addition, liver disease may impair drug detoxification, and renal disease may impair glomerular filtration, leading to reduced elimination of drugs that undergo renal excretion.

Anomalies of drug presentation and administration

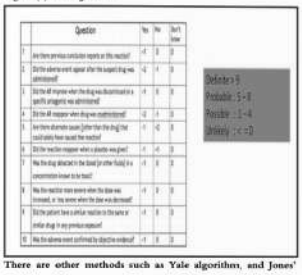
These reactions may be a consequence of excessive response, alterations in bioavailability or an inappropriate method of administration. There are three main potential sources of ADRs in this class. They include decomposition of active constituents, effects of by–products of the active constituents derived from chemical synthesis and effects of additives, solubilizing, stabilizing, coloring agents and excipients commonly incorporated in pharmaceutical preparations. Therefore, alteration in production methods may have marked adverse effects and consequences.

Drug interactions

These are ADRs resulting from interactions of more than one drug given at the same time and are likely to be proportional to the number of drugs given. However, some drug interactions may have both unwanted consequences and certain benefits (e.g. potentiation). The frequency of adverse drug interactions in clinical practice makes it mandatory for healthcare professionals

result of other factors. Probability is assigned via a score categorised as definite, probable, possible or doubtful. It is one of the most commonly used methods of causality assessment. Naranjo is used by the pharmacovigilance team in Kuwait to confirm the results obtained from the WHO–UMC probability scale as necessary.

Figure (1): Naranjo Scale



	Question	Yes	No	Don't know
1	Are there previous conclusive reports on this reaction?	+1	0	0
2	Did the adverse event appear after the suspected drug was administered?	+2	-1	0
3	Did the AE improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0
4	Did the AE reappear when drug was readministered?	+2	-1	0
5	Are there alternate causes (other than the drug) that could wholly have caused the reaction?	-1	+2	0
6	Did the reaction reappear when a placebo was given?	-1	+1	0
7	Was the drug detected in the blood (or other fluids) in a concentration known to be toxic?	+1	0	0
8	Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0
9	Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
10	Was the adverse event confirmed by objective evidence?	+1	0	0

Definite: ≥ 9
Probable: 5 – 8
Possible: 1 – 4
Doubtful: ≤ 0

There are other methods such as Yale algorithm, and Jones' algorithm. However, causality methods used should fulfill the above causality criteria.

3. Bradford Hill criteria for Causation

The Bradford Hill Criteria are a set of nine principles that help determine whether a relationship between two variables is causal. These were first proposed by Sir Austin Bradford Hill in 1965, primarily to assess causal links in epidemiology and public health research. The criteria are:

1. Strength: A stronger association between the cause and effect is more likely to suggest causation.
2. Consistency: The observed relationship should be consistently found across different studies, populations, and methods.
3. Specificity: A cause should lead to a specific effect, though this criterion is not always necessary or applicable, particularly for complex diseases.
4. Temporality: The cause must precede the effect in time. This is the most critical factor in establishing causation.
5. Biological Gradient: Also known as dose–response relationship, this criterion suggests that an increased exposure to the cause should lead to an increased risk of the effect.
6. Plausibility: The cause–and–effect relationship should make biological, logical, or scientific sense.
7. Coherence: The observed association should not conflict with existing knowledge or scientific understanding, and should fit within the broader body of evidence.
8. Experiment: If possible, experimental evidence (such as randomized controlled trials) should support the causal relationship.
9. Analogy: Similar factors or exposures known to cause similar effects can strengthen the argument for causation.

These criteria help reviewers assess whether an observed association between variables can reasonably be attributed to a causal relationship, although they do not guarantee causation on their own.

B. Seriousness

Seriousness of an ADR is related to its life–threatening nature and is defined as any untoward reaction to a medicinal product that

The World Health Organisation (WHO) defines Adverse Drug Reactions (ADRs) as noxious and unintended responses to a medicinal product. ADRs are also related to increased mortality and changes in morbidity patterns.

ADRs can be underreported and therefore their importance may be under–evaluated. Therefore, ADRs should be thoroughly assessed for causality, seriousness, severity, expectedness, and preventability.

A Causality

Causality is the relationship between cause and effect with the drug or the medical product being the suspected cause of the adverse event.

A1 Causality Assessment (relatedness assessment):

Causality assessment involves determining whether there is a reasonable possibility that the product is causally related to the adverse event. It includes evaluating the temporal relationships, dechallengeand rechallenge information, the association (or lack of association) of a more likely cause, and the medical and pharmacological plausibility.

A2 Causality Assessment Methods

There is no universally accepted method. Many researchers developed methods of causality assessment by using the following criteria:

- Chronological relationship between the administration of the drug and the occurrence of the event.
- Screening for drug and drug related outcomes.
- Screening for concomitant medical conditions.
- Confirmation of the reaction by in–vivo or in–vitro tests.
- Previous information on similar events.
- Other information that might benefit the assessment.

The most commonly used methods for causality assessment are:

1. World Health Organization–Uppsala Monitoring Center (WHO–UMC) Probability Scale

Causality assessment of ADRs obtained with the WHO–UMC criteria (Table 1) is the most commonly used method worldwide and is mostly used in Kuwait. It classifies the causal relationship between a drug and the effect as certain, probably, possible, unlikely, conditional/unclassified, and unassessable/unclassifiable.

Table (1): WHO–UMC Probability scale

Causality term	Assessment criteria
Certain	Event or laboratory test abnormality, with plausible time relationship to drug intake Cannot be explained by disease or other drugs Response to withdrawal plausible (pharmacologically, pathologically) Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognized pharmacologic phenomenon) Rechallenge satisfactory, if necessary
Probable/ likely	Event or laboratory test abnormality, with reasonable time relationship to drug intake Unlikely to be attributed to disease or other drugs Response to withdrawal clinically reasonable Rechallenge not required
Possible	Event or laboratory test abnormality, with reasonable time relationship to drug intake Could also be explained by disease or other drugs Information on drug withdrawal may be lacking or unclear
Unlikely	Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) Disease or other drugs provide plausible explanation
Conditional/ Unclassified	Event or laboratory test abnormality More data for proper assessment needed, or additional data under examination
Unassessable/ unclassifiable	Report suggesting an adverse reaction Cannot be judged because information is insufficient or contradictory

2. Naranjo Scoring

Naranjo scoring (Figure 1) is a questionnaire for determining the likelihood of whether an ADR is due to the drug rather than a

- Expectedness can go beyond just the listed side effects to include clinical judgment based on available safety data and patterns from other similar drugs or experiences.
- Example: If a patient reports a rash after taking a medication, and rash is commonly observed in patients treated with that class of drugs, this event may be classified as expected even if it is not specifically listed on the label.

Summary of Differences:

- Listedness focuses on whether the AE is explicitly mentioned in the product's official documentation.
- Expectedness takes into account the broader context of the drug's known safety profile, which may include unlisted side effects that are still expected due to the drug's properties or class.

In regulatory reporting (such as for Serious Adverse Events), these terms are important for determining how adverse events should be handled, particularly for expedited reporting to health authorities.

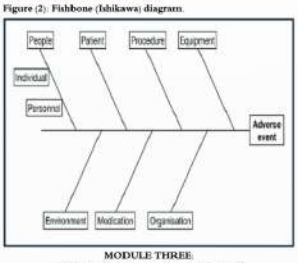
E. Preventability

There are 8 different general approaches to defining preventability:

1) Preventability linked to patient and relatives or caregivers.
2) Preventability linked to standard of care.
3) Preventability related to medication–related factors.
4) Preventability linked to information technology.
5) Preventability linked to inter–professional relationship.
6) Preventability linked to methods (regulation, procedures and protocols).
7) Preventability linked to resources and equipment
8) Preventability linked to workplace.

Preventability requires a proper root cause analysis. The most commonly used method for ADR root cause analysis is the Fishbone (Ishikawa) method which evaluates the factors that contribute to the occurrence of an AE. The results of this method assist in the determination of the possible source(s) of the ADR. The method uses a diagram as a visual representation (Figure 2) of the potential root cause(s) of an ADR or any drug related problems. This diagram is not only useful to understand the causal relationship but also for detecting areas where the root causes can be prevented or resolved.

Figure (2): Fishbone (Ishikawa) diagram.



MODULE THREE:
REPORTING OF ADVERSE EVENTS
REPORTING OF ADVERSE EVENTS

An adverse event (AE) is harm caused by appropriate or inappropriate use of a medical or pharmaceutical product. On the other hand, adverse drug reactions (ADRs) are a subset of may result in death, requires inpatient hospitalization or prolonged hospitalization, results in persistent or significant disability/incapacity, or causes a congenital anomaly/birth defect, or is a medically important event or reaction.

C. Severity

Severity describes the extent to which the ADRs influence the everyday life of patients. There are seven levels of severity from which ADRs can be categorized:

➢ Levels 1–2: Mild
➢ Levels 3–4: Moderate
➢ Levels 5–6: Severe
➢ Level 7: Lethal

Karch and Lasagna is a severity assessment method that classifies severity into mild, moderate, severe and lethal. In minor severity, there is no need for an antidote, therapy or prolongation of hospitalisation. Moderate severity requires a change in the drug therapy, specific treatment or an increase in hospitalisation by at least one day. The severe class includes all potentially life–threatening reactions causing permanent damage or requiring intensive medical care. Lethal reactions are the ones that directly or indirectly contribute to a patient's death.

D. Expectedness/Listedness

Expectedness of the ADRs depends on their connection with the main pharmacological action of the drug. The assessment of expectedness is deciding whether the adverse event presented is listed (expected) or not listed (unexpected) in the appropriate section of the reference safety information (RSI). The types of RSIs include:

1. Company Core Data Sheet (CCDS) – Global Document.
2. Summary of Product Characteristics (SmPC)– Regional or Country Specific Document.
3. Country Specific Prescribing Information (CSPI)– e.g. United States (US), Japan, Canada, Europe(EU), Gulf Cooperation Council (GCC) countries.
4. Investigators Brochure (IB)– Developmental Updates (Clinical Trials).

Listedness is expectedness assessed against Global Reference Document (which CCDS). So, in simple terms, all listedness are expectedness; but not all expectedness are listedness.

In pharmacovigilance, listedness and expectedness are terms used to describe the relationship between an AEand the use of a particular drug. These concepts are particularly relevant for determining the regulatory reporting requirements for AEs especially in clinical trials and post–marketing surveillance. The following explains the distinction between the two in detail:

1. Listedness:

- Listedness refers to whether an AE is already included in the product's label or SmPC as a known potential side effect.
- If an AE is listed, it means that it is a known, documented, and recognised potential effect of the drug, and it is included in the official product documentation.
- Example: If a drug's label mentions "headache" as a possible side effect, and a patient experiences a headache after taking the drug, this would be considered a listed AE.

1. Expectedness:

- Expectedness refers to whether the nature or severity of the AE is consistent with what is expected based on the known safety profile of the drug.
- It involves assessing whether the AE is within the range of events that can reasonably be expected from the drug, given its class, pharmacological properties, and previous data.

The pharmacovigilance team shall collect the ICSRs, detect them and address the safety issues of medicines with optimal efficiency, professionalism and confidentiality.

The reporting form contains information on the following elements (see KuGVP Annex 1p38); list does not comply exactly with the form

1.The patient: age, sex, weight, ethnic origin and brief medical history

2. Adverse event: description (nature, location, severity, characteristics), results of investigations and tests, start date, course, and outcome.

3. Suspected drug(s): name (brand or ingredient name and manufacture), daily dose, route of administration, start/stop dates, indication for use (with particular drugs, e.g. vaccines, a batch number is important).

4. All other drugs used (including self-medication): names, doses, routes of administration, start/stop dates.

5. Risk factors (e.g. impaired renal function, previous exposure to suspected drug, previous allergies, social drug use).

6. Name and address of reporter if the reporter is a healthcare professional (to be considered confidential and to be used only for data verification, completion and case follow-up). In the case of reporting an adverse event by the patient, the name and address of the physician who prescribed the medicine, or the pharmacist who dispensed it shall be stated. Otherwise, the hospital or the pharmacy from which the treatment was obtained shall be stated as necessary.

ARs are reported by telephone, fax and electronic mail or online submission of electronic forms.

Quality Defect Forms

This form is available online for healthcare professionals to report any defect in the pharmaceutical quality of the medicine e.g. change in color, suspected counterfeit, etc (see KuGVP Annex 2 p39).

https://eservices.moh.gov.kw/SPCMS/HSDrugComplaints.aspx

Quality defects may suggest failure in the finished product specifications due to manufacturing defects or supply chain malpractices. These defects can alter the safety profile of the medicine which may expose the patient to harmful effects.

Therefore, quality defects must be reported to KPVC to carry out all the necessary investigations and analyses and take the appropriate actions.

Vaccine Adverse Event Reporting System (VAERS)

VAERS is a system co-managed by the Public Health Officials and the Pharmacovigilance team at the KPVC at the Drug and Food Control Sector. The co-management is achieved by the vaccine adverse event monitoring (VAEM) committee of experts in multidisciplinary areas in the medical field. VAER system receives and evaluates reports of adverse events (possible side effects) after a person has received a vaccination. Anyone can report an adverse event using the online VAER form. Healthcare professionals are required to report certain adverse events and vaccine manufacturers are required to report all adverse events that come to their attention (See Annex 3 p40) KuGVP needs to be mentioned?All annex references should be the same

The reporting form for vaccine adverse events is

https://eservices.moh.gov.kw/SPCMS/HSDrugComplaints.aspx

VAER is a voluntary reporting system which relies on individuals to send in reports of their experiences to the VAER Committee . VAER is not designed to determine if a vaccine caused a health problem but is especially useful for detecting unusual or adverse events, where harm is directly caused by a drug (a pharmaceutical product) under appropriate use (i.e., at normal doses). An adverse reaction (AR) is an unexpected negative reaction to a medication or treatment that is used in an approved manner. However, when an AR is expected or known, the term side effect is used. Therefore, AR and side effects may be used interchangeably, but side effects are often expected and refer to ARs that are minor or confer less harm.

A suspected adverse drug reaction is a reaction which may or may not be known or expected but is suspected to be directly related to the use of a medication or treatment. Spontaneous reporting of suspected adverse drug reactions is the major source of safety information in pharmacovigilance. This information can be obtained from the local reporting system.

Monitoring of Adverse Drug Reactions (ADRs)

An adverse drug reaction (ADR) is an unwanted or harmful reaction experienced following the administration of a drug or combination of drugs under normal conditions of use, which is suspected to be related to the drug. The reaction may be a known side effect of the drug or it may be a new and previously unrecognized adverse reaction (AR). Rapid detection and recording of ADRs is vital so that hazards are identified and appropriate regulatory action is taken to ensure that medicines are used safely. Suspected ADRs to any therapeutic agent should be reported, including drugs (self-medication as well as prescribed), blood products, vaccines, complementary and herbal products.

Healthcare professionals (HCPs) are urged to report suspected ADRs directly to the KPVC team available as PDF and electronic forms at E-Services on the website of the Ministry of Health:

https://eservices.moh.gov.kw/SPCMS/HSDrugComplaints.aspx

Link takes you to a list of forms and not a particular one as is with the rest of the links in this section

The electronic reporting is also available in Sahel application under Ministry of Health services.

ADRs may be categorized into:

- Side effects
- Secondary effects
- Toxic effects and poisoning
- Intolerance
- Idiosyncrasy
- Drug Safety
- Photosensitivity
- Drug dependence
- Drug withdrawal reactions
- Teratogenicity
- Mutagenicity and carcinogenicityDrug Induced diseases

Reporting form

Individual Case Safety Report (ICSR)Format (ICSR)

ICSR is an adverse event report for individual patients and is an important source of data in Pharmacovigilance. The main focus of ICSRs is reports from healthcare professionals and patients.

ICSR shall be used for the purpose of obtaining the same format for the reports on individual cases of suspected adverse drug reaction in patients due to a medicine across the country. It is also expected to include useful information on medicines that might be associated with an adverse drug reaction and on the therapeutic uses of those medicines. In addition, patient confidentiality shall be ensured by applying personal data protection in the records of all collected ICSRs.

their products are reported to the competent authority. If adverse reactions are reported directly by patients to the KPVC, the department will communicate with the prescribing doctor or the dispensing pharmacist for additional information and data verification.

When to Report?

In general, any suspected ADR should be reported as soon as possible. Delay in reporting will make reporting inaccurate and unreliable. If possible, report while the patient is still in the health facility this gives a chance for the reporter to clear any ambiguity by re-questioning or examining the patient.

For pharmaceutical companies and manufacturers, the reporting of all domestic serious valid ICSRs is required as soon as possible, but in no case later than 15 calendar days after initial receipt of the information by any personnel of the marketing authorisation holder, including medical representatives and contractors. This applies to initial and follow-up information. Where a case initially reported as serious becomes non-serious, based on new follow-up information, this information should still be reported within 15 days; the reporting time frame for non-serious reports should then be applied for the subsequent follow-up reports.

Reporting of all domestic non-serious valid ICSRs is required within 90 calendar days from the date of receipt of the reports by the marketing authorisation holders.

KPVC has in place a system for the collection and recording of unsolicited and solicited reports of suspected adverse reactions that occur in its territory and which are brought to its attention by healthcare professionals, consumers, or MAHs.

How to Report?

In this context, the reporting of suspected adverse drug reactions is possible by all healthcare professionals, consumers and marketing MAHs by means of:

✓ Straightforward paper-based reporting forms,

✓ Web-based formats (https://eservices.moh.gov.kw/SPCMS/HSDrugComplaints.aspx).

✓ Other (e.g. telephone, or mobile apps – Sahel– as and when available)

Reporters should send accurate information to achieve high standard for monitoring AEs and/or to investigate quality defects efficiently.

The reporting process is as follows:

1. Fill in the AE standardised reporting form (or quality defect form) (KuGVP annex 1, KuGVP Annex 2) when encountering an AE or quality defect.

2.Use a separate AE form for each patient and a separate quality defect form for each pharmaceutical product.

3. Traditionally, a completed AE case (or quality defect) report form should immediately be sealed and mailed preferably directly to KPVC within three days or through other reporting healthcare professionals for onward transmission to the department. This is acceptable if other methods of submission are not available and is usually done as a back-up when the electronic reporting system faced technical problems.

4. Reports can also be submitted online by going to the MOH website

https://eservices.moh.gov.kw/SPCMS/HSDrugComplaints.aspx

and clicking "yes" if you are a healthcare professional and "no" if you are a patient, a consumer or a caregiver.

5. Reports may be sent by e-mail through the following e-mail address; adr_reporting@moh.gov.kw

unexpected patterns of adverse event reporting that might indicate a possible safety problem with a vaccine. This way, VAER can provide the regulators and public health officials with valuable information that additional work and evaluation is necessary to further assess a possible safety concern.

Global Adverse Event Database

VigiFlow

VigiFlow is a web-based ICSR management system that is available for use by the Pharmacovigilance Team at the KPVC and their Focal Points. Kuwait became a full member (#145) of the WHO Programme for International Drug Monitoring (WHO PIDM) on April 2021. It supports the collection, processing and sharing of data of ICSRs to facilitate data analysis.

Manual data entry from the collected ICSRs is performed with support from integrated international terminologies (latest versions) such as WHODrug and MedDRA.

ICSR data can be shared and exchanged (both import and export) in a harmonised format (as ICH E2B XML-files) with external stakeholders, such as pharmaceutical companies and public health programmes, and with the WHO global database of ICSRs, VigiBase.

VigiFlow is compliant with the international ICH E2B standard and maintained by Uppsala Monitoring Centre (UMC) in Uppsala, Sweden.

VigiFlow is available to all members of WHO PIDM. Due to the facilities provided by VigiFlow to member countries, Kuwait agreed to use it as an officially approved web-based ICSR management system for medicines and vaccines.

UMC charges a license fee for VigiFlow, determined by the World Bank Atlas method. The subscription fee is annual and the contract is automatically renewed every year.

VigiBase

VigiBase is the WHO global case safety report database which is maintained and developed on behalf of WHO by UMC. VigiBase is the single largest drug safety data repository in the world, used to obtain the information about a safety profile of a medicinal product. Such data is used by pharmaceutical industries, academic institutions and regulatory authorities for statistical signal detection, updating periodic reports (ICSR-comparison with company databases and studying the reporting patterns.

VigiLyze

VigiLyze is available to WHO PIDM member countries. It is used to provide a global, regional or national view of the reported adverse effects of a medicine. It is also used to find supporting evidence when, for example, assessing one country's case reports. Access to safety information on medicines and vaccines that are marketed elsewhere but are not yet on the local market is another benefit.

The use of VigiFlow provides the advantage of using VigiLyze services free of charge,

Who should report?

Professionals working in healthcare (private and government sectors) are the preferred source of information in pharmacovigilance. These include family practitioners, medical specialists, nurses, pharmacists and pharmacy technicians.

Other health workers and family members can play an important role in the stimulation of reporting and in the provision of additional information (e.g., on vaccine safety, co-medication and previous drug use).

Pharmaceutical manufacturers, applicants and research organizations have to ensure that suspected adverse reactions to

reporter specifically states the outcome was due to the progression of a disease and not related to the treatment. However, if the reporter believes the outcome was not due to disease progression, this MUST be reported even if the reporter disagrees with it. Reporter's opinions shall be included in the report.

When reporting a suspected lack of efficacy/effectiveness, indication must not be coded for which the suspected medicine was administered as an adverse reaction. For example, hypertension should not be coded as an adverse reaction to an anti-hypertensive medicine. Rather, where the existing condition was altered—that is, it progressed, recurred or was aggravated—by the lack of efficacy/effectiveness, this should be coded as such in the report.

Reports of lack of efficacy/effectiveness may help identify:

- Changes in the manufacturing quality and compliance with good manufacturing practice.
- Differences in how a particular subgroup of patients responds to the medicine
- In vaccines, reduced immunogenicity in a sub-group of vaccines, waning immunity and strain replacement.
- For anti-infectives, the development of resistance

If the reporter suspects any of these potential signals, she/he MUST report them to the KPVC as a significant safety issue. Additionally, the reporter should consider whether further investigation and prompt action is warranted.

Evidence for lack of effectiveness should not normally be expedited but should be discussed in the relevant Periodic Safety Update Report (PSUR) or Periodic Benefit-Risk Evaluation Report (PBRER). However, in certain circumstances, individual reports of lack of effectiveness are considered subject to expedited reporting. Medicinal products used for the treatment of life-threatening or serious diseases, vaccines, and contraceptives are examples of classes of medicinal products where lack of effectiveness should be considered for expedited reporting. Clinical judgment should be used in reporting, with consideration of the approved product labeling and disease being treated in Kuwait.

Spontaneous/Voluntary Reporting

Spontaneous/Voluntary reporting of ARs is the most common way of collecting safety information for medicines, vaccines and other treatments from healthcare professionals and patients. This helps the regulatory authority to take proper actions at the earliest possibility thereby preventing occurrence of the potential safety hazards on larger group of population by identifying and utilizing the most effective risk minimization measures.

What should healthcare professionals need to do with respect to voluntary AE reporting?

1. Should be aware and knowledgeable about platforms for reporting adverse experiences (side effects, AEs and ARs).
2. Should be cautious while prescribing (physicians and dentists), dispensing (pharmacists) and administering (nurses) medical or pharmaceutical products with complete awareness of the expected safety concerns and the respective risk minimization measures.
3. Should be vigilant in the identification of signs and symptoms of AEs and report proactively whenever the safety incident occurs.
4. Should inform patients and patient's care providers to observe and monitor for any possible AEs or ADRs (both expected and unexpected).
6. Reports may be obtained from regulatory authorities or MAHs or any government or private hospital or primary healthcare centres
7. Reports may be faxed in cases of perceived urgency
8. Electronic reporting is available on Sahel
9. Tawasol Platform is also available on Sahel for reporting general complaints from consumers on products or services regulated by the Ministry of Health.
10. Any follow-up information for an AE or a quality defect case that has already been reported can be sent on another AE or quality defect form, or communicated by telephone, fax or e-mail or via Tawasol platform. To enable this information be matched with the original report it is very important that follow-up reports are identified, and the following should be indicated in the report;

a. That it is a follow-up information,
b. The date of the original report and
c. The patient identities.

Where to Report?

Report any suspected ADRs for pharmaceutical products marketed in Kuwait to the appropriate channels as follows: -

1. Preferably directly to KPVC by post or online or by email or via Sahel
2. Onward transmission to KPVC via Deputy Focal Points in government hospitals, private hospitals, health centres, pharmacies
3. Onward transmission to KPVC via any other relevant institutions, drug information centres or health and research facilities

What to report?

- For "new" medicines and vaccines- report all suspected reactions, including minor ones.
- For established or well-known medicines and vaccines- report all serious or unexpected (unusual) suspected ARs.
- Report if an increased frequency of a given reaction is observed.
- Report all suspected ARs associated with drug-drug, drug-food or drug-food supplements (including herbal or complementary products) interactions. This also applies to vaccines interactions.
- Report ARs in special fields of interest such as abuse and misuse as well as use during pregnancy and/or lactation.
- Report when suspected ARs are associated with treatment withdrawals.
- Report ARs occurring from overdose or medication error.
- Report when there is a lack of efficacy or when suspected pharmaceutical defects
- Report when there is a pharmaceutical quality defect of poor quality standards.

Reporting Lack of Efficacy/effectiveness

Efficacy describes how a medication is used in an idealized or controlled setting- namely, a clinical trial or a bioequivalence study. Effectiveness describes how a medication is used in a real-world setting where the patient populations and other variables cannot be controlled.

Therefore, lack of efficacy indicates a problem from the treatment which is encountered during the study performed under idealized or controlled settings. However, lack of effectiveness indicates a problem from the treatment which occurs in real-world settings where the patient populations and other variables cannot be controlled. Incidents of unexpected lack of efficacy or effectiveness may not be reported if the

your suspicion or seem to exclude the reaction, please send in a supplementary note immediately using ADRs reporting form with the patient identifiers.

5. All reports must have the following four data elements:

i. An identifiable patient
ii. A suspected adverse effect
iii. A named suspected drug(s)
iv. An identifiable reporter

6. Always write legibly.

Duties and Responsibilities

Doctors, Nurses, Pharmacists and other healthcare professionals should report any suspected adverse drug reactions, drug interactions and unusual effects immediately.

ADR reporting forms and/ or quality defect reporting forms shall be filled and handed over to the PV Focal Point in the Pharmacy Unit of the health institution and/or mailed directly to KPVC. The PV team at KPVC will then provide feedback to the health institution about the reported case and whether any actions to be taken to ensure safe use of the medicine (see safety communication, Module 11). Once the health institution receives feedback from the KPVC team via the appointed focal point, the health institution shall promote rational use of drug(s) by distributing ADR information healthcare professionals and shall ensure all the ADR report be kept confidential. Focal points must ensure that all healthcare professionals received the feedback. Therefore, the role and responsibilities of the Pharmacovigilance team in the KPVC are:

1. Promote reporting.
2. Collect and collate report.
3. Give feedback.
4. Review the reported ADRs.
5. Compile and analyze data collected.
6. Promote prevention of ADR and rational use of drugs.
7. Search literature, collect, collate and analyze information on ADRs and distribute to healthcare professionals.
8. Communicate with the international ADR monitoring centers including the Uppsala Monitoring Center (UMC).
9. Decide on the appropriate action.

The Health Institutions shall retain the necessary documentation to ensure availability of reporting form with the detailed information about the reported case.

PLEASE DO NOT HESITATE TO CONTACT THE PHARMACOVIGILANCE TEAM AT THE DEPARTMENT OF PHARMACOVIGILANCE and SAFETY SURVEILLANCE (KPVC) if you have any comment or need clarification on the guidelines or the ADR reporting forms

Annex 1: Suspected ADR reporting form

5. Should educate patients and patient's care providers to report the adverse experiences (side effects/AEs/ADRs).
6. Should familiarize the patients and patient's care providers about voluntary reporting of adverse experiences to the regulatory authority.
7. Should report adverse experiences to the regulatory authority at the earliest possibility.

What should patients and patient's care providers need to do with respect to voluntary ADR reporting?

1. Should be aware of the existence of platforms for reporting adverse experiences (side effects/AE/ADRs).
2. Should be cautious while administering (self and patient care provider) the product with complete awareness of expected safety concerns.
3. Should be familiar with the available reporting channels for submitting information about the adverse experience to the regulatory authority.
4. Should take responsibility to report the adverse experience to the regulatory authority or to the respective healthcare professional.

Seriousness Determination

The following set of criteria within pharmacovigilance that are used to distinguish a serious adverse event from a non-serious one. An adverse event is considered serious if it meets one or more of the following criteria.

- Results in death, or is life-threatening.
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity.
- Results in a congenital anomaly (birth defect)
- Or is otherwise "medically significant" (i.e., that it does not meet preceding criteria, but is considered serious because treatment/intervention would be required to prevent one of the preceding criteria.)

Coding of Adverse Events

Adverse event coding shall be used to process information obtained from a reporter which is coded using standardized terminology from a medical coding dictionary, such as MedDRA (a commonly used medical coding dictionary). The purpose of medical coding is to convert adverse event information into terminology that can be readily identified and analyzed.

Basic Principles of Efficient Reporting

1. Report the adverse reaction or quality defect immediately after its encountered.
2. If possible, take the decision to report whilst the patient is still with you, so that the details can be filled in at once on the reporting form.
3. Think about any other factors which may contribute in causing the event such as other prescribed drugs, self-medication, herbal products, food, chemicals, ask the patient particularly about other medicines taken.
4. If you get any supplementary data later, e.g. if the same patient develops the effect again or if something happens which increases

Annex 2: Quality Defect Form

وزارة الصحة
قطاع الرقابة الدوائية والغذائية
مكتب الكويت لرقابة الجهات الدوائية
Ministry of Health
Drug & Food Control Sector
Kuwait Office For Pharmacovigilance Surveillance (KOPS)

Pharmaceutical Products Quality Reporting Form

1. Suspected drug/Product type: Drug Vaccine Herbal product Food supplement Other

Suspected Product Name (generic & brand)	Batch number	Dosage form (route/frequency)	Exp date	Purch. price	Manufacturer / Origin

2. Quality defect detected: (please attach photo if available)

Types of quality problems:
Packaging
Suspected counterfeit product
Product confusion (caused by name, labeling, design or packaging)
Questionable stability
Suspected contamination
Defective components
Labeling Problems (caused by printing error, omission)
Others:
More Details:

3. Consequences:
Patient died
Involved or Prolonged Hospitalization
Involved persistent or significant disability or incapacity
Life threatening
Congenital anomaly
Required intervention to prevent further damage/impairment Other

Is the Sample available for analysis? Yes No
Has the manufacturer or supplier has been informed? Yes No

4. Reporter Data: (All data will be kept confidential)

Name:	Profession (Specialty):	Date:
Email:	Phone:	Signature:
Organization:		
Department:		

Please send this form by email to: ... For the Whatsapp no: +965 2461 1078
Note: Identities of reporters, patient and institution will remain confidential

Annex 3: Vaccine Adverse Event Reporting (VAER) Form

وزارة الصحة
قطاع الرقابة الدوائية والغذائية
مكتب الكويت لرقابة الجهات الدوائية
Ministry of Health
Drug & Food Control Sector
Kuwait Office For Pharmacovigilance Surveillance (KOPS)

Vaccines Adverse Event Reporting Form (VAER)

1. Patient Details:

Name:	Civil ID:	Nationality:
Date of birth:	Gender: Male Female	Age at vaccination: Years Months Days
Address:	Phone number:	E-mail:

Pregnant at time of vaccination? Yes No Unknown
(If yes, describe the event, any pregnancy complications, and estimated due date (Trimester))

2. Health Facility (place or vaccination center):

Name:	Type (Government, Private):	Address:	Phone Number:

3. Vaccine / Vaccination Program:

Name of vaccine	Type of vaccination program (Mandatory, Voluntary)	Date and time of vaccination	Route of administration	Dose (1st, 2nd, etc.)	Batch/ Lot number	Expiry date

4. Description of adverse reaction:

Describe the adverse event(s), treatment, and outcome(s). (Example: symptoms, signs, time course, etc.)

Result or outcome of adverse event(s):
1 Healthcare professional office/clinic visit
2 Emergency room/department or urgent care
3 Hospitalization:
Duration (if known):
Hospital name:
4 Prolongation of hospitalization
5 Life-threatening illness (immediate risk of death from the event)
6 Disability or permanent damage
7 Patient died
Date of death: (if known)
8 Congenital anomaly or birth defect
9 Other

Past medical history: (including history of similar reaction or other allergies), concomitant medication and other relevant information (e.g. other cases).

Was vaccine received during hospitalization? Yes No

Medical tests and laboratory results related to the adverse event(s): (include dates)

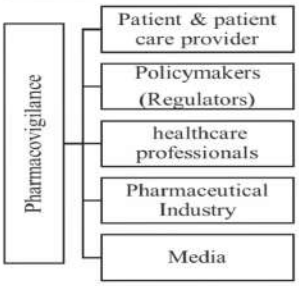
Has the patient recovered from the adverse event(s)? Yes No Unknown

Date reaction started: Date reaction stopped:

5. Reporter Data: (All data will be kept confidential)

Name:	Profession/Specialty:	Date:
Email:	Phone:	Signature:

Please send this form by email to: ... For the Whatsapp no: +965 2461 1078
Note: Identities of reporters, patient and institution will remain confidential



KPVC is responsible for continuous collection, assessment and storage of reports of, suspected adverse reaction to medicinal products marketed in the country.

Reports are initially separated according to their source. All case reports will be individually assessed and the following shall be considered:

1. Quality of documentation in respect to completeness of the four elements of a valid case report, integrity of data, quality of diagnosis and follow-up.

2. Analysis; this shall be based on the temporal relationship between the reaction and the drug, whether there was a positive dechallenge/rechallenge, the seriousness of the reaction, whether the current labeling lists the reaction and whether the reaction is reported on the medical literature.

3. Clinical relevance in respect to detection of new reaction especially for new drugs, unknown reactions or serious. If similar cases are found, the report becomes a monitored adverse drug reaction.

4. Quality control in respect to identification of duplicate reports. Certain characteristics of a case report for example, sex, date of birth or age, name of the suspected drug, dates of drug exposure etc. shall be used to identify duplicate reporting or follow up report.

5. Causality assessment and transmission of the assessed reports to a format which complies with the WHO-UMC format shall be performed regularly.

The causality assessment and ADR coding shall be based on WHO causality categories. The categories are based on four considerations:

i. The association in time between drug administration and event
ii. Pharmacology (including current knowledge of nature and frequency of adverse reactions)
iii. Medical or pharmacological plausibility (signs and symptoms, laboratory tests, pathological findings, mechanism)
iv. Likelihood or exclusion of other causes

6. The Coding; drug names shall be entered in a systematic way by using trade name of the suspected product. Diseases may be classified based on International Classification of Diseases (ICD) developed by WHO. The adverse events description shall be entered based on the WHO Adverse Reaction Terminology (WHO-ART) and also by MedDRA Dictionary which is widely used for this purpose.

MODULE FOUR:
PROCESSING OF
COLLECTED ADVERSE EVENT DATA

PROCESSING OF
COLLECTED ADVERSE EVENT DATA

Assessment of Case Reports

Assessment of case reports aim at identifying safety concerns, evaluating the benefit-risk ratio, and communicating the outcomes to all stakeholders (patients and patient care providers, policymakers (regulators), healthcare professionals, pharmaceutical industry, media). Communication methods differ between various stakeholders (Figure 3).

Figure (3): Pharmacovigilance communication with various stakeholders

one or more of the following:
1. Further investigation of signals. For example, identifying "at risk" group, a dose range which might be more suspected, suggesting a pharmaceutical group effect, pharmacological mechanisms, lack of effect by a particular drug or investigation into the use of a medication in the country.
2. Medicines regulation and dissemination of information of current importance.
3. Education and training initiatives to improve the safe use of the medication and other health promotion interventions as the situation may warrant including change in supply status or withdrawal.
Report on treatment problems from HCPs can prevent occurrence of new tragedies or can reduce suffering and save lives of thousands of patients.

MODULE FIVE:
RESPONSIBILITIES OF THE MARKETING AUTHORIZATION HOLDER (MAH), THE PHARMACEUTICAL COMPANY, THE QUALIFIED PERSON RESPONSIBLE FOR PHARMACOVIGILANCE (QPPV) and THE LOCAL SAFETY RESPONSIBLE PERSON (LSR)

Pharmacovigilance Responsibilities of the MAH
• The MAH is responsible for the respective PV tasks and responsibilities so MAH shall operate a PV system and a quality system that is adequate and effective for performing its PV activities.
• A description of the PV system shall be developed by the applicant for a MAH in the format of PSMF and shall be maintained by the MAH for all authorized medicinal products.
• MAH is also responsible for developing and maintaining products specific risk management systems.
• MAHs are required to submit the following PV documents as per the Arab guidelines for PV to KPVC in Kuwait:
1. Risk Management Plans (RMPs) when applicable
2. Individual Case Safety Reports (ICSRs)
3. Periodic Benefit-Risk Evaluation Reports (PBRER) or Periodic Safety Update Reports (PSURs) or Periodic Adverse Drug Experience Report (PADER) along with the waiver.
4. Reported new signals.
5. Dear Healthcare Professional Communication (DHPC).
6. Post-Authorization Safety Studies (PASS).
Note: Pharmacovigilance system master file (PSMF) and Pharmacovigilance Sub-System Master File (PSSMF) to be submitted for New Drug Application (NDA) to the Registration Department at the Medicines and Medical Product Registration and Regulatory Administration.

Responsibilities of the MAH in relation to the QPPV
• The MAH shall have full-time qualified person responsible for pharmacovigilance (QPPV) that should communicate directly with the Local Safety Responsible Person (LSR) in Kuwait.
• The names and contact details of the nominated QPPV and the LSR should be submitted to KPVC. Changes to this information should be submitted to KPVC for approval.
• Each Pharmacovigilance system can have only one QPPV
• For multinational MAHs, LSR is designated by the local agent who is legally representing the MAH/applicant and may be employed for one or more MAHs through the local representative, while a QPPV may be employed by the marketing authorization holder and communicates directly with the locally assigned LSR.

6. Generation of hypotheses or the identification of signals. This activity shall be strengthened by a search from the cumulative data in the global WHO database for similar reports.
7. Presentation of analyzed case reports requires the establishment of Kuwait Pharmacovigilance Risk Assessment Committee (KuPRAC). This committee of experts shall be responsible for evaluation and interpretation of the compiled coded case reports and provide advice on appropriate interventions.
8. Receipt and communication of appropriate safety information resulting from analysis of local reports, from UMC, other relevant national institutions or centers, regulatory agencies and literature.

Handling of Safety Data
An acknowledgement letter or note will be sent to the reporter for every additional case or quality defect reported to the KPVC.
The reports shall be stored in a database at KPVC with top confidentiality. Such reports are analyzed and sent to the WHO database using VigiFlow where all collected case reports by the department are sent.
The name of the reporter and the patient will be removed before any details about specific adverse drug reactions are used or communicated to others. Publications will not disclose trade name of products unless regulatory actions have been taken. In this regard information obtained from spontaneous ADR monitoring system will not be used for commercial purposes.
The information is only meant to improve the understanding on use of medical and pharmaceutical products by reducing the risks associated with drug prescribing and administration and to ultimately improve patient care, safety and treatment outcome.
In the same way suspected ADR reports cannot be used in a court of law under any circumstances.
KPVC is responsible for providing reporting forms, collecting, analyzing and communicating the findings and evaluation reports.
KPVC shall use the finding from the reporter for making regulatory decisions on how to prevent or minimize the risk of AEs from the use of medical and pharmaceutical products circulating in the country.
KPVC may communicate the findings, recommendations and directives to appropriate organizations or individuals. These include, healthcare professionals, pharmaceutical manufacturers, public health programmes within the country, other public and private health institutions, the media and the public.

Provision of Feedback to Reporters
The outcome of the report, together with any important or relevant information relating to the reported event, shall be communicated to the reporters and other parties as appropriate.
After a significant AE is detected and a decision on the course of action is determined, the information shall be communicated rapidly and systematically to HCPs, public and media.
In addition, healthcare professionals will have an increased advantage of access to feedback on information about the AE related to the suspected treatment reported locally and internationally, and the availability of additional database for further investigation.

Utilisation of AE Data
Data collected will be used for provision of timely advice to healthcare professionals and consumers on safety issues at the healthcare facility, national and international level. A well-documented AE related to a suspected medication could result in

2. The QPPV can be a pharmacist, a doctor, a nurse, or any person of a medical specialty with a minimum experience of 2 years in Pharmacovigilance.
3. The QPPV should have the skill for the management of PV systems as well as expertise or access to expertise in relevant areas such as medicine, pharmaceutical sciences, regulatory affairs, Pharmacoeconomics as well as epidemiology and biostatistics.
Qualifications of the LSR
• The local agent shall ensure that the LSR has the knowledge and experience for the performance of PV activities.
• The LSR should:
1. Have a minimum of Bachelor in Degree of Pharmacy or PharmD and a basic training in Pharmacovigilance.
2. The LSR can be a clinical pharmacist or a pharmacist with a minimum of 6 months of experience in pharmacovigilance. Other medical professions (Physician, Dentist or a nurse) can be accepted if a pharmacist or a clinical pharmacist are not available as long as a minimum of bachelor's degree in the medical field is fulfilled in addition of a minimum of 6 months training in PV.
3. The LSR should have the expertise or access to expertise in relevant areas such as medicine, pharmacy, epidemiology, regulatory affairs, Pharmacoeconomics and biostatistics

QPPV Responsibilities
• The QPPV shall be responsible for the establishment and maintenance of the MAH's PV system and therefore shall have sufficient authority to influence the performance of the quality system and the PV activities and to promote, maintain and improve compliance with the legal requirements in Kuwait and outside Kuwait.
• Having an overview of medicinal product safety profiles and any emerging safety concerns.
• Having awareness of any conditions or obligations adopted as part of the marketing authorizations and other commitments relating to safety or the safe use of the products.
• Having awareness of risk minimization measures.
• Being aware of and having sufficient authority over the content of risk management plans.
• Being involved in the review and sign-off of protocols of post-authorization safety studies conducted or pursuant to a risk management plan agreed in Kuwait and at the country where he/she resides.
• The QPPV can reside outside the country if the MAH authorization holder is not located in Kuwait.
• Having awareness of post-authorization safety studies requested by Kuwait including the results of such studies.
• Ensuring conduct of pharmacovigilance and submission of all pharmacovigilance-related documents through the LSR in accordance with the Kuwait legal requirements.
• Ensuring the necessary quality, including the correctness and completeness, of pharmacovigilance data submitted to KPVC.
• Ensuring a full and prompt response to any request from KPVC to the LSR for the provision of additional information necessary for the benefit-risk evaluation of a medicinal product.
• Providing any information related to the benefit-risk evaluation to the KPVC through the LSR.
• Providing input into the preparation of regulatory action in response to emerging safety concerns (e.g. variations, urgent safety restrictions, and communication to patients and healthcare professionals).

LSR Responsibilities
• The LSR shall be responsible for the maintenance of the MAH's
• LSR resides in Kuwait while the QPPV resides where the MAH headquarter is located.
• The MAH shall ensure that all information relevant to the risk-benefit balance of a medicinal product is reported fully to KPVC and on time in accordance with the guideline
• For local MAHs, there should be a dedicated QPPV who should be resident in Kuwait.
• Information relating to the QPPV shall be included in the PSMF, while information relating to the LSR should be included in the PSSMF
• The MAH should ensure that the QPPV has access to the PSMF as well as authority over it and is notified of any changes to it.
• The MAH and the local agent should specify the submission of the PSMF to be done by the LSR.
• The QPPV and the LSR should be able to trigger an audit where appropriate.
• The managerial staff should provide the QPPV and the LSR with a copy of the corrective and preventive actions (CAPA) following each audit relevant to the PV system.

Responsibilities of the Local Agent in Relation to LSR
• The Local Agent shall have full-time qualified LSR that should communicate directly with the Qualified Person for Pharmacovigilance (LSR) residing outside Kuwait.
• The names and contact details of the nominated QPPV and the LSR should be submitted to KPVC. Changes to this information should be submitted to KPVC for approval.
• For multinational MAHs, LSR is designated by the local agent who is legally representing the MAH/applicant and may be employed for one or more MAHs, while a QPPV cannot be employed by more than one marketing authorization holder.
• Each Pharmacovigilance system can have only one QPPV, However, an LSR can be appointed to have more than one pharmacovigilance system, but he/she cannot exceed 7 Pharmacovigilance systems and another LSR must be assigned to handle more systems.
• LSR resides in Kuwait while the QPPV resides where the MAH headquarter is located.
• The MAH shall ensure that all information relevant to the risk-benefit balance of a medicinal product is reported to KPVC in Kuwait fully through the QPPV and the LSR and on time in accordance with the guideline.
• Information relating to the QPPV shall be included in the PSMF, while information relating to the LSR should be included in the PSSMF.
• The QPPV should ensure that the LSR has access to the PSMF who can review it and notify the QPPV of any changes to be made according to local requirements.
• The MAH and the local agent should specify the submission of the PSMF by the LSR through the QPPV.
• The QPPV and the LSR should be able to trigger an audit where appropriate
The managerial staff should provide the QPPV and the LSR with a copy of the corrective and preventive actions (CAPA) following each audit relevant to the PV system.

Qualifications of the QPPV
• The MAH shall ensure that the QPPV has the knowledge and experience for the performance of PV activities.
• The QPPV should:
1. Have a minimum of Bachelor degree of Pharmacy or PharmD or has a medical degree, and basic training in pharmacovigilance, pharmaco-epidemiology and biostatics (KuGVP Annex 4).

new QPPV/LSR must be submitted.
4. Degree qualifications, proof of training courses on PV and experience certificates must be included.
5. A full job description and the roles within the MAH as QPPV or local agent as LSR must be stated.
6. A copy of the official ID of the QPPV/LSR must be submitted.
7. KPVC will validate all the submitted documents.
8. Decision will be made by KPVC for QPPV/LSR approval, and a letter is issued accordingly.

MODULE SIX:
PHARMACOVIGILANCE FOCAL POINTS IN HEALTHCARE INSTITUTIONS
PHARMACOVIGILANCE FOCAL POINTS IN HEALTHCARE INSTITUTIONS

Scope and Applicability
This Chapter applies exclusively to the following healthcare institutions operating in the private of government sectors in Kuwait:
- Government hospitals and health centers
- Private hospitals
- Private medical clinics and polyclinics

This Chapter does not apply to:
- Marketing Authorization Holders (MAHs)
- Local agents
- Pharmaceutical manufacturers, distributors, or wholesalers.

Definition
The Pharmacovigilance Focal Point (PVFP) is a licensed pharmacist designated by a hospital, medical clinic, or health center to coordinate and facilitate pharmacovigilance activities at the institutional level and to act as the primary point of contact with Kuwait Pharmacovigilance Center (KPVC).

Appointment of the Pharmacovigilance Focal Point
1. Each hospital, medical clinic, or health center shall designate at least one Pharmacovigilance Focal Point.
2. The designation shall be made by the healthcare institution's management and shall be formally documented.
3. Documentation of the designation shall be made available to KPVC upon request or during pharmacovigilance inspections.

Qualifications of the Pharmacovigilance Focal Point
The healthcare institution shall ensure that the PVFP meets all of the following requirements:
○ Professional Background
The PVFP must be a licensed pharmacist, limited to one of the following categories:
- Pharmacist holding a Bachelor Degree in Pharmacy or an MPharm
- Clinical Pharmacist
- PharmD

○ Minimum Professional Experience
- Pharmacist (Bachelor Degree in Pharmacy/MPharm):

A minimum of two (2) years of professional experience in a healthcare setting.
- Clinical Pharmacist or PharmD:

A minimum of six (6) months of professional experience in a healthcare setting.

○ Pharmacovigilance Training
The PVFP shall have completed basic pharmacovigilance training, covering at minimum:
- Identification and documentation of adverse drug reactions
- National reporting requirements and timelines

pharmacovigilance system (PSMF) and where applicable the establishment and maintenance of the local pharmacovigilance system (PSSMF). He/ She should have sufficient authority to influence the performance of the quality system and the PV activities particularly at the local level and to promote, maintain and improve compliance with the legal requirements in Kuwait.
- Having an overview of medicinal product safety profiles and any emerging safety concerns.
- Having awareness of any conditions or obligations adopted as part of the marketing authorizations and other commitments relating to safety or the safe use of the products.
- Having awareness of risk minimization measures.
- Being aware of and having sufficient authority over the content of risk management plans
- Being involved in the review and sign-off of protocols of post-authorization safety studies conducted or pursuant to a risk management plan agreed in Kuwait.
- LSR shall reside in Kuwait appointed by the local agent and their roles and responsibilities along with the QPPV responsibilities shall be clearly defined in the terms of the contract which must be agreed by the local agent and the MAH.
- Having awareness of post-authorization safety studies requested by Kuwait including the results of such studies.
- Ensuring conduct of pharmacovigilance and submission of all pharmacovigilance-related documents in collaboration with the QPPV in accordance with the Kuwait legal requirements.
- Ensuring the necessary quality, including the correctness and completeness, of pharmacovigilance data submitted to KPVC.
- Ensuring a full and prompt response to any request from KPVC for the provision of additional information necessary for the benefit-risk evaluation of a medicinal product.
- Providing the KPVC with any other information relevant to the benefit-risk evaluation after it has been approved by the QPPV.
- Providing input into the preparation of regulatory action in response to emerging safety concerns particularly of those raised in Kuwait (e.g. variations, urgent safety restrictions, and communication to patients and healthcare professionals)

The QPPV or the LSR shall act as a single pharmacovigilance contact point for the national regulatory authority on a 24-hour basis and also as a contact point for pharmacovigilance inspections.

Requirements to Register a QPPV and LSR in Kuwait
- KPVC must be notified of the QPPV and the LSR appointed by the MAH and the local agent respectively.
- If a change to the QPPV or LSR occurs within the respective MAH or local agent, KPVC must be notified.
- QPPV and LSR shall registered in KPVC records and receive an authorization letter from the of Pharmaceutical Inspection and Licensing Administration after credential validation is conducted by the PV team at KPVC (see KuGVP Annex 3 for QPPV and LSR practical experience and training check list).
- A leaving QPPV/LSR will need to be removed from KPVC's record.

The new QPPV/LSR will need to request to be registered in KPVC's records as follows:
1. A cover letter from the local agent/partner of the MAH to be submitted to KPVC requesting the approval of the QPPV/LSR in Kuwait.
2. The letter should state the name and position of the current QPPV/LSR and, where possible, the previous one as necessary.
3. Credentials, qualifications and complete contact details of the

Pharmaco-epidemiology		
Biostatistics		
Signal detection		
Medical Aspects of Adverse Drug Reactions		
Risk benefit assessment in Pharmacovigilance		
National pharmacovigilance regulations		
How to prepare PSUR		
Pharmacovigilance Planning & Risk Management Plan		
How to prepare PSMF		
Risk communication, DHPC		

MODULE SEVEN:
PHARMACOVIGILANCE SYSTEM MASTER FILE (PSMF)/PHARMACOVIGILANCE SUB-SYSTEM FILE (PSSMF)
PHARMACOVIGILANCE SYSTEM MASTER FILE (PSMF)/PHARMACOVIGILANCE SUB-SYSTEM FILE (PSSMF)

Pharmacovigilance System Master File (PSMF):
- PSMF is a comprehensive document that provides a global overview of a MAH's entire PV system. It is a detailed description of the pharmacovigilance system used by the MAH with respect to one or more authorized medicinal products.
- It applies to all products for which a MAH holds marketing authorizations in Kuwait
- It is recognized that a PSMF may be a global or EU document. In the case of Kuwait whenever theres an LSR there should be a national PSSMF which needs to include information and documents describing the pharmacovigilance sub-system at the national level in Kuwait

Pharmacovigilance Sub-System Master File (PSSMF)
- PSSMF is a subset of the PSMF that focuses on specific PV activities in Kuwait.
- PSSMF is typically implemented to support compliance with local PV guidelines or specific ministerial laws and regulations in Kuwait.
- PSSMF helps MAH to maintain detailed operational control over their local PV system in Kuwait
- The MAH shall maintain a local PV file, that captures the following:

○ Local PV processes (e.g. AE reporting channels, local SOPs).
○ Roles and responsibilities of any Kuwait-based PV personnel or local safety contact.
○ Interaction with global PSMF, ensuring consistency while highlighting country-specific differences.
- Input from MAH:

○ MAHs shall provide the relevant data for any local file:
○ Local SOPs for AE reporting and follow-up, and risk management.
○ Training records for Kuwait-based staff (if applicable).
○ Risk management measures implemented specifically in Kuwait.
○ Any contractual agreements with local partners that define the local PV obligations.
- Content of the PSSMF:

○ Local AE reporting requirements and timelines.
○ Local PV structure, including key personnel and responsibilities.
- Use of national pharmacovigilance reporting tools

The Pharmacovigilance Focal Point role shall be restricted to pharmacists only and shall not be assigned to physicians, nurses, or other healthcare professionals.

Responsibilities of the Pharmacovigilance Focal Point
The PVFP shall be responsible for the following:
1. Acting as the single institutional pharmacovigilance contact point with KPVC.
2. Promoting pharmacovigilance awareness and reporting culture among healthcare professionals within the institution.
3. Coordinating the collection, validation, and timely submission of Individual Case Safety Reports (ICSRs) to KPVC.
4. Ensuring that serious, unexpected, and fatal adverse events are reported immediately in accordance with KPVC requirements.
5. Supporting the use of national pharmacovigilance reporting systems, including electronic reporting tools.
6. Disseminating Dear Healthcare Professional Communications (DHPCs) and safety alerts issued by KPVC within the institution.
7. Maintaining internal documentation, records, and traceability of reported cases.
8. Supporting pharmacovigilance inspections, audits, and data verification activities conducted by KPVC.

Regulatory Clarifications
1. The PVFP does not replace the MAH's Qualified Person for Pharmacovigilance (QPPV) or Local Safety Responsible Person (LSR).
2. The PVFP does not hold regulatory responsibility for pharmacovigilance obligations assigned to MAHs.
3. The PVFP role is institutional and operational and is limited to healthcare service providers.

Inspection and Compliance Considerations
During pharmacovigilance inspections, KPVC may verify:
- Formal designation of the PVFP
- Compliance with qualification and experience requirements
- Evidence of pharmacovigilance training
- Timeliness and quality of submitted ICSRs
- Internal documentation and record availability
- Dissemination of safety communications

Failure to designate or maintain an effective Pharmacovigilance Focal Point may be considered a deficiency in institutional pharmacovigilance practices.

Annex Reference
This Chapter shall be read in conjunction with KuGVP Annex 3 and Annex 4, including the QPPV / LSR / PVFP Practical Experience and Training Checklist.

Annex 4: QPPV/ LSR/PVFP practical experience/ training checklist

Topic	Practical experience	Training
Pharmacovigilance methods		
MedDRA coding		
ICSRs processing activities		
Evidence based –medicine, How to conduct literature search		
Causality assessment		
Case Narrative Writing for Reporting Adverse Events		
Pharmacovigilance quality management		

for assessment and feedback during marketing authorization application(s) or post-authorization.

• Through the production and maintenance of the PSMF and PSSMF, the MAH should be able to:

1. Gain assurance that a PV system is implemented in accordance with the requirements.

2. Obtain information about system deficiencies, or non-compliance with the requirements.

3. Obtain information about risks or actual failure in the conduct of aspects of GPV.

4. Confirm aspects of compliance in relation to the system.

Location

• The PSMF and PSSMF shall be located either at the site where the main PV activities are performed or at the site where the QPPV and the LSR operate, irrespective of the format (paper-based or electronic format file).

• Where the PSMF is held in electronic form, the location stated must be a site where the stored data can be directly and easily accessed.

• An exception is applied in situations where the main activities take place outside Kuwait (e.g. multinational MAHs/applicants), the location should default to the site where the QPPV operates or where the main pharmacovigilance activities are performed (e.g. located in the country of headquarter) provided that:

- The PSMF is made available to KPVC at any time; and
- The local office/affiliate/agent of the MAH/MAA has a detailed description of the pharmacovigilance system/activities on the local level.

• Details about the location of the PSMF should be notified to KPVC, and any change to the location shall be notified immediately to them.

Submission of PSMF/PSSMF

• The full PSMF (along with its summary) and the national PSSMF (along with its summary) are requested to be submitted to KPVC in the following situations:

1. The applicant has not previously held a marketing authorization in Kuwait.
2. The applicant has not previously submitted the PSMF or PSSMF in Kuwait or is in the process of establishing a new PV system.
3. The applicant had major changes in its organisation, such as merges and acquisitions or in its PV system.
4. The applicant has major or critical findings in the previous PV system assessment (global and/or local) by KPVC.
5. The applicant has a history or culture of PV noncompliance; previous information (e.g., inspection history and non-compliance notifications or information from other authorities).

N.B. In addition to the submission of the full PSMF and national PSSMF, if the MAH has a history of serious and/or persistent PV non-compliance, a pre-authorization PV inspection may be one mechanism to confirm that improvements have been made to the system before a new authorization is granted.

6. Where specific concerns about the PV system (global and/or local) and/or the product safety profile exist.

7. Any other situation deemed appropriate by KPVC.

• Only a summary of the MAH's PV system is required to be included in the MAA.

• Changes to the PSMF or PSSMF should be recorded, such that a history of changes is available (specifying the date and the nature of the change), descriptive changes to the PSMF or PSSMF must be recorded in a logbook.

- How data is integrated into the global PV system.
- Record retention policies to ensure compliance.

Table (2): Key Differences Between PSMF and PSSMF

Feature	PSMF	PSSMF
Scope	Global PV System	Specific subsystem in Kuwait
Regulatory Requirements	Required for NDAs and product registration renewal	Not explicitly required but used for operational management. Submitted upon request.
Content	Covers all PV activities, including governance, quality, and risk management	Focuses on specific areas (e.g. signal detection, risk management, local PV)
Applicability	All products- Global document	Specific products and PV processes and activities for Kuwait.

PSMF Requirements:

• MAHs must maintain a PSMF detailing their global PV system.

• The PSMF should be available upon request by KPVC and must be kept up-to-date.

PSSMF Requirements:

• The PSSMF must be submitted as part of the marketing authorisation application (MAA) and shall be available for PV inspections.

Key Considerations:

• Local Safety Responsible Person (LSR): A Kuwait based PV responsible person, registered with KPVC, is required to oversee PV activities.

• Documentation: The PSSMF should detail local PV procedures, including AE reporting systems, risk management plans, and training programs.

Scope of Information:

• Focus on local PV system Details: The file should reflect the Kuwait-Specific PV structure – reporting timelines, local contact details, and how local data feed into the global safety database.

• A summary PSSMF should be sufficient, but full PSSMF is recommended for compliance.

• A summary of PSSMF shall be submitted upon for renewal of product marketing approval.

• The MAH shall maintain a full PSSMF for inspections.

The PSMF General Consideration

• PSMF and PSSMF are the regulatory requirements in Kuwait to be submitted for New Drug Applications (NDAs) and for renewal of product marketing approval as and when required.

• MAHs shall maintain and make available upon request PSMF and PSSMF to strengthen the conduct of pharmacovigilance activities in Kuwait.

• KPVC should manage a national list/database which provides a practical mechanism for maintaining up-to-date information about:

1. MAH's (or contractual partner) PSMF, and PSSMF at the national level whenever there is LSR.
2. Its status
3. Its location,
4. The QPPVand/or LSR contact information and
5. The products relevant to the pharmacovigilance system described in the PSMF.

Objectives

• The PSMF and PSSMF provide an overview of the pharmacovigilance system, which may be submitted to KPVC

recommended.

• Documents such as copies of signed statements or agreements should be included as annexes and described in the index.

• The documents and particulars of the PSMF shall be presented with the following headings and, if hardcopy, in the order outlined:

Qualified person responsible for pharmacovigilance (QPPV)

• Description of the responsibilities guaranteeing that the qualified person has sufficient authority over the PV system in order to promote, maintain and improve compliance.

• A summary curriculum vitae with the key information on the role of the QPPV.

• Contact details.

• Details of back-up arrangements to apply in the absence of the QPPV; and

• Checklist on the required practical experience/training upon request by KPVC.

N.B: Taking into consideration that PV practice and regulations are relatively new in Kuwait, thus having an experienced QPPV or LSR may be challenging. Accordingly, it is accepted by KPVC that for only a transitional period, the QPPV or LSR qualifications may be expressed in terms of his/her PV training rather than his/her practical experience in PV.

Organisational structure of the marketing authorisation holder

• The organizational structure of the MAH(s), showing the position of the QPPV in the organization.

• The site(s) where the PV functions are undertaken covering individual case safety report collection, evaluation, safety database case entry, periodic benefit risk evaluation report (PBRER) production, signal detection and analysis, risk management plan, pre- and post-authorization study management, and management of safety variations.

• Diagrams may be particularly useful; the name of the department or third party should be indicated.

• Delegated activities

Sources of Safety Data

• The description of the main units for safety data collection should include all parties responsible, on a global basis, for solicited and spontaneous case collection for products authorized in Kuwait.

• Flow diagrams indicating the main stages, timeframes and parties involved may be used.

• The description of the process for ICSRs from collection to reporting to KPVC should indicate the departments and/or third parties involved.

• For the purposes of inspection and audit of the PV system, sources include data arising from study sources, including any studies, registries, surveillance or support programmes sponsored by the MAH through which ICSRs could be reported.

• MAHs should be able to produce and make available a list of such sources to support inspection, audit and QPPV oversight.

• In the interests of harmonization, it is recommended that the list should be comprehensive for products authorized in Kuwait, irrespective of indication, product presentation or route of administration.

• The list should describe, on a global basis, the status of each study/programme, the applicable country(ies), the product(s) and the main objective. It should distinguish between interventional and non-interventional studies and should be organized per active substance.

• The list should be comprehensive for all studies/programmes

• There is no requirement for variations for changes in the content of the PSMF or PSSMF.

• The PSMF and PSSMF will be kept up to date by the MAH, without the need for submitting variation applications. Only a notification letter and the updates should be submitted to KPVC.

• It is anticipated that there will be circumstances where a single MAH may establish more than one PV system e.g., specific systems for particular types of products (vaccines, consumer health, etc.), or that the PV system may include products from more than one MAH. In either case, a single and specific PSMF shall be in place to describe each system.

• A QPPV shall be appointed to be responsible for the establishment and maintenance of the PV system described in the PSMF. On the other hand, theLSR is responsible for the establishment and maintenance of the PV system described in the PSSMF.

• The PSMF and PSSMF shall be maintained and be permanently available to the QPPV and LSR respectively. It shall also be permanently available for inspection at the site where it is kept (the stated location), irrespective of whether the inspection has been notified in advance or is unannounced.

• The MAH shall maintain and make available upon request a copy of the PSMF and PSSMF.

• The MAH must submit the copy within 14 days after receipt of the request from KPVC (unless otherwise stated in the request)

Special considerations for the multinational MAHs

• The content of the PSMF should reflect the global availability of safety information for medicinal products authorized for the MAH, with information on the PV system to the local or regional activities.

• PV activities on the national level as described in the PSSMF may not be applied to the same extent by all the MAH's national offices/ affiliates; furthermore, some additional national requirements and details may also apply.

• Accordingly, multinational MAHs/Applicants should provide clear illustration of the key elements of both global PV system and local PV sub-system, highlighting the role of QPPV and LSR respectively, the PV activities are carried out in Kuwait, the activities carried out in the headquarter or globally, and how they integrate together.

• For the multinational MAH/Applicant the following two documents are required for submission:

1. The PSMF (according to European Good PV Practice) and/or
2. Local PSSMF, which describes the key elements of PV activities in Kuwait.

The information to be contained in the PSMF

• The PSMF content and format shall be according to the latest version of Arab GVP.

• The PSMF may be in electronic form and a printed copy may be made available to KPVC upon request.

• PSMF should be legible, complete, ensures accessibility of all documents and allows full traceability of changes.

• It may be appropriate to restrict access to the PSMF in order to ensure appropriate control over the content and to assign specific responsibilities for the management of PSMF in terms of change control and archiving.

• The PSMF should be written in English, indexed in a manner consistent with the headings described in this Module, and allow easy navigation to the contents.

• Embedded documents are discouraged.

• The use of electronic book-marking and searchable text is

risks of medicinal products;
- The submission of accurate and verifiable data on serious and non-serious adverse reactions within the time limits provided in the local guidelines;
- The quality, integrity and completeness of the information submitted on the risks of medicinal products, including processes to avoid duplicate submissions and to validate signals;
- Effective communication by the MAH to the regulatory authority (RA) , including communication on new risks or changed risks, the PSMF, risk management systems, risk minimization measures, periodic safety update reports, corrective and preventive actions, and post-authorization studies;
- The update of product information by the MAH in the light of scientific knowledge, and on the basis of a continuous monitoring by the MAH of information released by the national regulatory authorities;
- Appropriate communication by the MAH of relevant safety information to healthcare professionals and patients.

• These interfaces with other functions include (but are not limited to) the roles and responsibilities of the QPPV, responding to requests made by the KPVC for information, literature search, safety database change control, safety data exchange agreements, safety data archiving, PV auditing, quality control and training.

• The list, which may be located in the Annexes, should comprise in cross matching with each one of the topics highlighted above in this section the topic name, procedural document reference number, title, effective date and document type (for all standard operating procedures, work instructions, manuals etc.). Procedures belonging to service providers and other third parties should be clearly identified. Documents relating to specific local/country procedures need not be listed, but a list may be requested on a per country basis. If no or only some countries use specific local procedures, this should be indicated (and the names of the applicable countries provided).

PSMF section on pharmacovigilance system performance

• The PSMF should contain evidence of the ongoing monitoring of performance of the PV system including compliance of the main outputs of PV. The PSMF should include a description of the monitoring methods applied and contain as a minimum:
- An explanation of how the current reporting of ICSRs is assessed. In the annex, figures/graphs should be provided to show the timeliness of 15-day and 90-day reporting over the past year;
- A description of any metrics used to monitor the quality of submissions and performance of pharmacovigilance. This should include information provided by KPVC regarding the quality of ICSR reporting, PSURs/PBRER or other submissions;
- An overview of the timeliness of PSUR/PBRER reporting to KPVC (the annex should reflect the latest figures used by the MAH to assess compliance); An overview of the methods used to ensure timeliness of safety variation submissions compared to KPVC deadlines, including the tracking of required safety variations that have been identified but not yet been submitted;
- Where applicable, an overview of adherence to risk management plan commitments, or other obligations or conditions of marketing authorization(s) relevant to PV

PSMF section on quality system

• A description of the quality management system (QMS) should be provided, in terms of the structure of the organization and the application of the quality to PV. This shall include:

A. Document and Record Control

and should include ongoing studies/programmes as well as studies/programmes completed in the last two years and may be located in an Annex or provided separately.

Computerised Systems and Databases

• The location, functionality and operational responsibility for computerized systems and databases used to receive, collate, record and report safety information and an assessment of their fitness for purpose shall be described in the PSMF.

• Where multiple computerized systems/databases are used, the applicability of these to PV activities should be described in such a way that a clear overview of the extent of computerization within the PV system can be understood.

• The validation status of key aspects of computer system functionality should also be described; the change control, nature of testing, back-up procedures and electronic data repositories vital to PV compliance should be included in summary, and the nature of the documentation available should be described.

• For paper-based systems (where an electronic system may only be used for expedited submission of ICSRs), the management of the data, and mechanisms used to assure the integrity and accessibility of the safety data, and in particular the collation of information about adverse events, should be described.

PSMF section on pharmacovigilance processes

• A description of the procedural documentation available (Standard operating procedures, manuals, at a global and/or National level etc.), the nature of the data held (e g., the type of case data retained for ICSRs) and an indication of how records are held (e g , safety database, paper file at site of receipt) should be provided in the PSMF.

• A description of data handling and records for the performance of PV, covering the following aspects shall be included (but not limited to):
- Continuous monitoring of product risk–benefit profile(s), result of evaluation, decision making process for taking appropriate measures; signal generation, its detection and evaluation. This may also include several written procedures and instructions concerning safety database outputs, interactions with clinical departments etc.;
- Risk management system(s) and monitoring of the outcome of risk minimization measures; several departments may be involved in this area, and interactions should be defined in written procedures or agreements;
- ICSR collection, collation, follow-up, assessment and reporting; the procedures applied to this area should clarify what are local and what are global activities;
- PBRER scheduling, production and submission, if applicable.
- Communication of safety concerns to consumers, healthcare professionals and medicines authorities.
- Implementation of safety variations to the summary of product characteristics (SPC) and patient information leaflets (PIL); procedures should cover both internal and external communications.

• The MAH should be able to provide evidence of a system that supports appropriate and timely decision making and action.

• The description must be accompanied by the list of the following processes for compliance management, as well as interfaces with other functions:
- The continuous monitoring of PV data, the examination of options for risk minimization and prevention and appropriate measures are taken by the MAH;
- The scientific evaluation by the MAH of all information on the

verified. The addition, amendment or removal of the notes must therefore be recorded in the logbook.

○ As a means of managing the PV, and providing a basis for audit or inspection, the PSMF should also describe the process for recording, managing and resolving deviations from the quality system. The master file shall also document deviations from PV procedures, their impact and management until resolved. This may be documented in the form of a list referencing a deviation report, and its date and procedure concerned.

Annex to the PSMF

• An annex to the PV system master file shall contain the following documents:

○ A list of medicinal products covered by the PSMF including the name of the medicinal product, the name of the active substance(s) and the Arab Country(ies) in which the authorization is valid.

○ (The list should be organized per active substance and, where applicable, should indicate what type of product specific safety monitoring requirements exist (for example risk minimization measures contained in the risk management plan or laid down as conditions of the marketing authorization (MA), non-standard PSUR/PBRER periodicity). The monitoring information may be provided as a secondary list. For marketing authorizations (MAs) that are included in a different PV system, for example, because the MAH has more than one PV system or third-party agreements exist to delegate the system, reference to the additional PSMF(s) should also be provided as a separate list in the Annexes, such that, for a MAH, the entire product portfolio can be related to the set of PV system master files.)

○ Where PV systems are shared, all products that utilize the PV system should be included, so that the entire list of products covered by the file is available. (The list of products may be presented separately, organized per MAH. Alternatively, a single list may be used, which is supplemented with the name of the MAH(s) for each product, or a separate note can be included to describe the product(s) and the MAH(s) covered.)

○ A list of contractual agreements covering delegated activities, including the medicinal products.

○ A list of tasks that have been delegated by the qualified person for pharmacovigilance.

○ A list of all completed audits, for a period of five years, and a list of audit schedules.

○ Where applicable, a list of performance indicators.

○ Where applicable, a list of other PV system master files held by the same MAH. This list should include the PSMF number(s), and the name of MAH of the QPPV responsible for the PV system used. If another party that is not the MAH manages the PV system, the name of the service provider should also be included. The MAH shall record in the logbook any alteration of the content of the PV system master file made within the last five years. Also, the MAH shall indicate in the logbook the date, the person responsible for the alteration and, where appropriate, the reason for the alteration, and other change control documentation as appropriate. Documented changes shall include at least the date, person responsible for the change and the nature of the change.

Format and layout of PSMF

Cover Page

• Name of the MAH, the MAH of the QPPV responsible for the PV system described (if different), as well as the relevant QPPV third party company name (if applicable).

○ A description of the archiving arrangements for electronic and/or hardcopy versions of the PSMF should be provided, as well as an overview of the procedures applied to other quality system and PV records and documents.

B. Procedural documents

○ A general description of the types of documents used in PV (standard operating procedures, work instructions etc.), and the controls that are applied to their accessibility, implementation and maintenance.

○ Information about the documentation system applied to relevant procedural documents under the control of third parties.

○ A list of specific procedures and processes related to the PV activities and interfaces with other functions, with details of how the procedures can be accessed must be provided.

○ Training

○ A description of the resource management for the performance of PV activities (an organizational chart showing the number of people involved in PV activities should be provided. These data may be given in the section describing the organizational structure)

○ Information about sites where the personnel are located whereby the sites are provided in the PSMF in relation to the organization of specific PV activities and in the Annexes which provide the list of site contacts for sources of safety data.

○ A description should be provided in order to explain the training organization in relation to the personnel and site information

○ A summary description of the staff-training concept, including a reference to the location training files.

○ Staff should be appropriately trained for performing PV related activities and this includes not only staff within PV departments but also any individual that may receive ICSR.

○ Auditing

○ Information about quality assurance auditing of the PV system should be included.

○ A description of the approach used to plan audits of the PV system and the reporting mechanism and timelines should be provided, with a current list of the scheduled and completed audits concerning the PV system maintained in the annex.

○ This list should describe the date(s) of audit conduct and of report, scope and completion status of audits of service providers, specific PV activities or sites undertaking PV and their operational interfaces relevant to the fulfillment of the obligations and cover a rolling 5-year period.

○ The PSMF shall also contain a note associated with any audit where significant findings are raised. This means that the presence of findings that fulfill Kuwait's criteria for major or critical findings must be indicated.

○ The audit report must be documented within the quality system; in the PSMF it is sufficient to provide a brief description of the corrective and/or preventative action(s) associated with the significant finding, the date it was identified and the anticipated resolution date(s), with cross reference to the audit report and the documented corrective and preventative action plan(s).

○ In the annex, in the list of audits conducted, those associated with unresolved issues in the PSMF should be identified.

○ The note and associated corrective and preventative action(s), shall be documented in the PSMF until the corrective and/or preventative action(s) have been fully implemented, that is, the note is only removed once corrective action and/or sufficient improvement can be demonstrated or has been independently

N.B: Taking into consideration that PV practice and regulations are relatively new in Kuwait, thus having an experienced LSR may be challenging. Accordingly, it is accepted by KPVC that for only a transitional period the LSR qualifications may be expressed in terms of his/her PV training rather than his/her practical experience in PV.

Local PSSMF section on Organisational structure of the MAH's local office:

- A description of the organizational structure of the MAH's local office relevant to the local PV sub-system must be provided.
- The description should provide a clear overview of the company(ies) involved, the main PV department and the relationship(s) between organizations and operational units relevant to the fulfillment of PV obligations. This should include third parties.
- The local PSSMF shall describe:

○ The organizational structure of the MAH's local office, showing the position of the QPPV in the organization.

○ The PV structure at the local agent and the position of the LSR within the structure as well as his/her method of contact and relationship with the MAH's QPPV

○ The site(s) where the pharmacovigilance functions on the national level are undertaken covering individual case safety report collection, evaluation, safety database case entry, periodic safety update report production (integration with global system), signal detection and analysis (integration with global system), risk management plan management, pre- and post-authorization study management, and management of safety.

- Diagrams may be particularly useful; the name of the department or third party should be indicated.
- Delegated activities:

○ The local PSSMF, where applicable, shall contain a description of the delegated activities and/or services relating to the fulfillment of PV obligations.

○ Links with other organizations, such as co-marketing agreements and contracting of PV activities on the national level should be outlined.

○ A description of the location, nature of contracts and agreements relating to the fulfillment of PV obligations should be provided.

○ This may be in the form of a list able to show the parties involved, the roles undertaken, the concerned product(s) and territories.

○ The list should be organized according to service providers (e.g., medical information, auditors, patient support programme providers, study data management etc.), commercial arrangements (distributors, licensing partners, co-marketing etc.) and other technical providers (hosting of computer systems etc.).

○ Individual contractual agreements should be annexed to the local PSSMF and shall be available upon request at any time or during inspection and audit.

Local PSSMF section on Sources of Safety Data

- A description supported by flow diagrams shall be used to indicate the main stages of safety data collection for solicited and spontaneous case collection for products authorized in Kuwait, timeframes and parties involved.
- The description of the process for ICSRs from collection to reporting to the national regulatory authority should indicate the departments and/or third parties involved.
- For the purposes of inspection and audit of the PV system,
- The name of other concerned MAH(s) (sharing the P.V system)
- List of PSMFs for the MAH (concerning products with a different P.V system)
- Date of preparation /last update.

PSMF section of QPPV responsible for pharmacovigilance:

The information relating to the QPPV provided in the PSMF shall include:

- The list of tasks that have been delegated by the QPPV, or the applicable procedural document (to be included in the annexes)
- The curriculum vitae of the QPPV and associated documents
- Contact details
- Details of back-up arrangements to apply in the absence of the QPPV

PSMF section of The Organisational Structure of the MAH:

- The lists of contracts and agreements

PSMF section of Sources of safety data:

- Lists associated with the description of sources of safety data e.g. affiliates and third party contacts

PSMF section of computerised systems and Databases:

- Lists of procedural documents

PSMF section of Pharmacovigilance System Performance:

- Lists of performance indicators
- Current results of performance assessment in relation to the indicators

PSMF section of Quality System:

- Audit schedules
- List of audits conducted and completed

PSMF section of Products:

- List(s) of products covered by the P.V system
- Any notes concerning the MAH per product

PSMF section of Document and Record Control:

- Logbook

The information to be contained in the Local PSSMF

- The PSSMF contents and format shall be according to the current version of Arab GVP.
- Local PSSMF shall include information and documents to describe the PV sub-system at the local level.
- The content of the local PSSMF shall be indexed to allow for efficient navigation around the document and follow the modular system described in the following sections and the annex.
- The local PSSMF shall be maintained in its current state and be permanently available to the LSR.
- The information provided in the local PSSMF shall focus on the local PV sub-system.

Local PSSMF section on Local Safety Responsible Person (LSR):

- Contact details shall be provided in the marketing authorization application.
- The information relating to the LSR provided in the national PSSMF shall include:

A. Job description of the LSR, guaranteeing that the LSR has sufficient authority over the pharmacovigilance activity on the national level in order to promote, maintain and improve compliance with national regulations.

B. Summary curriculum vitae with the key information on the role of the LSR.

C. Contact details.

D. Details of back-up arrangements to apply in the absence of the LSR.

E. Checklist on the required practical experience andtraining requested by KPVC.

○ The scientific evaluation by the MAH of all information on the risks of medicinal products.

○ The submission of accurate and verifiable data on serious and non-serious adverse reactions to KPVC within the timelines provided in the local guidelines;

○ The quality, integrity and completeness of the information submitted on the risks of medicinal products, including processes to avoid duplicate submissions and to validate signals;

○ Effective communication by the MAH with KPVC, including communication on new risks or changed risks, the PSMF and local PSSMF, risk management systems, risk minimization measures, PBRERs, corrective and preventive actions, and post-authorization studies;

○ The update of product information by the MAH in the light of scientific knowledge, and on the basis of a continuous monitoring by the MAH of information released by KPVC;

○ Appropriate communication by the MAH of relevant safety information to healthcare professionals and patients.

- These interfaces with other functions include, but are not limited to, the roles and responsibilities of the LSR, responding to KPVC requests for information, literature searching, safety database change control, safety data exchange agreements, safety data archiving, pharmacovigilance auditing, quality control and training.
- The list, which may be located in the Annexes, should comprise of a cross-reference, matching with each one of the topics mentioned above, including the topic name, the procedural document reference number, title, effective date and document type (for all SOPs, instructions, manuals etc.).
- Procedures belonging to service providers and other third parties should be clearly identified.
- Any specific local (in Kuwait) procedures should also be indicated.
- National PSSMF section on Pharmacovigilance Sub-System Performance:
- Local PSSMF should contain evidence of the ongoing monitoring of performance of the local PV sub-system including compliance with the main outputs of PV, such as:

○ An explanation of how the correct reporting of domestic ICSRs is assessed. In the annex, figures/graphs should be provided to show the timeliness of 15-day and 90-day reporting to KPVC over the past year.

○ A description of any metrics used to monitor the quality of submissions and performance of PV. This should include information provided by KPVC regarding the quality of ICSR reporting, PSURs/PBRERs or other submissions.

○ An overview of the timeliness of PSUR/PBRER reporting to KPVC (the annex should reflect the latest figures used by the MAH to assess compliance on the local level).

○ An overview of the methods used to ensure timeliness of safety variation submissions compared to internal and locally applied deadlines, including the tracking of required safety variations that have been identified but not yet been submitted.

○ Where applicable, an overview of adherence to National Display of RMP commitments, or other obligations or conditions of marketing authorization(s) relevant to PV.

- Targets for the performance of the PV sub-system shall be described and explained.
- A list of performance indicators must be provided in the Annex to the national PSSMF, alongside the results of (actual) performance measurements.

safety data sources include data arising from study sources, including any studies, registries, surveillance or support programmes sponsored by the MAH through which ICSRs could be reported.

- MAHs should be able to produce and make available a list of such sources to support inspection, audit and headquarter QPPV and QPPV oversights.
- It is recommended that the list should be comprehensive for products authorized in Kuwait, irrespective of indication, product presentation or route of administration.
- The list should describe, on the local basis, the status of each study/programme, the product(s) and the main objective.
- It should distinguish between interventional and non-interventional studies and should be organized per active substance.
- The list should be comprehensive for all studies/programmes and should include ongoing studies/programmes as well as studies/programmes completed in the last two years and may be located in an Annex or provided separately.

National PSSMF section on computerised systems and databases

- QPPV and LSR must have online access to local safety cases and all local PV data in Kuwait; or at least backup database of the local data should always be kept in the local office.
- The location, functionality and operational responsibility for computerized systems and databases used (on the local level) to receive, collate, record and report safety information and an assessment of their fitness for purpose shall be described in the local PSSMF.
- Where multiple computerized systems/databases are used on local level, the applicability of these to PV activities should be described in such a way that a clear overview of the extent of computerization within the PV system can be understood.
- The validation status of key aspects of computer system functionality should also be described; the change control, nature of testing, back-up procedures and electronic data repositories vital to PV compliance should be included in summary, and the nature of the documentation available should be described.
- For non-electronic systems (where an electronic system may only be used for expedited submission of ICSRs), the management of the data, the mechanisms used to assure the integrity and accessibility of the safety data, and in particular the collation of information about adverse drug reactions, should be described.

Local PSSMF section on Pharmacovigilance Processes:

- A description of the procedural documentation available on local level (standard operating procedures SOPs , manuals, etc.), the nature of the data held (e.g., the type of case data retained for ICSRs) and an indication of how records are held (e.g., safety database, paper file at site of receipt) should be provided in the local PSSMF.
- A description of the process, data handling and records for the performance of PV (on the local level and as appropriate in integration with MAH's headquarter).
- The description must be accompanied by the list of the following processes for compliance management, as well as interfaces with other functions (on the local level and as appropriate in integration with MAH's headquarter):

○ The continuous monitoring of PV data, the examination of options for risk minimization and prevention and appropriate measures are taken by the MAH.

associated with the significant finding, the date it was identified and the anticipated resolution date(s), with cross reference to the audit report and the documented corrective and preventative action plan(s).

➢ In the annex, in the list of audits conducted for the national pharmacovigilance subsystem, those associated with unresolved notes in national PSSF, should be identified.

➢ The note and associated corrective and preventative action(s), shall be documented in the national PSSMF until the corrective and/or preventative action(s) have been fully implemented, that is, the note is only removed once corrective action and/or sufficient improvement can be demonstrated or has been independently verified.

➢ The addition, amendment or removal of the notes must therefore be recorded in the logbook.

➢ As a means of managing the national pharmacovigilance sub-system, and providing a basis for audit or inspection, the national PSSMF should also describe the process for recording, managing and resolving deviations from the quality system.

➢ The national PSSMF shall also document deviations from pharmacovigilance procedures at the national level, their impact and management until resolved. This may be documented in the form of a list referencing a deviation report, its date and the procedure concerned.

Annex to the national PSSMF

➢ An annex shall contain the following documents: A list of medicinal products covered by this national PSSMF in Kuwait; the following should be provided for each medicinal product in the list:

- The name of the medicinal product.
- The name of the active substance(s).
- The authorization number in Kuwait.
- The presence on the market in the Kuwait (i.e., marketing status)
- Other country (ies) in which this product is authorized.
- The presence on the market in these other country (ies) (i.e., marketing status)

• The list should be organized per active substance and, where applicable, should indicate what type of product-specific safety monitoring requirements exist (e.g., risk minimization measures contained in the RMP). The monitoring information may be provided as a secondary list.

➢ For marketing authorizations that are included in a different pharmacovigilance system, for example, because the MAH has more than one pharmacovigilance system on the national level or third-party agreements exist to delegate the system, reference to the additional national PSSMF(s) should also be provided as a separate list in the Annexes, such that, for a MAH, the entire product portfolio can be related to the set of national PSSMF.

➢ Where national pharmacovigilance sub-systems are shared, all products that utilize the national pharmacovigilance sub-system should be included, so that the entire list of products covered by the file is available. The products lists may be presented separately, organized per MAH. Alternatively, a single list may be used, which is supplemented with the name of the MAH(s) for each product, or a separate note can be included to describe the product(s) and the MAH(s) covered.

- A list of written policies and procedures for compliance management.
- A list of contractual agreements covering delegated activities in the Kuwait including the medicinal products (a copy of the

Local PSSMF section on quality system

• description of the QMS should be provided, in terms of the structure of the organization and the application of the quality to PV.

• This shall include:

A. Document and Record Control

➢ Provide a description of the archiving arrangements (at the local level) for electronic and/or hardcopy versions of the different types of records and documents for PV and the quality system

B. Procedural documents

➢ A general description of the types of documents used in pharmacovigilance (SOPs, work instructions, manuals etc.), the applicability of the various documents at the local level within the organization, and the controls that are applied to their accessibility, implementation and maintenance.

➢ Information about the documentation systems applied to relevant procedural documents under the control of third parties.

➢ Provide a list of specific procedures and processes related to the PV activities (at the local level) and interfaces with other functions, with details of how the procedures can be accessed must be provided.

C. Training

➢ Staff should be appropriately trained for performing PV related activities and this includes not only staff within PV departments but also any individual that may receive safety reports such as sales personnel or clinical research staff. Provide a description of the resource management for the performance of PV activities on the local level.

➢ The organizational chart showing the number of people (full time equivalents) involved in pharmacovigilance activities (This may be provided in the section describing the organizational structure).

➢ Information about sites where the personnel are located, whereby the sites are provided in the national PSSMF in relation to the organization of specific pharmacovigilance activities

➢ A summary description of the training concept, including a reference to the location of training files, records, as well as the trainings materials.

D. Auditing

➢ Information about quality assurance auditing of the national pharmacovigilance subsystem should be included in the national PSSMF.

➢ A description of the approach used to plan audits of the national pharmacovigilance sub-system , the reporting mechanism and timelines should be provided, with a current list of the scheduled and completed audits concerning the national pharmacovigilance sub-system. This list should describe the date(s) (of conduct and of report), scope and completion status of audits of service providers, specific pharmacovigilance activities or sites undertaking pharmacovigilance and their operational interfaces relevant to the fulfillment of the pharmacovigilance obligations and cover a rolling 3-year period.

➢ The national PSSMF shall also contain a note associated with any audit where significant findings are raised. This means that the presence of findings that fulfill the national criteria for major or critical findings must be indicated.

➢ The audit report must be documented within the quality system; in the national PSSMF it is sufficient to provide a brief description of the corrective and/or preventative action(s)

renamed to Annex D in circumstances where no Annex concerning computerized systems and databases is used. Annex D should simply be described as "unused" in the indexing, in order that recipients of the PV system master file are aware that missing content is intended.

Cover Page to include

• The unique number assigned by KPVC to the local PSSMF (if applicable).

• Name of the MAH, the MAH of the LSR responsible for the PV sub-system described (if different), as well as the relevant LSR third party company name (if applicable).

• The name of other concerned MAH(s) (sharing the local PV sub-system) (if applicable).

• List of local PSSMFs for the MAH (concerning products with a different PV sub-system) (if applicable).

• Date of preparation / last update

The LSR for national pharmacovigilance sub-system, Annex A

• The list of tasks that have been delegated to the LSR, or the applicable procedural document.

• The curriculum vitae of the LSR and associated documents

• Contact details

The Organisational Structure of the MAH, Annex B

• The lists of contracts and agreements.

• A copy of the individual contractual agreements relevant to Kuwait.

Sources of safety data, Annex C

• A list of sources used for obtaining the safety data related to the medicine

Computerised systems and Databases, Annex D

• A list of programs, computerised systems and databases used

Pharmacovigilance Process, and written procedures, Annex E:

• Lists of procedural documents, policies, manuals and SOPs

Pharmacovigilance Sub-System Performance, Annex F:

• Lists of performance indicators.

• Current results of performance assessment in relation to the indicators.

Quality System, Annex G

• Audit schedules (for national pharmacovigilance sub-system)

• List of audits conducted and completed (for national pharmacovigilance sub-system) Products, Annex H

• List(s) of products covered by the national pharmacovigilance sub-system described in this national PSSF.

• Any notes concerning the MAH per product.

Document and Record Control, Annex I

• Logbook

• Documentation of history of changes for Annex contents, indexed according to the Annexes A–H and their content if not provided within the relevant annex itself.

MODULE EIGHT:

PHARMACOVIGILANCE AUDIT AND INSPECTION

PHARMACOVIGILANCE AUDIT AND INSPECTION

Marketing Authorization Holders (MAHs) are required to fulfill the local pharmacovigilance (PV) requirements applicable in the State of Kuwait. To support regulatory oversight and facilitate compliance, the Pharmacovigilance Team at the Kuwait Pharmacovigilance Center (KPVC) may conduct pharmacovigilance audits and inspections of MAHs, as well as any local, regional, or international entities engaged by the MAH to perform pharmacovigilance activities on its behalf. Pharmacovigilance audits and inspections are complementary regulatory tools serving distinct purposes.

individual contractual agreements shall be included).

- A list of tasks that have been delegated by the QPPV to the LSR.
- A list of all completed audits on the national level, for a period of five years, and a list of audit schedules on the national level.
- Where applicable, a list of performance indicators.
- Where applicable, a list of other national PSSMF(s) held by the same marketing authorization holder. This list should include the national PSSMF number(s), the name of MAH and the name of the QPPV responsible for the pharmacovigilance sub-system used. If another party that is not a MAH manages the pharmacovigilance system, the name of the service provider should also be included.
- A logbook of any change to the content of the national PSSMF made within the last five years, except for the changes in annexes and the following QPPV or LSR information: CV, contact details, back-up arrangements and contact person for pharmacovigilance on the national level. In addition, other change control documentation should be included as appropriate. Documented changes shall include at least the date, person responsible for the change and the nature of the change.

Local PSSMF Presentation

• The National PSSMF shall be continuously accessible to the QPPV and LSR and to KPVC at any time on request.

• The information shall be succinct, accurate and reflect the current system in place, which means that whatever format is used, it must be possible to keep the information up to date and, when necessary, to revise it to take account of experience gained, technical and scientific progress and amendments to the legislative requirements.

• Although provision of the document within 7 days of request by KPVC is required, MAH should be aware that immediate access to the National PSSMF may also be required by the department.

Format and layout of Local PSSMF:

• The national PSSMF may be in electronic form, on condition that a clearly arranged printed copy can be made available to KPVC if requested.

• In any format, national PSSMF should be legible, correct, provided in a manner that ensures all documentation is accessible and allow full traceability of changes.

• It may be appropriate to restrict access to the national PSSMF in order to ensure appropriate control over the content and to assign specific responsibilities for the management of the PSSMF in terms of change control and archiving.

• The National PSSMF should be written in English, indexed in a manner consistent with the headings described in the current version of Arab GVP, and allow easy navigation to the contents.

• Embedded documents are discouraged.

• The use of electronic bookmarking and searchable text is recommended.

• Documents such as copies of signed statements or agreements should be included as appendices and described in the index.

• The documents and particulars of the local PSSMF shall be presented with the following headings, in the order outlined below:

- Documentation to support notifications and signatures concerning the local PSSMF, as required.
- Where there is no content for an Annex, there is no need to provide blank content pages with headings.
- The Annexes that are provided should still be named according to the format described. For example, Annex E should NOT be

inspection (routine/targeted) and on the requirements of the inspection request.

Preparing a PV inspection should involve the collaboration of the PV team at KPVC with the Pharmaceutical Inspection and Licensing Administration (PHILA) delegated to conduct the PV inspection process. The preparation may also involve the reviewers of a particular product or other specialists/experts as necessary, e.g., IT specialists, depending on the scope of the inspection. An inspection plan should be prepared in line with the scope and objectives of the inspection process and should cover all the relevant aspects of the inspection procedure. MAHs may distribute PV and safety evaluation tasks to more than one country. It is important to ascertain (from the DDP or by obtaining additional information, organizational charts, contracts/agreements and SOPs) how PV responsibilities are divided within the company and with marketing partners/contractors. It is also important to ascertain where the required information resides when planning the PV inspection in order to obtain a complete picture of the PV activities of the MAH and their locally registered agents.

Access to the global PV database, and provision of MAH resources to conduct searches on the database, should be arranged with the MAH prior to the inspection. The DDP provided at the point of registering a new local agent and their MAH will provide the inspector(s) with information relating to the MAH. However, prior to the inspection, it should be confirmed that there have been no significant changes in the system that will have an impact on inspection planning.

The data and documentation review that should be performed as part of the PV inspection (general sampling or with respect to a particular product or therapeutic area), shall be determined prior to the inspection and should address the scope and objectives of the inspection. Additional data and documentation for review may also be identified during the inspection. An adequate sample of data and documentation to undergo review shall be determined and may be requested for review by the inspector(s), as part of the preparation. The basis for selecting the sample size may depend on the following factors:

- The organization of the MAH and the distribution of the PV and safety evaluation tasks,
- The number of products registered and marketed,
- The types of products and therapeutic areas,
- The specific questions raised by the Pharmacovigilance Team which need to be addressed during the inspection,
- The clinical studies and post-authorization safety studies conducted by the MAH, The different possible origins of the reports (i.e., local, other GCC, non-GCC, licensed agent/distributor, spontaneous reports, clinical studies),
- Issues of non-compliance identified during previous inspections.

The sample should give a good representation of the conduct of PV at the marketing authorization site or the local agent/distributor's site. The data and documentation request should be performed in a timely manner in order to allow inspectees to provide all the requested documents for review by the inspection team prior to the inspection.

Regulatory Clarification

Where the term inspection is used in procedural, enforcement, or compliance-related contexts within this document, it refers exclusively to pharmacovigilance inspection activities conducted under regulatory authority and does not apply to Pharmacovigilance audits are conducted to assess the competency, efficiency, and quality of the pharmacovigilance system and its ability to function effectively and sustainably.

Pharmacovigilance inspections are conducted to assess compliance with pharmacovigilance laws, regulations, and obligations, and to prevent violations or misconduct.

The focus of pharmacovigilance audits and inspections includes assessment of the MAH's pharmacovigilance system for the management of safety data and the conduct of pharmacovigilance activities for selected centrally or locally authorized medicinal products within the GCC region, as part of the overall safety assessment performed by KPVC.

This assessment may include, but is not limited to:

- Spontaneously reported adverse drug reactions
- Adverse drug events arising from clinical studies subject to expedited reporting
- Periodic Safety Update Reports (PSURs) and Periodic Benefit–Risk Evaluation Reports (PBRERs)

In addition, the MAH's ability to identify, evaluate, and report all relevant safety information arising from clinical studies and post-authorization safety studies for medicinal products authorized in Kuwait may be subject to pharmacovigilance audit or inspection, as appropriate.

Pharmacovigilance audits and inspections may be conducted at a single site or at multiple sites, depending on the nature, scope, and objectives of the activity. Sites may be determined based on whether the activity is conducted as an audit or as an inspection, and on the regulatory purpose for which it is initiated.

Activities may be conducted on a routine basis or may be targeted in response to specific concerns.

During routine activities, audits or inspections may verify that the Detailed Description of Pharmacovigilance (DDP) submitted to KPVC accurately reflects the pharmacovigilance system in place. Targeted activities may focus on specific systems, processes, or products, depending on regulatory need.

Any party carrying out pharmacovigilance activities in whole or in part, on behalf of, or in conjunction with, the MAH may also be subject to pharmacovigilance audit or inspection, in order to confirm their capability to support the MAH's compliance with pharmacovigilance obligations.

Responsibilities

Kuwait PV Inspectors are required to fulfill the following credentials

1. Should hold a Pharmacy degree
2. Should have at least 6 months of experience in PV practices
3. Should receive the required PV inspection training by the PV Teams in KPVC

Description of Procedures,Requirements and Responsibilities

The objectives of a pharmacovigilance audit or inspection may vary depending on the regulatory context under which the activity is initiated.

- Pharmacovigilance audits are conducted to assess system quality, competency, efficiency, and overall performance.
- Pharmacovigilance inspections are conducted to verify compliance with pharmacovigilance legislation and regulatory obligations, and to prevent violations or misconduct.

The decision to conduct a pharmacovigilance audit or inspection is determined by KPVC based on regulatory priorities, risk considerations, or specific triggers.

Preparation for Pharmacovigilance Audit and inspection

The scope of the inspection will depend on the nature of the

Product-related inspections

Product-related PV inspections primarily focus on product-related PV issues, including product-specific activities and documentation, rather than reviewing the system overall. They are likely to be 'for cause' inspections to investigate a specific product issue. Some aspects of the wider system may be examined during a product-related inspection (that is, the system used for that product).

Announced and unannounced inspections

The PV team in Kuwait anticipates that the majority of inspections will be announced—that is, they will notify the inspectee's of them in advance to ensure the relevant personnel will be available for the inspection.

However, it may sometimes be appropriate to conduct unannounced inspections or to perform an inspection at short notice (for example, when an announcement could compromise the objectives of the inspection or when prompt inspection is required due to urgent public health concerns).

Re-inspections

The PV team in Kuwait re-inspects the inspectee's PV system as part of the routine inspection program.

Re-inspections are prioritized by assessing risk factors. If a previous inspection identified a high level of compliance, the time between re-inspections may increase.

More frequent re-inspections may occur:

- Where significant noncompliance has been identified
- To verify action(s) taken to address previous inspection findings
- To evaluate ongoing compliance with obligations
- To assess changes to the inspectee's PV system
- To ensure proper corrective and preventive actions (CAPA system) are in place to address previous inspection failures.

Remote inspections

These are PV inspections of the inspectee's premises (or the premises of a firm they have contracted to help fulfill their PV activities) performed by the inspection team remotely using communication technology such as the internet or video/tele-conferencing.

For example, where key sites for PV activities are located outside Kuwait or a third-party service provider is not available at the inspection site, it may be feasible to interview relevant staff and review documentation via remote access. If the remote inspection reveals issues that require on-site inspection, or the inspection objectives could not be met remotely, an inspection visit may be performed onsite.

Risk-Based prioritization of Pharmacovigilance Inspections

Inspectors take a risk-based approach to scheduling PV inspections and prioritize routine inspections based on the risk assigned to the inspectee's PV system. Systems with lower risk products or good compliance history are less likely to be inspected regularly. However, random inspections as well as "for cause" inspections may also occur.

The elements considered when assigning risks to the inspectee and consequently determining whether and when to inspect them include, but are not limited to:

Product-related factors such as:

- Uncertainty about a medicine's risk profile (including new classes of medicines and newly registered medicines)
- Whether the product has additional PV or risk-minimization activities
- Whether the medicine had specific condition(s) of registration applied due to safety concerns

pharmacovigilance audits, which are non-enforcement, quality-focused activities.

Inspection notification

The inspection team has the right to perform a PV inspection at any time. In exceptional circumstances, inspectors can perform an inspection without notice. However, the inspectee would normally receive an advance notice from the KPVC stating their intention to conduct a pharmacovigilance inspection by selected members of the inspection team comprising of a inspection pharmacist, a regulatory reviewer, and a quality control laboratory Pharmacist, and a pharmacist from the PV team. The notice period served should be sufficient for the inspectee to make logistic arrangements, and ensure key personnel are available and have access to relevant data. As a guide, the inspectors consider six to eight weeks' notice sufficient for a routine inspection.

Notice of the inspection could include, for example, the inspector's name(s), the inspection's objectives and nature, the inspection date and, if known, the address (es) to be inspected. Inspectors will also request information about the inspectee's PV system to aid in planning for the inspection. The inspectors will notify the inspectee's of the PV inspection in writing, unless an unannounced inspection is required. The inspection notification shall be issued to the email address of the inspectee's local safety responsible (LSR) person. A confirmation of the inspectee's availability shall be received from the LSR's email address. The inspectee shall be requested to ensure the cooperation of all parties and to confirm in writing that they agree to the inspection of all relevant sites and will make all required documents and databases directly accessible to the inspectors.

The LSR should inform the QPPV of the notification. Inspectors may also request supporting data demonstrating how the inspectee's PV system operates, for example the global PV System Master File (where available), a description of the local PV system or further information on specific issues of interest.

Types of Pharmacovigilance Inspection

Routine Inspections

Routine PV inspections are scheduled as part of the inspection program. There is no specific trigger for these inspections, although we take a risk-based approach to prioritizing them.

These inspections are usually system-related inspections, but one or more products may be selected as examples to verify the implementation of the system and provide practical evidence of its functioning and compliance.

'For cause' inspections

'For cause' inspections are undertaken in response to specific triggers where a PV inspection is the appropriate way to examine the issues.

'For cause' inspections generally focus on specific aspects of the PV system or examine identified compliance issues and their impact on a specific product.

However, the entire PV system may be inspected as a result of a trigger. Significant public health concerns or identified noncompliance are expected to be the most common triggers.

System-related inspections

PV system-related inspections review the procedures, systems, personnel and facilities in place and determine whether the system meets the regulatory PV obligations.

As part of this review, product-specific examples may be used to determine how the PV system operates and whether it complies with requirements.

described in the PV Inspection Plan should be re-confirmed and inspection logistics should be discussed. The lead inspector should re-confirm that the resources, documents and facilities required by the inspector(s) are available. Confirm the time and date for the closing meeting and any interim meetings.

✓ Appropriate site personnel should provide background information about the MAH and/or supporting contractor(s). This would normally include an overview of the organization and links with other commercial organizations relevant to PV/drug safety, the systems used for the collection, collation, and evaluation and reporting of adverse drug reactions, a summary of significant changes since the previous inspection (where applicable) and a summary of significant changes that are planned for the future.

Collecting information and recording observations

The inspection activities should be detailed in the PV Inspection Plan. Nevertheless, during the inspection, the inspector(s) may amend the plan to ensure that the inspection objectives are achieved.

Sufficient information to fulfill the inspection objective(s) should be collected through examination of relevant documents and computer systems, as well as through the conduct of interviews. If access to records or copying of documents is refused for any reason or there is any withholding of documents or denial of access to areas to which the inspector has a legal right of access, these refusals should be documented and included in the inspection observations.

The following items should be reviewed as part of the PV inspection:

Legal and administrative aspects

• Documentation of the responsible parties for PV/drug safety activities

• Identifying the QPPV at the MAH's site and the LSR appointed locally

• Availability of information on all suspected AEs at least at a single point within the community

• Contractual documentation with respect to any PV/drug safety responsibilities being outsourced by the MAH

• Documentation regarding the delegation of responsibilities for PV/drug safety with respect to co-marketing agreements

• Commitments for AE reporting to KPVC and GCC in relation to Centrally Registered Products

• Special requirements for reporting of AEs to KPVC or for monitoring safety i.e., post-authorization commitments and follow-up measures for centrally registered products; compliance with Risk Management Plans (RMPs), where applicable

• Preparation and submission of Periodic Safety Update Reports – PSURs- (including discussion relating to off-label use/ SPCs (including revisions)

• Documentation of responsibilities in relation to PV/drug safety of products undergoing clinical studies

• Collection and reporting of SAEs in clinical studies

• Collection and reporting of spontaneous AEs

• Provision to the competent authorities with any other information relevant to the evaluation of the risks and benefits of a medicinal product, particularly information concerning post-authorization safety studies

Organisational structure

(i) Quality system and for PV activities

The pharmacovigilance audit and inspection process shall include review of documented SOPs and instructions covering all aspects of PV/drug safety, in order to assess system quality and regulatory compliance, as applicable.

These SOPs and instructions should include, but are not limited to, the following activities:

• Collection and management of PV data (from healthcare professionals, medical information departments, quality complaint departments, regulatory affairs departments, legal departments, manufacturing sites, sub-contractors, co-marketing organizations, etc.), and when applicable, of serious adverse events (SAEs) in clinical or post-authorization safety studies.

• Causality assessment

• Determination of seriousness and whether AE reports are expeditable

• Coding

• Avoidance of duplicate reporting

• Ensuring reporting compliance

• Identifying and tracking initial and follow-up reports

• Ensuring an adequate and complete follow-up

• Handling of reports to and from other organizations (e.g. licensing partners)

• Handling of reports relating to comparator, product or placebo in clinical studies or post-authorization safety studies

• Ensuring completeness of the information contained in database(s)

• Review, validation and follow-up of suspected AEs

• Data Management (accurate storage and retrieval of information, tracking of reports and ensuring timeliness, compliance with local requirements of confidentiality)

• Expedited reporting to the national competent authority (for national and GCC centralized procedures)

• Monitoring of worldwide scientific literature

• Collation and submission of Periodic Safety Update Reports

• Management of requests for information

• Management of urgent safety restrictions and type II variations

• Updating of core safety information, if available

• Signal detection/trend analysis activities

• Management of communications with the national competent authority

• Production of Risk Management Plans, when applicable

• Organizational charts to identify the key personnel

• Control of SOPs and other procedural documentation including writing, review, approval, updating, distribution and implementation, as part of the pharmacovigilance quality system subject to audit and inspection.

• Review of Quality Control processes and documentation

• Review of corrective and preventive action (CAPA) processes and documentation, including actions arising from internal audits and inspection findings.

• Internal auditing of the PV system, including verification of whether audits are conducted and how audit findings are documented, communicated, and addressed as part of the quality management system.

(ii) Qualified Person (QPPV)

• Documentation identifying the QPPV along with qualifications and training

• Documentation of QPPV and contact details in the PV system

• Verification that the QPPV has adequate (direct, timely) access to all relevant PV/drug safety information

• Verification that the same QPPV has been notified to all

• If a large number of patients are exposed to the medicine

• Product(s) with limited alternatives in the marketplace

• Products with known or emerging important safety concerns

• The type of medicine —complementary, over the counter or prescription medicines.

Sponsor-related factors such as:

• Evidence of failure to comply with other local regulatory requirements such as good manufacturing practice (GMP), RMP activities or the submission of PBRER.

• Data analysis that indicates failure to comply with legislative PV requirements, such as:

○ Evidence of failure to submit adverse drug reaction reports within required timeframes, or

○ Erroneous adverse drug reaction reports, or information from prior inspections in Kuwait or overseas

• Volume of supply of products to the Kuwaiti market

• Changes to, or suspected lack of, resources for PV activities

• Any organizational changes such as mergers and acquisitions.

Pharmacovigilance system-related factors such as:

• Whether PV activities have been subcontracted, or multiple firms have been employed to undertake PV activities

• Change of QPPV or LSR

• Changes to the PV safety database(s). These could include changes to the database or associated databases; the database's validation status and the transfer or migration of data

• Changes to the contractual arrangements with PV service providers or to the sites where PV is conducted.

Inspection-related factors such as:

• The inspectee's compliance history, including previous PV or other inspection findings

• Any previous PV inspections that the inspectee was subjected to

• Whether previous inspector(s) recommended re-inspection(s)

• How long it has been since the last PV inspection

Sites to be inspected

The type and number of sites to be inspected are specified to ensure that the inspection process meets the objectives. Inspections may be carried out to local, regional or international sites as necessary. Inspectors will liaise with the relevant regulators in preparation of any inspection, as appropriate.

Any party or organization contracted to carry out some or all PV activities in conjunction with, or on behalf of, the inspectee may be inspected to confirm they are capable of supporting the inspectee's compliance with local PV obligations. Such inspections will generally be arranged through the inspectee as part of an overall PV inspection.

Conduct of a Pharmacovigilance Inspection

Opening Meeting

Before the start of the inspection, an opening meeting must take place between the inspector(s) and the inspectee(s), for the purpose of introduction and to discuss the arrangements for the inspection.

In particular, the following points should be covered where relevant:

✓ The lead inspector should describe the purpose and the scope of the inspection,

✓ The lead inspector should outline the inspection references (e.g., regulations and guidelines that provide the basis for the inspection), and summarize the methods and procedures to be used to conduct the inspection.

✓ The activities and personnel to be interviewed that are

relevant competent authorities

• Verification that the QPPV has sufficient authority within the company to make amendments to the PV system in order to ensure compliance

• Documentation for delegation of tasks

• Verification of the back-up process when the QPPV is absent

(iii) Resources and training of Personnel

• Interview of personnel involved in any PV activity, including technical representatives, regulatory affairs, legal, clinical trial and product quality personnel if appropriate

• Documentation of job descriptions, qualifications and training of individuals involved in any stage of the PV and safety evaluation process, which may be assessed during pharmacovigilance audits and verified during inspections.

• Documentation on policies and procedures for training of personnel

• Allocation of deputies to key personnel

Facilities and computer systems

• Computer systems in use (administration, use and hardware/software specifications and validation).

• Migration of data and legacy system, where relevant

• System for the archiving and retrieval of documents

• Archiving and filing facilities

• Controlled access to the archives

Collecting and verifying information

Pharmacovigilance inspections examine compliance with the relevant Kuwaiti legislation and guidelines. The scope of inspections includes, but is not limited to, the following elements as appropriate to the system being reviewed:

A. Adverse reaction reports

• Collection and collation of reports from all sources and sites, including but not limited to cases reported via medical information enquiries, international literature, social media and the internet, market research programs, patient support programs, patient registries, post-registration studies etc.

• Assessment (validation, seriousness, expectedness and causality), coding and processing

• Follow-up and outcome recording

• Reporting within the specified timeframes to KPVC where required

• Record keeping and archiving

B. Periodic safety update reports (PSURs)

• Completeness and accuracy of the data included,

• Appropriateness of decisions concerning data that are not included

• Addressing safety topics, providing relevant analyses and actions

• Formatting according to requirements

• Timeliness of submissions.

C. Ongoing safety evaluation

• Use of relevant information sources for signal detection (including relevant global data)

• Appropriately applied analytical methodology

• Appropriateness of investigations and follow-up actions such as the implementation of recommendations following data review, including updating reference safety information

• Notification to the Pharmacovigilance team, in the KPVC, about significant safety issues identified internationally within the specified timeframes

• Implementation and ongoing review of the Risk Management Plan (RMP) and other safety commitments

serious spontaneously reported AEs) been discussed or included in the line listings of the PSUR/PBRER covering the relevant time period?
• Have qualifying serious reports from clinical or post-authorization safety studies been reported in an expedited manner and included in PSURs?
• Have specific requests from the NCAs been appropriately addressed?
• Can serious AEs be identified in the listings of non-serious AEs?
• Have literature searches been conducted and reviewed appropriately?
• Can specific literature cases be retrieved from the database?
• Have new safety issues arising from post-authorization safety studies, conducted worldwide, been reported promptly to competent authorities if appropriate?
• Adequacy of quality control process and follow-up measures taken (corrective action process)
• Has the correct format been used when reporting to the competent authorities?

G. Recording inspection observations

All inspection observations should be documented. If appropriate, copies should be made of records containing inconsistencies or illustrating non-compliance.

At the end of the inspection, the inspector(s) should review all observations to determine which are to be reported as not being compliant with Kuwaiti legislations and/or guidelines and/or as PV system deficiencies. The inspector(s) should then ensure that these documented observations are organized in a clear, concise manner and are supported by objective evidence. All reported observations (findings) should be identified with reference to specific requirements of the regulations or other related documents against which the inspection has been conducted. The names and titles of persons interviewed or present during the inspection meetings and the details of the inspected organization should be documented.

If required by local regulations, the inspection observations may be collected in a minute (or similar), to be written by the inspector(s) at the end of the inspection (see Ref. VII, annex 4 for the PV inspection template and report writing).

• Closing Meeting with the inspectee(s)

At the end of the inspection, the inspector(s) should conduct a closing meeting with the inspectee. The QPPV, his deputy, LSR or other responsible persons for PV activities should attend the meeting. The purpose of the closing meeting is:

• To summarize inspection findings and observations to ensure that the results of the inspection are clearly understood and that there is no misunderstanding by either the inspector(s) or the inspectee(s).
• To provide the inspected party with an opportunity to correct any misconceptions made by the inspector(s) or to supply additional information in response to the findings. However, all efforts should be made during the inspection in order to minimize the misconceptions and discuss them during the closing meeting.
• To clarify the procedures for the distribution of the inspection report, for the production of responses to the inspection report and for inspection follow-up (as appropriate)
• To request copies of any documents that may be required by the inspector, e.g., to assist with the preparation for other activities associated with the inspection.
• An inspection may consist of visits to more than one location.
• Timely identification and provision of complete and accurate data, in particular in response to specific requests for data from the Pharmacovigilance team at the KPVC
• Implementation of new/updated reference safety information, including internal distribution and external publication
• Examination of processes, decision-making, communications and actions relating to a specific trigger and/or product

D. Pharmacovigilance systems

• The integration of PV activities within the inspectee's quality management system and proof of adherence to it, including quality control and quality assurance processes
• Up-to-date and comprehensive policies and procedures in place regarding roles and responsibilities in relation to the inspectee's PV system, with appropriate document control
• Accuracy, completeness, and maintenance of records as indicators of pharmacovigilance system performance and sustainability, which may be assessed through audit and inspection activities.
• Quality and adequacy of training, qualifications and experience of the PV staff
• The fitness for purpose of computerized systems
• Contracts and agreements with all relevant parties which reflect the inspectee's PV responsibilities and activities to which they are adhered
• Defined roles and responsibilities for the PV personnel including the QPPV, including access to the quality system, performance metrics, audit and inspection reports, availability and their ability to take action to improve compliance.
• The QPPV's involvement and awareness of product-specific issues.

E. Previous pharmacovigilance inspection findings

• Review of the status of the system and/or CAPA plan(s) resulting from previous PV inspections(s)
• Review of any significant changes to the PV system since the last PV inspection (such as a change in the PV database, company mergers or acquisitions, significant changes in contracted activities or change of the QPPV)
• Review of process and/or product-specific issues from the assessment of information provided or not covered in a prior inspection.

F. Data/documentation review

The following are examples of testing that may be performed. However, this is not an exhaustive list and the strategies used will depend on the objectives of the inspection:

• Confirmation that potential AEs from any source, e.g., product complaints, product information enquiries, technical representatives, post-authorization studies, etc., have been processed appropriately. This may include a review of compliance reports
• Determination of seriousness
• Causality assessment
• Consistency and correctness of coding with terminologies used and internal procedures
• Quality of the information included in case summaries
• Adequacy of follow-up measures taken
• Adequacy of follow-up information collection and reporting
• Any specific questions raised in the inspection request
• Submission of expedited and PSURs/PBRERs to the authorities. Have all relevant reports been submitted within the correct timeframes?
• Have all relevant cases (all serious AEs and all applicable non-

have not been observed or resolved in clinical studies;
• AEs observed in clinical trials or epidemiological studies for which the magnitude of the difference, compared with the comparator group (placebo or active substance, or unexposed group), on a parameter of interest raises a suspicion of an association, but is not large enough to suggest a causal relationship.
• A signal arising from a spontaneous adverse reaction reporting system.
• An event known to be associated with other active substances within the same class or which could be expected to occur based on the properties of the medicinal product.

Missing information:

Gaps in knowledge about a medicinal product, related to safety or use in particular patient populations, which could be clinically significant (e.g., pregnant women or patients with severe renal impairment) or where there is a high likelihood of off-label use.

Important identified risk and important potential risk:

An identified risk or potential risk that could have an impact on the risk-benefit balance of the product or have implications for public health.

• What constitutes an important risk will depend upon several factors, including:

1. The impact on the individual
2. The seriousness of the risk
3. The impact on public health.

• Normally, any risk that is likely to be included in the contraindications or warnings and precautions section of the product information should be considered important.

Target population (treatment):

The patients who might be treated with the medicinal product in accordance with the indication(s) and contraindications in the authorized product information.

Pharmaceutical Product Recall:

Medicine recalls are conducted for critically defective medicines and medicines that pose health risks to patients.

Recalls occur either voluntarily by manufacturers or mandated by the Ministerial Regulations which apply the necessary recall actions according to the seriousness and severity of the safety issue and the appropriate risk measures suggested by the KPVC after conducting thorough investigations about the relevant case (s).

Classification of Recalls:

• Class I Recalls: refer to medicinal products that lead to the most severe adverse effects and indicate that exposure and/or consumption of the product will lead to serious adverse health effects or death.
• Class II Recalls: refer to medicinal products that induce temporary and/or medically reversible health effects.
• Class III Recalls: Occur when adverse effects are not likely to occur when consuming the medicinal product or being exposed to it.

Responsibilities for risk management for both MAHs and KPVC:

• Applicants/MAHs and KPVC are directly involved in the medicinal products' RMP.

Marketing Authorisation Holders/Applicant's Responsibilities:

• Ensuring that it constantly monitors the risks of its medicinal products in compliance with relevant legislation and reports the results of this, as required, to KPVC;

If appropriate, a closing meeting may be held at each location inspected.

Preparation of inspection report:

The Lead Inspector, in agreement with the inspection team, shall prepare an inspection report.

MODULE NINE:

RISK MANAGEMENT SYSTEMS / RISK MANAGEMENT PLANS (RMP)

RISK MANAGEMENT SYSTEMS / RISK MANAGEMENT PLANS (RMP)

The Risk management system is a set of PV activities and interventions designed to identify, characterize, prevent or minimize risks related to medicinal products including the assessment of the effectiveness of those activities and interventions.

The Risk Management Plan (RMP) is a detailed description of the risk management system, which are applied to medicinal products at any point in their lifecycle.

RMP guidelines are based on The Arab Guidelines for Good Pharmacovigilance Practice which are adopted from the European Good Pharmacovigilance Practice Guidelines.

Risk management system has three stages, which are inter-related and reiterative:

• Characterization of the safety profile of the medicinal product, including what is known and not known.
• Planning of PV activities to characterize risks and identify new risks and increase the knowledge in general about the safety profile of the medicinal product.
• Planning and implementation of risk minimization and assessment of the effectiveness of these activities.
• RMPs can be applied to Medical Devices (MDs), biotechnology products, and health products (HPs) as applicable Terminology

Risk Minimisation Activity:

An intervention intended to prevent or reduce the probability of the occurrence of an adverse reaction associated with the exposure to a medicine or to reduce the severity of its occurance.

Safety Concern:

An important identified risk, important potential risk or missing information.

Identified Risk:

An untoward occurrence for which there is adequate evidence of an association with the medicinal product of interest. Examples include:

• An adverse reaction adequately demonstrated in non-clinical studies and confirmed by clinical data;
• An adverse reaction observed in well-designed clinical trials or epidemiological studies for which the magnitude of the difference compared with the comparator group, on a parameter of interest suggests a causal relationship;
• An adverse reaction is suggested by a number of well-documented spontaneous reports where causality is strongly supported by temporal relationship and biological plausibility, such as anaphylactic reactions or application site reactions.

In a clinical trial, the comparator may be a placebo, active substance or non-exposure.

Potential risk:

An untoward occurrence for which there is some basis for suspicion of an association with the medicinal product of interest but where this association has not been confirmed. Examples include:

• Toxicological findings seen in non-clinical safety studies which

Kuwait.
- Module SVII Identified and potential risks
- Module SVIII Summary of the safety concerns
• Part III: Pharmacovigilance plan
• Part IV: Plans for post-authorization efficacy studies.
• Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization measures)
• Part VI: Summary of the risk management plan
• Part VII: Annexes
Legal basis for the implementation of risk management within Kuwait:
• The RMP is a dynamic, standalone document which should be updated throughout the life-cycle of the products (during both the pre- and post-authorization phases)
• Producing a RMP requires the input of different specialists and departments within and/or outside an organization such as toxicologists, clinical pharmacists, clinical research physicians, pharmaco-epidemiologists and PV experts.
• Since a risk management plan is primarily a PV document, ideally personnel should manage the production of it with appropriate PV training in either the PV or regulatory departments, depending upon company structure.
• Regardless of who prepares the RMP, the responsibility for the content and accuracy of the RMP remains with the MAA/MAH who should ensure oversight by someone with the appropriate scientific background within the company.
• For an individual MAH and MAA, all products containing the same active substance should be included in one RMP unless separate presentations are requested by the KPVC or agreed by the same at the request of the MAH/MAA.
• Where a RMP concerns more than one medicinal product, a separate RMP part VI (Plans for post-authorization efficacy studies) must be provided for each medicinal product.
• Information should be provided in enough detail to enable an assessor to understand the issues being presented
Situations when a RMP should be submitted:
- For new medicinal product applications with an ongoing RMP
at least, or at the request of KPVC, a RMP shall be submitted, together with a summary, thereof.
• Situations, in addition, where a RMP or RMP update will normally be expected include:
1. An application involving a significant change to an existing marketing authorization
• New dosage form
• New route of administration
• New manufacturing process of biotechnologically derived product
• Pediatric indication
• Other significant change in the indication
2. At the request of KPVC when there is a concern about a risk affecting the risk-benefit balance;
3. With a submission of final study results impacting the RMP;
4. With a PBRER for medicinal product, when the changes to the RMP are a direct result of data presented in the PBRER.
5. At the time of the renewal of the MA if the product has an existing RMP.
• If an RMP has previously been submitted by the MAA/MAH for the active substance, any following submissions shall be in the form of an update unless requested
• An updated RMP should always be submitted if there is a significant change to the benefit-risk balance of one or more

• Taking all appropriate actions to minimize the risks of the medicinal product and maximize the benefits including ensuring the accuracy of all information produced by the company in relation to its medicinal products, and actively updating and promptly communicating it when new information becomes available.
Responsibilities of KPVC:
• Constantly monitoring the benefits and risks of medicinal products including assessing the reports submitted by pharmaceutical companies, healthcare professionals, patients and, where appropriate, other sources of information;
• Taking appropriate regulatory actions to minimize the risks of the medicinal product and maximize the benefits including ensuring the accuracy and completeness of all information produced by the company in relation to its medicinal products;
• Ensuring the implementation of risk minimization activities.
• Effectively communicating with stakeholders when new information becomes available. (Providing information in an appropriate format to patients, healthcare physicians, patient groups, learned societies etc.)
• When necessary, ensuring that the MAH of generic and/or similar biological medicinal products make similar changes to their risk minimization measures when changes are made to those of the reference medicinal product;
• Providing information to other regulatory authorities, this includes notification of any safety activities in relation to a product, including changes to the product information of originator and/or reference medicinal products.
Objectives of a risk management plan and RMP:
The RMP must contain the following elements which:
• Identify or characterize the safety profile of the medicinal product(s) concerned.
• Indicate how to characterize further the safety profile of the medicinal product(s) concerned.
• Document measures to prevent or minimize the risks associated with the medicinal product including an assessment of the effectiveness of those interventions.
• Document post-authorization obligations that have been imposed as a condition of the marketing authorization.
There is an implicit requirement that to fulfill these obligations a RMP should also:
• Describe what is known and not known about the safety profile of the concerned medicinal product(s);
• Indicate the level of certainty that efficacy shown in clinical trial populations will be seen when the medicine is used in the wider target populations seen in everyday medical practice and document the need for studies on efficacy in the post-authorization phase (also known as effectiveness studies);
• Include a description of how the effectiveness of risk minimization measures will be assessed.
Structure of the Risk Management Plan:
The RMP consists of seven part (see KuGVP Annex 5)
• Part I: Product(s) overview
• Part II: Safety Specification
- Module SI Epidemiology of the indication(s) and target population(s)
- Module SII Non-clinical part of the safety specification
- Module SIII Clinical trial exposure
- Module SIV Populations not studied in clinical trials
- Module SV Post-authorization experience
- Module SVI Additional requirements for safety specification in

consecutive and without added text. The numbering is independent of whether the RMP was endorsed by the KPVC or not. The new version of the RMP should be dated.
Formats for RMPs:
This guidance provides three formats for RMPs:
1. Integrated RMP: with all modules in one document (e.g., for innovators not having EU RMP, biosimilars…, etc.)
2. Abridged format: suitable for use for generic medicines;
3. National Display of RMP format: suitable for any MAH/MAA having EU RMP in place (whether innovators, generics or importers), submitted altogether with most updated version of EU RMP.
Requirements in specific situations:
• Normally all parts of a RMP should be submitted but in certain circumstances certain parts or modules may be omitted unless otherwise requested by KPVC.
• Any safety concerns identified in a reference medicinal product in a module which is omitted from the RMP of a generic product should be included in RMP module SVIII unless clearly no longer relevant.
• The naming and numbering of the RMP parts, modules and sections are standardized thus should NOT be changed or renumbered due to the omission of un-required sections.
New application of generic medicinal product (abridged RMP):
• RMP modules SI to SVII may be omitted.
• RMP module SVIII should be based on the safety concerns of the reference medicinal product unless the generic product differs significantly in properties which could relate to safety, or unless requested otherwise by KPVC.
• Provided the reference medicinal product does not have any additional PV activities or efficacy studies imposed as a condition of the MA, RMP parts III (PV Plan) and IV (Plan for post-authorization efficacy studies) may be omitted.
• Part VI should be based on an appropriately modified version of the summary of the reference medicinal product.
• For updates to the RMP, RMP module SV (post-authorization experience) should be included.
National Display of the RMP – for MAH/Applicants having EU RMP in place:
• The purpose of the "National Display of the RMP" is:
○ To highlight to what extent the risk management activities proposed to be implemented nationally adhere to the globally implemented plan and;
○ To provide justification for any difference (apart from what is implemented in EU) whenever exist including the needed national tailoring if any.
○ In addition, it should include an assessment whether there are any additional national/ region-specific risks or not, describing the possibly added activities to manage those additional risks.
○ It provides good evidence that the LSR has clear understanding and commitment about the activities that will be implemented on the national level and how they will be implemented.
• Because of differences in indication and healthcare systems, target populations may be different across the world and risk minimization activities will need to be tailored to the system in place in Kuwait or global region.
• In addition, differences in disease prevalence and severity, for example, may mean that the benefits of a medicinal product may also vary between regions.
• Therefore, a product may need different activities or medicinal products included in the RMP.
• Each submission of the RMP shall have a distinct version number and shall be dated.
• When technically feasible, clean and track change versions should be submitted along with a cover letter detailing the changes since the last submitted version.
• There are no scheduled "routine" updates to the RMP.
• In exceptional cases, when justified by risk, KPVC may still specify a date for submission of the next RMP as a condition of the MA, this condition is communicated with the Medicines and Medical Product Registration and Regulatory Administration, which the responsible for generating MA Approvals.
• It is the responsibility of the MAH to monitor the safety profile of the product(s) and to update and submit the RMP if there is a significant change to the risk-benefit balance of one or more medicinal products included in the RMP.
• A significant change would, in particular, usually include extension of indications, clinically important changes to the product information, reaching an important PV milestone and also certain new strengths and formulations.
• An updated RMP should be submitted:
○ At the request of KPVC.
○ Whenever the risk-management system is modified, especially as the result of new information being received that may lead to a significant change to the risk-benefit balance or as a result of an important PV or risk-minimization milestone being reached.
• When preparing a PBRER, there is a need for consequential changes to the RMP as a result of new safety concerns, or other data, then an updated RMP should be submitted at the same time.
• In this case no standalone RMP variation is necessary. Should only the timing for submission of both documents coincide, but the changes are not related to each other, the RMP submission should be handled as a standalone variation.
• When the RMP is updated, the risk minimization plan should include an evaluation of the impact of routine and/or additional risk minimization activities as applicable.
• For MAH/MAA submitting EU RMP and its National Display, when the referenced EU RMP is subject to update the National Display of RMP should be updated in accordance.
Updates to the RMP submitted during a procedure:
• A medicinal product can only have one —current version of RMP.
• If several updates to the RMP are submitted during the course of a procedure, the version considered as the (current RMP) shall be the last one submitted before the Opinion (e.g. changed indications, changes in SmPC wording which affect risk minimization)
• Following the finalization of the procedure, the final version of the RMP should be provided in the CTD/eCTD file.
• The RMP should reflect the outcome of the procedure – i.e. removal of all references and data which were subject to a negative opinion, the exception to this requirement is that populations studied in clinical trials related to a negative opinion may be included in suitably annotated exposure data in RMP module SIII.
• Unless requested otherwise, for RMPs updated during (after the start) of a procedure, track changes should show changes since the start of the procedure whilst the cover letter should show changes since the last version was submitted.
• For versioning of the RMP the numbering should be

Some sections may not be relevant to all medicinal products and there may be additional topics, which need to be included but are not mentioned (see Annex).

Part I: Product(s) overview

1. Active substance information:
– Active substance(s).
– Pharmaco–therapeutic group(s) (ATC code).
– Name of MAH or MAA.
– Date and country of first authorization worldwide (if applicable).
– Date and country of first launch worldwide (if applicable).
–Number of medicinal product(s) to which this RMP refers.

2. Administrative information on the RMP:
–Data lock point of the current RMP.
–Date submitted and the version number.
–List of all parts and modules of the RMP.

3. Brief description of the product including:
– Chemical class.
– Summary of mode of action.
– Important information about its composition (e.g. origin of active substance of biological, relevant adjuvants or residues for vaccines).

4. Indications: (current and proposed).

5. Dosage: (current and proposed).

6. Pharmaceutical forms and strengths: (current and proposed).

Part II: Safety Specification

Module SI: "Epidemiology of the indications and target population"

• The epidemiology of the indication(s) includes (incidence, prevalence, mortality and relevant co–morbidity, concomitant medication), stratified by age, sex, and racial and/or ethnic origin.

Module SII: "Non–clinical part of the safety specification"

• Toxicity for active substance and its impurities (e.g. repeat–dose toxicity, reproductive/developmental toxicity, nephrotoxicity, hepatotoxicity, genotoxicity, carcinogenicity).
• General pharmacology (e.g. cardiovascular, including QT interval prolongation, nervous system).
• Drug interactions.
• Other toxicity–related information or data.

Module SIII: "Clinical trial exposure" (tables, graphs)

• Type of trial and number of patients.
• Age and gender.
• Indication and dose.
• Racial origin.
• Duration of exposure.
• The exposure of special populations (pregnant women, breastfeeding women, renal impairment, hepatic impairment, cardiac impairment, sub–populations with relevant genetic polymorphisms, immuno–compromised).

Module SIV: "Populations not studied in clinical trials" (Limitations and exclusion criteria) Populations to be considered for discussion should include (but might not be limited to)

• Pediatric population (under 18 years).
• Elderly population (over 65 years).
• Pregnant or breast–feeding women.
• Patients with hepatic/ renal impairment.
• Patients with other relevant co–morbidity (e.g. cardiovascular or immuno–compromised including organ transplant patients).
• Patients with disease severity different from that studied in clinical trials.
• Sub–populations carrying known and relevant genetic polymorphism.
• Patients of different racial and/or ethnic origins.

Module SV: "Post–authorization experience"

• Action taken by Medicines and Medical Product Registration and Regulatory and/or MAH for safety reasons (a restriction to the approved indication, a new contra–indication, a new or strengthened warning or any action to suspend or revoke a MA) (List should be cumulative, and specify the country, action taken and the date as appropriate)

1. Non–study post–authorization exposure (patients exposed post–marketing stratified by age, sex, indication, dose and region)

2. Post–authorization uses in populations not studied in clinical trials.

3. Post–authorization off–label use.

4. Epidemiological studies which are, or have been, conducted to elucidate safety or efficacy issues, study drug utilization or measure effectiveness of risk minimization measures.

Module SVI: "Additional requirements for the safety specification"

• Potential for harm from overdose (whether intentional or Accidental)
• Potential for transmission of infectious agents (vaccines)
• Potential for misuse for illegal purposes.
• Potential for medication errors (wrong patient, wrong medication, wrong dose, wrong route of administration)
• Potential for off–label use.
• Specific pediatric issues (follow up of safety or efficacy issues in relation to pediatric use and potential for pediatric off–label use).

Module SVII: "Identified and potential risks"

• Newly identified safety concerns (tables) (Important identified and important potential risks) identified since the last submission of the RMP.
• The source of the safety concern should be stated (clinical development, post–authorization experience, identified and potential interactions including food–drug and drug–drug interactions and pharmacological class effects) and whether new studies or risk minimization activities are proposed.

Module SVII: "Identified and potential risks, advanced therapy medicinal products" (ATMP version)

• Newly identified safety concerns (tables) (Important identified and important potential risks) identified since the last submission of the RMP.
• The source of the safety concern should be stated (clinical development, post authorization experience, identified and potential interactions including food–drug and drug–drug interactions and pharmacological class effects) and whether new studies or risk minimization activities are proposed.
• The additional risks specific to ATMPs which should be considered for discussion include:
○ Risks to living donors.
○ Risks to patients related to the storage and distribution of the product.
○ Risks to patients related to administration procedures.
○ Risks related to interaction of the product and the patient (immunogenicity e.g. anaphylaxis, graft rejection)
○ Risks related to persistence of the product in the patient.
○ Risks related to re–administration.
○ Specific parent–child risks.

Module SVIII: "Summary of the safety concerns" tables

• Important identified risk.
• Important potential risk.
• Missing information

Part III: Pharmacovigilance plan:

Structure plan for:

• The identification of new safety concerns
• Further characterization of known safety concerns
• The investigation of whether a potential safety concern is real or not.
• How missing information will be discussed.
• Routine pharmacovigilance activities.
• Additional pharmacovigilance activities.

(Pharmacokinetics studies, drug utilization studies, studies to measure the effectiveness of risk minimization measures, non–interventional studies, pharmaco–epidemiology studies)

Action plans for safety concerns with additional pharmacovigilance requirements.

Summary table of additional pharmacovigilance activities.

Part IV Plans for post–authorization efficacy studies

(The KPVC may require post–authorization efficacy studies for products where there are concerns about efficacy which can only be resolved after the product has been marketed, or when knowledge about the disease or the clinical methodology used to investigate efficacy indicate that previous efficacy evaluations may need significant revision.

1. Summary of existing efficacy data.

2. Tables of post–authorization efficacy studies (description of study, milestones, due date)

Note: The requirement for efficacy studies post authorization refers solely to the current indication(s) and not to studies investigating additional indications.

Part V Risk minimization measures

1. Routine risk minimization
• Summary of product characterizations and package leaflet.
• Pack size and labeling.
• Legal status of the product (restricted and special medical prescription).

2. Additional risk minimization activities. (only agreed by the KPVC)

3. Direct healthcare professional communications.
• Educational materials (patient alert cards and monitoring cards).
• Controlled distribution systems.

4. Evaluation of the effectiveness of risk minimization activities.

5. Summary of risk minimization measures (table).

Part VI Summary of activities in the RMP by medicinal product. (Tables)

1– Summary of safety concerns. – Important identified risks. – Important potential risks. – Missing information.

2– Summary of risk minimization measures by safety concern.

3– Planned post–authorization development plan (studies).

4– Summary of changes to the risk management plan over time.

Part VII Annexes to the risk management

Go to KuGVP Annex 6

Annex 5: Risk Management Plan (RMP) check list

RMP check list

Part I	Product overview
	1– Active substance information.
	– Active substance(s).
	– Pharmacotherapeutic group(s) (ATC code).
	– Name of marketing authorization holder or applicant.

supplementary activities in the RMP for each region although there will be core elements which are common to all.

• Furthermore, individual countries may have different health systems and medical practice may differ between them so the conditions and restrictions in the MA may be implemented in different ways depending upon national customs.

• MAH/ MAAs are required to submit RMP to KPVC in the situations described above .Taking into consideration that the core elements of the product's RMP are common and as this guideline was based on the European Good Pharmacovigilance Practice, thus for simplification; MAH/MAAs having EU RMP in place submit both of the following:

1. The most updated version of the EU RMP (referenced EU RMP including its annexes; altogether with

2. The National Display of the RMP (including its annexes) (template shall comply with the Arab Guidelines for Good Pharmacovigilance Practice (current version)).

In these circumstances (submitting the National Display and the EU RMP), the following conditions apply:

• When the referenced EU RMP is subject to update the National Display of RMP should be updated in accordance.

• Minor differences may exist between this guidance and the EU RMP, in this case MAH/Applicant may be asked by the national medicines authority in the Arab Country concerned to submit additional information, use different tables, and/or provide clarification.... etc.

• The submitted EU RMP shall be the most updated version.

• The EU RMP shall be submitted with its annexes and reference materials

• Generally, it is required that all the risk management activities applied globally/in the EU to be applied in Kuwait as well, especially the risk minimization measures including the measurement of their effectiveness. Accordingly, all activities, action plans and details especially the risk minimization ones (including the measurement of their effectiveness) stated in the submitted EU RMP –although unjustifiably skipped in the —National Display of the RMP)– are expected by default to apply to Kuwait and the MAH is required to adhere to them, EXCEPT otherwise clearly stated and justified by the MAH/MAA in the —National Display of the RMP) and agreed by KPVC.

Requirements for new marketing applications:

➢ Such requirements shall be submitted to the Medicines and Medical Product Registration and Regulatory as part of the pre–marketing approval process.

Table (3): Regulatory requirements to be submitted to the PHRA as part of the pre–marketing approval

Type of new application	Part I	Part	Part	Part	Part	Part	Part	Part	Part	Part	Part	Part	Part	Part V	Part V
New active substance	Ó	Ó	Ó	Ó	Ó	Ó	Ó	Ó	Ó	Ó	Ó	Ó	Ó	Ó	Ó
Similar biological	Ó		Ó	Ó	Ó	Ó	Ó	Ó	Ó	Ó	Ó	Ó	Ó	Ó	Ó
Generic medicine	Ó								Ó	*	*	Ó	*	Ó	

* Modified requirement: Please note that the naming and numbering of the RMP parts, modules and sections are standardised thus should NOT be changed or renumbered due to the omission of un–required sections.

Structure of the RMP (Detailed description of each part of the RMP):

(As per Arab Guidelines for Good Pharmacovigilance Practice, current version)

	approved indication, a new contra-indication, a new or strengthened warning or any action to suspend or revoke a marketing authorization). (List should be cumulative, and specify the country, action taken and the date as appropriate)
	1- non-study post-authorization exposure (patients exposed post-marketing stratified by age, sex, indication, dose and region).
	2- Post-authorization use in populations not studied in clinical trials.
	3- Post-authorization off-label use.
	4- Epidemiological studies which are, or have been, conducted to elucidate safety or efficacy issues, study drug utilization or measure effectiveness of risk minimization measures.
	Module SVI. "Additional requirements for the safety specification"
	- Potential for harm from overdose (whether intentional or accidental).
	- Potential for transmission of infectious agents (vaccines).
	- Potential for misuse for illegal purposes.
	- Potential for medication errors (wrong patient, wrong medication, wrong dose, wrong route of administration).
	- Potential for off-label use.
	- Specific pediatric issues (follow up of safety or efficacy issues in relation to pediatric use and potential for pediatric off-label use).
	Module SVII. "Identified and potential risks"
	- Newly identified safety concerns (tables) (Important identified and important potential risks) identified since the last submission of the RMP.
	- The source of the safety concern should be stated (clinical development, post-authorization experience, identified and potential interactions including food-drug and drug-drug interactions and pharmacological class effects) and whether new studies or risk minimization activities are proposed.
	Module SVII. "Identified and potential risks Advanced Therapy Medicinal Products (ATMP Version) - Newly identified safety concerns (tables) (Important identified and important potential risks) identified since the last submission of the RMP.
	- The source of the safety concern should be stated (clinical development, post-authorization experience, identified and potential interactions including food-drug and drug-drug interactions and pharmacological class effects) and whether new studies or risk minimization activities are proposed.
	The additional risks specific to ATMPs which should be considered for discussion include: - Risks to living donors. - Risks to patients related to the storage and distribution of the product. - Risks to patients related to administration procedures. - Risks related to interaction of the product and the patient (immunogenicity e.g. anaphylaxis, graft rejection). - Risks related to persistence of the product in the patient. - Risks related to re-administration. - Specific parent-child risks.
	Module SVIII. "Summary of the safety concerns" tables
	- Important identified risk.
	- Important potential risk.
	- Missing information.
Part III	Pharmacovigilance plan
	Structure plan for: - The identification of new safety concerns. - Further characterization of known safety concerns. - The investigation of whether a potential safety concern is real or not. - How missing information will be discussed.
	1- Routine pharmacovigilance activities.
	2- Additional pharmacovigilance activities. (Pharmacokinetics studies, drug utilization studies, studies to measure the effectiveness of risk minimization measures, non-interventional studies, pharmacoepidemiology studies). - Action plans for safety concerns with additional pharmacovigilance requirements. - Summary table of additional pharmacovigilance activities.
Part IV	Plans for post-authorization efficacy studies.
	- The KPVC may require post-authorization efficacy studies for products where there are concerns about efficacy which can only be resolved after the product has been marketed, or when knowledge about the disease or the clinical methodology used to investigate efficacy indicate that previous efficacy evaluations may need significant revision.
	1- Summary of existing efficacy data.
	2- Tables of post-authorization efficacy studies (description of study, milestones, due date). Note: The requirement for efficacy studies post authorization refers solely to the current indication(s) and not to studies investigating additional indications.
Part V	Risk minimization measures.
	1- Routine risk minimization.
	- Summary of product characterizations and package leaflet.
	- Pack size and labeling.
	- Legal status of the product (restricted and special medical prescription).
	2- Additional risk minimization activities (Only agreed by the KPVC)
	- Direct healthcare professional communications.
	- Educational materials (patient alert cards and monitoring cards).
	- Controlled distribution systems.
	3- Evaluation of the effectiveness of risk minimization activities.
	4- Summary of risk minimization measures (table).
Part VI	Summary of activities in the risk management plan by medicinal product (tables)
	1- Summary of safety concerns.
	- Important identified risks.
	- Important potential risks.
	- Missing information.
	2- Summary of risk minimization measures by safety concern.
	3- Planned post-authorization development plan (studies).
	4- Summary of changes to the risk management plan over time.
Part VII	Annexes to the risk management.
	Annex 1
	- Interface between RMP and —National Pharmacovigilance and Safety reports database/National Pharmacovigilance Issues Tracking Tool" (electronic only), applicable only in

	- Date and country of first authorization worldwide (if applicable).
	-Date and country of first launch worldwide (if applicable).
	- Number of medicinal product(s) to which this RMP refers.
	2- Administrative information on the RMP.
	- Data lock point of the current RMP.
	- Date submitted and the version number.
	- List of all parts and modules of the RMP.
	3- Brief description of the product including:
	- Chemical class.
	- Summary of mode of action.
	- Important information about its composition (e.g. origin of active substance of biological, relevant adjuvants or residues for vaccines);
	4- Indications (current and proposed).
	5- Dosage (current and proposed).
	6- Pharmaceutical forms and strengths. (current and proposed).
Part II	Safety specification.
	Module SI. "Epidemiology of the indications and target population"
	- The epidemiology of the indication(s) includes (incidence, prevalence, mortality and relevant co-morbidity, concomitant medication), stratified by age, sex, and racial and/or ethnic origin.
	Module SII. "Non-clinical part of the safety specification"
	- Toxicity for active substance and its impurities (e.g. repeat-dose toxicity, reproductive/developmental toxicity, nephrotoxicity, hepatotoxicity, genotoxicity, carcinogenicity).
	- General pharmacology (e.g. cardiovascular, including QT interval prolongation, nervous system).
	- Drug interactions.
	- Other toxicity-related information or data.
	Module SIII. "Clinical trial exposure" (tables/ graphs)
	- Type of trial and number of patients.
	- Age and gender.
	- Indication and dose.
	- Racial origin.
	- Duration of exposure.
	- The exposure of special populations (pregnant women, breastfeeding women, renal impairment, hepatic impairment, cardiac impairment, sub-populations with relevant genetic polymorphisms, immuno-compromised).
	Module SIV. "Populations not studied in clinical trials" (Limitations and exclusion criteria) Populations to be considered for discussion should include (but might not be limited to)
	- Pediatric population (under 18 years).
	- Elderly population (over 65 years).
	- Pregnant or breast-feeding women.
	- Patients with hepatic/ renal impairment.
	- Patients with other relevant co-morbidity (e.g., cardiovascular or immunocompromised including organ transplant patients).
	- Patients with disease severity different from that studied in clinical trials.
	- Sub-populations carrying known and relevant genetic polymorphism.
	- Patients of different racial and/or ethnic origins.
	Module SV. "Post-authorization experience"
	- Action taken by regulatory authorities and/or MAHs for safety reasons (a restriction to the

	some Arab Countries hence this annex should be submitted only upon request. Further details will be announced by authorities who require such annex. In Arab Countries who do not require this annex, it should be omitted (WITHOUT changing the numbering of the following annexes).
	Annex 2
	- Current summary of product characteristics (SmPC) and package leaflet.
	Annex 3
	- Worldwide marketing authorization status by country (approved/ refused/ suspended/ withdrawn/ marketed/ not marketed).
	Annex 4
	- Synopsis of on-going and completed clinical trial programme.
	Annex 5
	- Synopsis of on-going and completed pharmaco-epidemiological study programme.
	Annex 6
	- Protocols for proposed and on-going studies in the section Summary table of additional pharmacovigilance activities in RMP part III.
	Annex 7
	- Specific adverse event follow-up forms.
	Annex 8
	- Protocols for proposed and on-going studies in RMP part IV.
	Annex 9
	- Synopsis of newly available study reports for RMP parts III-IV.
	Annex 10
	- Details of proposed additional risk minimization activities (if applicable).
	Annex 11
	- Mock up examples in English of the material provided to healthcare professionals and patients. For those materials directed to patients, in addition to the English version, Arabic translation of the mock up shall be included as well.
	Annex 12
	- Other supporting data (including referenced material).

MODULE TEN:

PERIODIC BENEFIT RISK EVALUATION REPORT (PBRER)

PERIODIC BENEFIT RISK EVALUATION REPORT (PBRER)

A Periodic Benefit Risk Evaluation Report (PBRER) is an analysis of the safety, efficacy, and efficiency of a drug, once it is already in the market. It is a comprehensive, concise, and critical analysis of new or emerging information on the risks and benefits of a medicine compiled by the marketing authorization holder (MAH). PBRER replaces the PSUR (Periodic Safety Update Report). These ongoing appraisals aid both the MAH and the regulator in maintaining confidence in the benefit-risk balance of the medicine based on the regulatory options currently imposed (such as approved indications, warnings, labelling) and those yet available (e.g., limiting the indications, expanding warnings and precautions, creating contraindications, rescheduling, re-labelling or restricting use to a subset of the population). KPVC recommends that MAHs follow the guidance in relation to PBRERs found in the ICH guideline E2C (R2).

necessary. Retrospective submission of PBRERS is not required. KPVC does not require routine submission of PBRERs for other medicines. However, it is acceptable for MAHs to submit PBRERs routinely for all their medicines if they wish to do so.

4. PBRERs submission timelines in Kuwait:

• Within 70 calendar days of the data lock point (day 0) for PBRERs covering intervals up to 12 months (including intervals of exactly 12 months)

• Within 90 calendar days of the data lock point (day 0) for PBRERs covering intervals in excess of 12 months

• The timeline for the submission of ad hoc PBRERs requested by KPVC will be specified, otherwise the ad hoc PBRERs should be submitted within 90 calendar days of the data lock point.

5. For active substances or combination of active substances not included in the EURD list, the submission of the PBRER should be as follows starting from the IBD:

• 6-monthly PBRER submission until two full years of marketing experience has been gained.

• Then PBRERs should be submitted once a year for the following two years.

• Then PBRERs should be submitted at 3-yearly intervals.

6. PBRERs should also be submitted upon request by KPVC at any time after granting of the marketing authorization.

7. Each PBRERs should include interval as well as cumulative data. As the PBRERs should be a single stand-alone document for the reporting interval, based on cumulative data, summary bridging reports and addendum reports, introduced in ICH-E2C (R1) guideline, will not be accepted.

8. The MAH should continuously evaluate whether any revision of the reference product information/reference safety information is needed whenever new safety information is obtained during the reporting interval and ensure that significant changes made over the interval are described in PBRERs.

9. Changes in the safety information may include:

• Changes to contraindications, warnings/precautions sections

• Addition to adverse reactions and interactions

• Addition of important new information on use in overdose; and

• Removal of an indication or other restrictions for safety or lack of efficacy reasons.

10. When no relevant information is available for any of the sections, this should be stated under the section but do NOT omit any section.

11. The adoption of the 'Arab Good Pharmacovigilance Practice' as a base for PV guideline does not undermine the right of KPVC to have additional or sometimes changed requirements as applicable for Kuwait regulations.

12. For generic medicinal products:

a. PBRERs for generic medicinal products are required to be submitted.

b. An abridged PBRERs can be used.

• The cover letter should state "abridged PBRERs.

• Sections that are not required from generics in the abridged PBRER should NOT be omitted instead state that it is not applicable for generics with referral to this guideline.

The Full Modular Structure of PBRERs

Should contain:

As per Arab Guidelines for Good Pharmacovigilance Practice, Version 2

(See KuGVP Annex 6 for content and format of a PBRER)

Annex 6: Format and Content of a PBRER

Periodic benefit–risk evaluation report.

• PBRER submission is intended to present a periodic, comprehensive, brief and critical evaluation of new or emerging information on the risks of the health product and the product's overall benefit–risk profile. It provides an evaluation of the risk–benefit balance of a medicinal product at defined time points post–authorization.

• The objective of the PBRER is to present a comprehensive and critical analysis of the risk–benefit balance of the product taking into account new or emerging safety information in the context of cumulative information on risks and benefits. This document is approved worldwide.

• Periodic Safety Update Report (PSUR) is a pharmacovigilance document intended to provide an update of the worldwide safety experience of a medicinal product to regulatory authorities at defined time points post–authorisation. This document is now replaced with PBRER. However, both documents are currently accepted by the KPVC until the full transition is made to PBRER.

• Periodic Adverse Drug Experience Report (PADER) is a part of post–cumulative safety reports which need to be submitted to the United States (USFDA). The main purpose of a PADER is to update and evaluate a medicine's global data and provide information about drug safety. It provides a brief summary of changing post–approval information of a drug along with benefit–risk profile evaluation.

○ This evaluation provides insights, whether further changes are required for a medicine's labeling or if additional investigations are required.

○ For the three years, the MAH needs to submit the report quarterly and, thereafter, annually upon obtaining approval from USFDA

○ Post 2015, PADER is accepted in USFDA in electronic format with descriptive information.

○ A PADER waiver may be accepted with the condition of providing:

• Worldwide approval

• Adverse events occurring around the world or in GCC region

• Overall safety information with specific highlighting

• Final conclusion about benefit–risk balance from the analysis of the cumulative data as required by the PBRER.

The Legal Requirements for Submission of PBRER:

1. All PV guidelines are based on Arab guidelines on Good Pharmacovigilance Practice which are adopted from European Good Pharmacovigilance guidelines

2. PBRERs (or PSURs) should be submitted according to the list of EU reference dates (EU RD list)

3. PBRERs are required to be routinely submitted for the following types of medicines:

a. vaccines that are included in the routine National Immunization Schedule

b. biological medicines (excluding vaccines)

c. biosimilars

d. medicines where a specific requirement for the submission of PBRERs has been imposed as a condition of approval.

For treatments funded only for a limited patients population and not included in routine use, the routine submission of PBRERs is not required. However, the KPVC may occasionally request the submission of a PBRER for a specific medicine if enhanced safety monitoring is deemed necessary. PBRERs should be submitted in line with the European Union reporting timetable. KPVC will advise MAHs when routine submission is no longer

4.0	summary tabulations	adverse events from clinical trials, spontaneous serious and non–serious reactions from marketing experience	
VIIB5 6.1	Reference information	Specification of the version(s) of the coding dictionary used for presentation of adverse events/reactions	
VIIB5 6.2	Consolidative summary tabulations of serious adverse events from clinical trials	Present safety data through summary tabulations of serious adverse events from clinical trials, spontaneous serious and non–serious reactions from marketing experience (including reports from HCPs, consumers, scientific literature, medicines authorities (worldwide)) and serious reactions from non–interventional studies and other non–interventional solicited source	(Not applicable for generics)
VIIB5 6.3	Consolidative and interval summary tabulations from post–marketing data sources	background for the appendix that provides cumulative and interval summary tabulations of adverse reactions, from the IBD to the data lock point of the current PBRER.	
VIIB5 7.0	Summaries of significant findings from clinical trials during the reporting interval	The listing should include the following information for each trial: ○ Study ID (e.g., protocol number or another identifier). ○ Study title (abbreviated study title, if applicable; study type (e.g. randomized clinical trial, cohort study, case–control study). ○ Population studied, including country and other relevant population descriptors (e.g. pediatric population or trial subjects with impaired renal function). ○ Study start (as defined by the marketing authorization holder) and projected completion dates. ○ Status: ongoing (clinical trial has begun) or completed (clinical study report is finalized).	(Not applicable for generics)
VIIB5 7.1	Completed clinical trials	Summary of clinically important emerging efficacy and safety findings obtained from clinical trials completed during the reporting interval.	
VIIB5 7.2	Ongoing clinical trials	Information that supports or refutes previously identified safety concerns, as well as evidence of new safety signals.	
VIIB5 7.3	Long–term follow–up	From clinical trials of investigational drugs, particularly advanced therapy products (e.g. gene therapy, cell therapy products and tissue engineered products).	
VIIB5 7.4	Other therapeutic use of medicinal product	Clinically important safety information from other programmes conducted by the MAH that follow a specific protocol (e.g. expanded access programmes, compassionate use programmes, particular patient use, and other organized data collection).	
VII B5 7.5	New safety data related to fixed combination therapies	The following options can be used to present data from combination therapies: • If the active substance is also authorized or under development as a component of a fixed combination product or a multi–drug regimen,	

Part	Section Title	Contents and Requirements	Notes
I	Title page	1. Name of the medicinal product 2. IBD 3. Reporting interval, date of the report 4. MAH details and statement of confidentiality of the information included in the PBRER 5. Signature of QPPV	
II	Executive Summary	1. Introduction and reporting interval 2. Medicinal product(s), therapeutic class(es), mechanism(s) of action, indication(s), pharmaceutical formulation(s), dose(s)and route(s) of administration 3. Estimated cumulative clinical trials exposure 4. Estimated interval and cumulative exposure from marketing experience 5. Number of countries in which the medicinal product is authorized 6. Summary of the overall benefit risk evaluation. 7. Actions taken due to safety reasons (e.g. significant changes to the reference product information, or other risk minimization activities). 8. Conclusions	
III		Table of Contents	
VIIB5 1.0	Introduction	• IBD, and reporting interval • Medicinal product(s), therapeutic class(es), mechanism(s) of action, authorized indication(s), pharmaceutical form(s), dose(s) and route(s) of administration • Description of the population(s) being treated and studied.	
VIIB5 2.0	Worldwide MA status	• Date of the first authorization worldwide • Indications(s) and authorized dose(s) • Since when and where authorized	
VIIB5 3.0	Actions taken in the reporting interval for safety reasons	1. Actions related to investigational uses and/or 2. Actions related to marketing experience	(Not applicable for generics)
VIIB5 4.0	Changes to reference safety information	Significant changes made to the reference safety information (contraindications, warnings, precautions, serious adverse drug reactions, interactions)	
VIIB5 5.0	Estimated exposure and use patterns	Estimate the population exposed to the medicinal product, including all data relating to the volume of sales and volume of prescriptions.	
VIIB5 5.1	Consolidative subject exposure in clinical trials	clinical trials sponsored by the MAH (tabular formats)	(Not applicable for generics)
VIIB5 5.2	Cumulative and interval patient exposure from marketing experience	• The IBD and since the data lock point of the previous PBRER. • The data should be presented according to the following categories: 1. Post–authorisation (non–clinical trial) exposure. 2. Post–authorization use in special populations 3. Other post–authorization use	
VIIB5	Data in	Summary tabulations of serious	

15.0	of signals: new, ongoing or closed	was completed).	
VIIB5 16.0	Signal and risk evaluation	The purpose of this section is to provide: • important identified and potential risks and missing information • all signals • An evaluation of new information with respect to previously recognized identified and potential risks • updated characterization of important potential and identified risk • effectiveness of risk minimization activities in any country or region which may have utility in other countries or regions These sub-sections should not summaries or duplicate information presented in previous sections of the PBRER but should provide interpretation and critical appraisal of the information, with a view towards characterizing the profile of those risks assessed as important.	
VIIB5 16.1	Summaries of safety concerns	Important identified risks; important potential risks; and missing information	
VIIB5 16.2	Signal evaluation	• The two main categories to be included in this sub-section are: 1. Signals that, following evaluation, have been refuted as 'false' signals 2. Signals that, following evaluation, have been categorized as either a potential or identified risk, including lack of efficacy. • Each evaluation should include the following information as appropriate: 1. source or trigger of the signal 2. evaluation, including data sources, search criteria 3. results 4. discussion 5. conclusion	
VIIB5 16.3	Evaluation of risks and new information	A critical appraisal of new information relevant to previously recognized risks or to those already included in the ongoing 'Signal evaluation'. • New information may be organized as follows: 1. New information on important potential risks. 2. New information on important identified risks 3. New information on other potential risks not categorized as important. 4. New information on other identified risks not categorised as important. 5. Update on missing information.	
VIIB5 16.4	Characterization of risks	Characterise important identified and potential risks based on cumulative data (i.e. not restricted to the reporting interval); and describe missing information.	
VIIB5 16.5	Effectiveness of risk minimisation activities (if applicable)	effectiveness of risk minimisation activities relevant to the risk-benefit assessment.	
VIIB5	Benefit		

		this subsection should summarize important safety findings from use of the combination therapy. • If the product itself is a fixed combination product, this PBRER sub-section should summarize important safety information arising from the individual components whether authorized or under development.	
VII B5 8.0	Findings from noninterventional studies	Summaries relevant safety information or information with potential impact in the benefit-risk assessment from MAH-sponsored non-interventional studies that became available during the reporting interval.	
VII B5 9.0	Information from other clinical trials and sources		(Not applicable for generics)
VIIB5 9.1	Other clinical trials	Findings from pooled analysis or meta-analysis of randomised clinical trials, as well as safety data provided by co-development partners or obtained from investigator-initiated studies.	(Not applicable for generics)
VII B5 9.2	Medication errors	patterns of medication errors and potential medication errors, even when not associated with adverse outcomes	
VII B5 10.0	Non-clinical Data	nonclinical in vivo and in vitro studies (e.g. carcinogenicity, reproduction or immunotoxicity studies)	(Not applicable for generics)
VII B5 11.0	Literature	Literature searches for PBRERs should be wider than those for individual adverse reaction cases as they should also include studies reporting safety outcomes in groups of subjects and other products containing the same: • Pregnancy outcomes (including termination; with no adverse outcomes • Pregnancy outcomes (including termination; with no adverse outcomes • Use in pediatric populations • Compassionate supply, named patient use • Lack of efficacy • asymptomatic overdose, abuse or misuse • Medication error where no adverse events occurred • important non-clinical safety results.	
VIIB5 12.0	Other periodic reports		
VIIB5 13.0	Lack of efficacy in controlled clinical trials	Data from clinical trials indicates lack of efficacy relative to established therapy(ies), for products intended to treat or prevent serious or life-threatening illnesses that could reflect a significant risk to the treated population.	(Not applicable for generics)
VIIB5 14.0	Late-breaking information	Potentially important safety, efficacy and effectiveness findings that arise after the data lock point but during the period of preparation of the PBRER.	
VIIB5	Overview	Signals that were closed (evaluation	

		sources. 3. Tabular summary of safety signals (if not included in the body of the report). It is preferred to include the tabulation of signals in the body of the PBRER, if feasible. 4. Listing of all the marketing authorisation holder-sponsored interventional and non-interventional studies with the primary aim of identifying, characterising, or quantifying a safety hazard or confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures, in case of non-interventional studies. Final study reports for those completed during the reporting interval should also be included as an annex to the PBRER. 5. List of the sources of information used to prepare the PBRER.	

MODULE ELEVEN:

SIGNAL MANAGEMENT

A signal is defined as information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify an action.

For the purpose of this module, only new information related to adverse effects will be considered.

Structures and Processes

Sources of Data and Information

- The sources for identifying new signals are diverse.
- They potentially include all scientific information concerning the use of medicinal products including quality, non-clinical, clinical, PV and pharmaco-epidemiological data.
- Specific sources for signals include:
  - Spontaneous adverse drug reaction (ADR) reporting systems
  - Active surveillance systems
  - Non-interventional studies
  - Clinical trials
  - Scientific literature
  - Other sources of information.
- Signals arising from spontaneous reports may be identified through the monitoring of ICSRs, AE databases, scientific literature or through the evaluation of information provided by MAHs within regulatory procedures (e.g., variations, renewals, post-authorisation commitments, PBRERs, RMP updates, as well as from other activities related to the continuous benefit-risk assessment of medicinal products.
- Spontaneous reports of ADRs may also be notified to poison centers, teratology information services, vaccine surveillance programmes, reporting systems established by MAHs, and any other structured and organised data collection schemes allowing patients and HCPs to report suspected adverse reactions related to medicinal products.
- KPVC is expected to liaise with other institutions or organizations managing such reporting system so as to be informed of these suspected adverse reactions.
- Due to the increase in volume of spontaneous reports of ADRs, the introduction of electronic safety reporting by patients and HCPs and the mandatory electronic submission of case reports from MAHs to KPVC, signal detection is now increasingly based

17.0	evaluation		
VIIB5 17.1	Important baseline efficacy and effective-ness information	• Efficacy and effectiveness of the medicinal product and provides the basis for the benefit evaluation. • For medicinal products with multiple indications, populations, and/or routes of administration, the benefit should be characterised separately by these factors when relevant.	
VIIB5 17.2	Newly identified information on efficacy and effective-ness	• Additional information on efficacy or effectiveness in authorized indications may have become available. Characterization of benefits available during the reporting interval. • New information on efficacy and effectiveness in uses other than the authorized indications should not be included unless relevant for the benefit-risk evaluation in the authorized indications. • Particular attention should be given to vaccines, anti-infective agents or other medicinal products where therapeutic environment changes may impact efficacy/effectiveness over time.	
VIIB5 17.3	Characteri-zation of benefits	Generalizable to patient populations treated in medical practice	
VIIB5 18.0	Integrated benefit-risk analysis for authorized indications	A critical analysis and synthesis of the key information presented in the preceding sections should be provided, avoiding mere duplication of the previously benefit and risk characterisations.	
VIIB5 18.1	Benefit-risk context – Medical need & important alternatives	Brief description of the medical need for the medicinal product in the authorised indications & summarised alternatives (medical, surgical or other; including no treatment).	
VIIB5 18.2	Benefit-risk analysis evaluation	• A risk-benefit balance is specific to an indication and population. • Products authorised for more than one indication, risk benefit balances should be evaluated and presented by each indication individually. • If there are important differences in the risk benefit balance among populations within an indication, the benefit risk evaluation should be presented by population, if possible.	
VIIB5 19.0	Conclusions and actions	• Overall evaluation of benefit-risk for each authorized indication • Preliminary proposal(s) to optimise or further evaluate the risk-benefit balance for further discussion with the relevant medicines authority(ies). • This may include proposals for additional risk minimization activities. • Proposed changes to the reference product information.	
VIIB5 20.0	Appendices to the PBRER	1. Reference information 2. Cumulative summary tabulations of serious adverse events from clinical trials; and cumulative and interval summary tabulations of serious and non-serious adverse reactions from post-marketing data	

rationale for the method and periodicity of the signal detection activity

• Detection of signals may be performed based on a review of ICSRs, from statistical analyses in large databases, or from a combination of both as follows:

B. Review of Individual Case Safety Reports (ICSRs):

• ICSRs may originate from a spontaneous reporting system, post-authorization studies and monitoring of literature.

• Even a single report of a serious or severe adverse reaction may be sufficient to raise a signal and to take further action.

• A review of ICSRs for this purpose should consider:

○ The number of cases (after exclusion of duplicates),

○ The patient's demographics (including age and gender),

○ The suspected medicinal product (including dose administered, formulation)

○ The suspected adverse reaction (including signs and symptoms, the temporal association, the clinical outcome in relation to drug continuation or discontinuation (i.e., de-challenge / re-challenge information).

• An assessment of causality or a suspected association should also consider the presence of potential alternative causes including other concomitant medications, the underlying disease, the reporter's evaluation of causality and the plausibility of a biological and pharmacological relationship

C. Statistical analyses:

• Signal detection is now increasingly based on a regular periodic monitoring of large databases of reports of ADRs. Such databases allow generation of statistical reports presenting information on adverse reactions received over a defined time period for defined active substances or medicinal products.

• Various methods have been developed to identify statistics of disproportionate reporting, i.e., higher reporting than expected for a suspected adverse reaction for an active substance/medicinal product of interest compared to all other active substances/medicinal products in the database.

• Given the limitations of these methods, statistics of disproportionate reporting alone do not necessarily indicate that there is a signal to be further investigated or that a causal association is present.

• Use of statistical tools may not be appropriate in all situations.

• When considering the use of statistical methods and the selection of criteria for the detection of signals these factors should be taken into account:

○ The size of the data set

○ The completeness of the available information

○ The severity of the adverse reaction(s)

• The periodicity at which statistical reports should be generated and reviewed may vary according to the active substance/medicinal product, its indication and any known potential or identified risks.

• Some active substances/medicinal products may be subject to an increased frequency of data monitoring. The duration for this increased frequency of monitoring may vary with the accumulation of knowledge of the risk profile associated with the use of the concerned active substance/medicinal product.

D. Combination of Statistical Methods and Review of ICSRs:

• The statistical method should be a supporting tool in the whole process of signal detection and subsequent validation.

2. Signal Validation:

• Signal validation is the process of evaluating the data supporting the detected signal in order to verify that the available on periodic monitoring of large databases of ADRs reports.

• Published results of relevant studies is expected to be identified by MAHs by screening the scientific literature.

Methodology for Signal Detection

• As a general principle, signal detection is expected to follow a recognised methodology, which may vary depending on the type of medicinal product it is intended to cover. Vaccines may, for example, require other methodological strategies.

• Different factors may be taken into account for the prioritization of signals, namely whether the association or the active substance/medicinal product is new, the strength of the association, the seriousness of the reaction involved and the documentation of the reports in the AEs database.

The Signal Management Process

The signal management process is the set of activities performed to determine whether, based on an examination of individual case safety reports (ICSRs), aggregated data from active surveillance systems or studies, literature information or, other data sources, there are new risks associated with an active substance or a medicinal product or whether known risks have changed.

• The signal management process concerns all stakeholders involved in the safety monitoring of medicinal products including patients, HCPs, MAHs, RA, and scientific committees.

• The signal management process covers all steps from detecting signals to recommending action(s) as follows:

1. Signal detection;
2. Signal validation;
3. Signal analysis and prioritization
4. Signal assessment;
5. Recommendation for action;
6. Exchange of information

• Although these steps generally follow a logical sequence, the wide range of sources of information available for signal detection may require some flexibility in the conduct of signal management. E.g.:

○ When signal detection is primarily based on a review of ICSRs, this activity may include validation and preliminary prioritization of any detected signal;

○ When a signal is detected from results of a study, it is generally not possible or practical to assess each individual case, and validation may require collection of additional data;

○ Recommendation for action (followed by decision in accordance with the applicable legislation) and exchange of information are components to be considered at every step of the process.

• Signals originating from data monitoring from spontaneous reporting systems are considered the starting point of the signal management process. The same principles are expected to apply to data originating from other sources.

1. Signal Detection:

A. Practical Aspects of Signal Detection:

○ The method used should be appropriate for the data set; for example, complex statistical tools may not be appropriate for smaller data sets.

○ Data from all appropriate sources should be considered;

○ Systems should be in place to ensure the quality of the signal detection activity;

○ Any outputs from a review of cumulative data should be assessed by an appropriately qualified person in a timely manner;

○ The process should be adequately documented, including the

measure over time and the identification of the signal in different settings (e.g., general practice and hospital settings), data sources or countries;

○ Clinical context (e.g., whether the association suggest a clinical syndrome that may include other reactions).

○ The public health impact encompassess factors such as extent of product use within the general population and among special groups (e.g., pregnant women, children, or the elderly), as well as patterns of medicinal product use, including off-label use or misuse. It may also involve estimating the number of patients potentially affected by an adverse reaction, which can be assessed in relation to the size of the general population, the target disease population and the traeted populations.

○ Increased frequency or severity of a known adverse reaction.

○ Novelty of the suspected adverse reaction, e.g., when an unknown suspected adverse reaction occurs shortly after the marketing of a new medicinal product.

○ If a marketing authorisation application for a new active substance is still under evaluation.

• In some circumstances, priority can also be given to signals identified for medicinal products or events with potential high media and PV stakeholder interest in order to communicate the result to the public and HCPs as early as possible.

• The outcome of signal prioritisation should include a recommendation of the timeline for the management of the signal.

• The outcome of the signal prioritisation process should be entered in the tracking system, with the justification for the priority attributed.

4. Signal assessment:

• The objective of signal assessment is to further evaluate a validated signal to identify the need for additional data collection or for any regulatory action.

5. Signal Escalation:

• After signal has been assessed and validated, a report with the suggested recommendations is raised to Kuwait Pharmacovigilance Risk Assessment Committee (KuPRAC) who make the decision to prioritise the signal according to information, strength of evidence, and public health context.

• Where appropriate, signals escalated to a formal safety referral, as necessary.

6. Recommendation for action:

• Recommended action may involve requesting:

○ Immediate measures including the possibility of suspending the marketing authorization of the medicinal product.

○ Additional information to be provided by the MAH.

○ Periodic review of the signal, for example through PBRER.

○ Additional investigations or risk minimization activities.

○ An update of the product information through a regulatory procedure.

○ Conduct of a post-authorization safety study.

• When requesting actions form a MAH, the request is expected to specify a timeframe by which they should be completed, including provision of progress reports and interim results, proportionate to the severity and public health impact of the signal

• Information on validated signals, emerging safety issues and the outcome of signal assessments should be exchanged between the KPVC and MAHs

• MAHs is expected to communicate signals that may have implications for public health and the benefit-risk profile of a documentation contains sufficient evidence demonstrating the existence of a new potentially causal association or a new aspect of a known association, and therefore justifies further analysis.

To validate a signal, the following should be taken into account:

• Clinical relevance including, for example:

○ Strength of evidence for a causal effect (e.g., number of reports, exposure, temporal association, plausible mechanism, de/re-challenge, alternative explanation/confounders);

○ Seriousness and severity of the reaction and its outcome;

○ Novelty of the reaction (e.g., new and serious adverse reactions)

○ Drug–drug interactions;

○ Reactions occurring in special populations.

• Previous awareness:

○ The extent to which information is already included in the summary of product characteristics (SmPC) or patient leaflet;

○ Whether the association has already been assessed in a PBRER or RMP, or was discussed at the level of a scientific committee or has been subject to a regulatory procedure

• Availability of other relevant sources of information providing a richer set of data on the same association:

○ Literature findings regarding similar cases;

○ Experimental findings or biological mechanisms;

○ Screening of databases with larger datasets [e.g. —National Pharmacovigilance and Safety reports database] when the signal was sourced initially by data from MAH specific database (if accessible to MAH), and UMC VigiBase when the signal was sourced initially from the local PV reports database

• The magnitude and clinical significance of a signal may also be examined by descriptive analyses in other available data sources or by analysis of the characteristics of exposed patients and their medicinal product utilization patterns.

• Signals for which the validity is not confirmed may deserve special attention in subsequent analyses i e., it may be appropriate to continue to monitor the potential signal until there is enough evidence to confirm the signal. For example, there might be an inadequate case documentation or supporting evidence of a causal association only in some of the ICSRs. In such scenarios, new cases of the same adverse reaction or follow-up reports of previously received cases should be reviewed at appropriate time intervals to ensure that all relevant cases are considered.

• MAHs and KPVC is expected to establish tracking systems to capture the outcome of the validation of signals including the reasons why signals were not validated as well as information that would facilitate further retrieval of ICSRs and validation of signals.

3. Signal Analysis and Prioritization:

• A key element of the signal management process is to promptly identify validated signals with important public health impact or that may significantly affect the benefit-risk profile of the medicinal product in treated patients.

• These signals require urgent attention and need to be prioritised for further management without delay.

• This prioritisation process is expected to consider:

○ The impact on patients depending on the severity, reversibility, potential for prevention and clinical outcome of the association;

○ The consequences of treatment discontinuation on the disease and the availability of other therapeutic options;

○ The strength and consistency of the evidence supporting an association, e.g., biological plausibility, the high number of cases reported in a short period of time, the measure of disproportionality of reporting, the rapid increase of that

communicated by a MAH for an active substance/medicinal product authorised in its territory. In this context, where the validity of the signal is not confirmed, special attention will be paid to any follow-up information which may allow for the signal's confirmation

6. Should validate and enter into PITT any other signal communicated by a third party (e.g., regulatory authority from other Arab, non- Arab Country or from the UMC) for these substances/medicinal products.

7. Inform the concerned MAHs of the conclusions of the assessment of any confirmed signal;

8. Will take the appropriate action following the signal assessment;

9. KPVC should keep an audit trail of its signal detection activities.

10. In addition, the KPVC as appropriate:

a. May maintain, review and publish a list of medical events that have to be taken into account for the detection of a signal.

b. Ensure appropriate support for the monitoring of the data within the pharmacovigilance and safety reports database by MAHs (applicable in only some Arab Countries).

c. Administer a Pharmacovigilance Issues Tracking Tool (PITT) for validated signals that require further assessment.

d. Perform a regular review of the signal management methodology to be used and publish recommendations as appropriate.

Marketing Authorisation Holders and Applicants'

Responsibilities:

1. Will monitor the data in its AEs database; the frequency of monitoring is expected to be at least once monthly and will be proportionate to the identified risk, the potential risk and the need for additional information.

2. Will validate any signal detected and shall inform KPVC.

3. Should notify in writing as an emerging safety issue to KPVC for authorized medicinal products, any safety issue arising from its signal detection activity which could have a significant impact on the benefit-risk balance for a medicinal product and/or have implications for public health;

4. Should collaborate with KPVC for the assessment of the signals by providing additional information upon request;

5. Should keep an audit trail of its signal detection activities.

Periodicity of Data Monitoring in the PV and Safety Reports Database:

• KPVC will ensure the continuous monitoring of data in the the Pharmacovigilance and Safety reports database) with a frequency proportionate to the identified risk, the potential risk and the need for additional information.

• The monitoring is expected to be based on a periodic review of statistical outputs (e.g., reaction monitoring reports) to determine whether there are new or changed risks in the safety profile of an active substance/medicinal product.

• The statistical outputs should contain AEs in a structured hierarchy (e.g. MedDRA hierarchy) by active substance(s)/medicinal product(s) and allow filters and thresholds to be applied on several fields as appropriate.

• The baseline frequency for reviewing the statistical outputs from the Pharmacovigilance and Safety reports database) should be once monthly.

• An increase to the baseline frequency of this data monitoring may be decided by KPVC if justified by the identified or potential risks of the product or by the need for additional information.

product immediately to KPVC as an emerging safety issue, and when appropriate this should include proposals for action.

• The outcomes of signal assessment involving new or changed risks and risks that have an impact on the benefit-risk balance of the concerned active substance/medicinal products should be communicated to the public including HCPs and patients as well as to the concerned MAHs.

Quality Requirements

1. Tracking

• All validation, prioritisation, assessment, timelines, decisions, actions, plans, reporting as well as all other key steps should be recorded and tracked systematically.

• Tracking systems should be used for documentation and should also include signals, for which the validation process conducted was not suggestive of a new potentially causal association, or a new aspect of a known association.

• All records need to be archived.

2. Quality Systems and Documentation

• A fundamental characteristic of a signal management system is thepresence of clear and comprehensive documentation, which ensure proper and effective system functioning, standardisation of roles, responsibilities, and tasks, execution of these tasks by appropriately qualified personnel, clarity forall stakeholders, and the establishment of mechanisms for adequate oversight and, when necessary system improvement.

• Therefore, a system of quality assurance and quality control consistent with the quality system standards should be in place and applied to all signal management processes

• Detailed procedures for this quality system should be developed, documented and implemented.

• The organisational roles and responsibilities for the activities and maintenance of documentation, quality control and review, and for ensuring corrective and preventive action need to be assigned and recorded. This should include the responsibilities for quality assurance auditing of the signal management system, including auditing of sub-contractors.

• Data and document confidentiality (per the applicable regulations), security and validity (including integrity when transferred) should be guaranteed.

• Through their tracking system, all parties should keep an audit trail of their signal management activities and of the relevant queries and their outcomes, including how signals have been detected, validated, confirmed and assessed.

• Documentation may be requested from the MAHs demonstrating compliance with these provisions and reviewed before and after marketing authorization. Staff should be specifically trained in signal management activities in accordance with their roles and responsibilities. The training system and location of the training records should be documented, and curricula vitae and job descriptions should be archived.

Responsibilities of Signal Management for Both MAHs and KPVC:

KPVC Responsibilities:

1. Will monitor the data of the (the PV and safety reports database)

2. Will validate and confirm any signal it has detected;

3. Shall prioritise validated and confirmed signals for further assessment

4. Shall enter validated and confirmed signals into a Pharmacovigilance Issues Tracking Tool (PITT).

5. Shall confirm as soon as possible any validated signal

• Any signal that has been detected and validated by KPVC should be entered into a Pharmacovigilance Issues Tracking Tool (PITT).

• All subsequent evaluations, timelines, decisions, actions, plans, reporting and all other key steps should be recorded and tracked systematically in PITT by KPVC.

MODULE TWELVE:

SAFETY COMMUNICATIONS

SAFETY COMMUNICATIONS

• Safety communication: is the response to safety concern(s) that provides the basis to MAH and local pharmaceutical companies, regulators and HCPs for communicating safety information and for supporting rational prescribing.

• Communicating safety information to patients is a public health responsibility and is essential for achieving the goals of pharmacovigilance and risk management plans and to promote safe use of medicines amongst consumers of pharmaceutical, biological, general health products and food supplements.

• The ultimate goal for safety communication is to encourage safe, effective and rational use of medicines, protect patients from the harmful effects of the above stated products and improve the quality of public health services.

Who is the target?

1. The main target of safety communication is HCPs and patients. HCPs provide patients with clear, useful and understandable information to promote adherence to the prescribed treatment, to increase confidence in the healthcare services provided to the public, and to raise trust in the national regulatory system.

2. HCPs in clinical practice as well as those involved in clinical trials should be provided with detailed information about any emerging safety concern simultaneously.

3. Patients, consumers, and HCPs can play a pivotal role in disseminating critical information to the general public. Therefore, all types of media should also be targeted to communicate critical information accurately and precisely as this is an important element for ensuring safe and effective use of medicines and other health products by the public.

Who issues the safety communication?

1. Kuwait Office for Pharmacovigilance Surveillance (KPVC)

2. The pharmaceutical companies representing the MAH.

How to disseminate safety communication?

Step one:

The information must be assessed and classified as:

1) Valid

2) Invalid

Step two:

Once validity has been confirmed, a decision must be made on the urgency of the safety concern:

1) Emergency case

2) Non-emergency case

Step three:

Once the urgency has been confirmed, the criticality of the case must be decided:

1) Critical case

2) Major case

3) Minor case

Each category is given a time limit for a scientific response to be issued:

1) Critical case, requires immediate response within 24 hours and further communication of additional information if further

• For products subject to additional monitoring, the frequency for reviewing the statistical outputs should be every 2 weeks until the end of additional monitoring.

• A 2-week frequency for reviewing the statistical outputs may also be applied for any other products taking into account the following criteria:

○ Any product considered to have an identified or potential risk that could impact significantly on the benefit-risk balance or have implications for public health. This may include risks associated with significant misuse, abuse or off-label use. The product may be moved back to baseline frequency of monitoring if risks are not confirmed.

○ Any product for which the safety information is limited due to low patient exposure during drug development, including products authorized under conditional approval or under exceptional circumstances59, or for which there are vulnerable or poorly studied patient populations or important missing information (e.g. children, pregnant women, renal-impaired patients) while post-marketing exposure is likely to be significant;

○ Any product that contains active substances already authorized in the Arab Country concerned but is indicated for use in a new patient population or with a new route of administration.

○ Any product for which the existing marketing authorization has been significantly varied (e.g., changes to indication, posology, pharmaceutical form or route of administration), thereby modifying the exposed patient population or the safety profile.

• Confirmation of a signal arising from the Pharmacovigilance and Safety reports database; data monitoring activities does not necessarily imply that the product has to be more frequently monitored and a risk proportionate approach should be applied.

• More frequent monitoring than every 2 weeks may be proposed. It should be targeted to a safety concern of interest especially during public health emergencies (e.g. pandemics) and may be applied in the context of customized queries

Processes for Regulatory Follow-up in Kuwait:

• KPVC may decide on any or a combination of the following actions:

• MAH should conduct further evaluation of data and provide the results of that evaluation according to a defined timeline;

• MAH should submit an ad-hoc PBRER.

• MAH should sponsor a post-authorization study according to an agreed protocol and submit the final results of that study;

• MAH should be requested to submit a RMP or an updated RMP.

• MAH should take any measures that are required for ensuring the safe and effective use of the medicinal product;

• MAH should be varied, suspended, revoked or not renewed.

• urgent safety restrictions may be imposed.

• an inspection should take place in order to verify that the marketing authorization holder for the medicinal product satisfies the pharmacovigilance requirements.

• The medicinal product should be included in the list of medicinal products that are subject to additional monitoring.

• Where decided by the KPVC; a procedure should be initiated with a timetable in which the marketing authorization should be varied, suspended, revoked or not renewed where applicable.

Signal Record Management in Kuwait:

• KPVC will keep an audit trail of all their signal management activities and of the relevant queries and their outcomes.

Content of safety communication:

• Emerging information on any authorized medicinal product which has an impact on the medicine's benefit–risk balance under any conditions of use.

• The reason(s) for initiating safety communication should clearly be explained.

• Any recommendations to HCPs and patients on how to deal with a safety concern

• Information on any proposed changes to the product information (e.g. SmPC or PIL)

• A list of references.

• A reminder of the need to report suspected adverse reactions to KPVC.

Means of Safety Communication

1. Direct HCP Communication (DHPC)

• DHPC is a communication method by which important safety information is delivered directly to individual HCPs by a MAH or KPVC (in special cases), to inform them of the need to take certain actions or adapt their practices in relation to a medicinal product.

• DHPCs are not replies to enquiries from HCPs, nor are they meant as educational material for routine risk minimization activities.

• Preparation of DHPCs depends on cooperation between the MAH and KPVC.

• DHPC should be approved by KPVC before it is communicated.

• Where there are several MAHs for the same active substance for which a DHPC is to be issued, a single consistent message should normally be delivered.

• Other communication tools and channels may complement a DHPC.

• A DH may be an additional risk minimization measure as part of a risk management plan.

• KPVC may disseminate or request the MAH to disseminate a DHPC in any situation if necessary and should inform other concerned administrations about the approved DHPC.

• DHPC should encourage close monitoring of the safety concern in clinical practice and encourage reporting, and possibly provide information on how to minimize the potential risk.

• After dissemination of the DHPC, MAH should provide or KPVC with confirmations from HCPs that they have received the letter.

• The MAH has submitted to DHPC in a form of one full original hard copy and one soft copy, after approval by or KPVC; the administration will issue an approval letter to MAH.

• The MAH may receive comments from or KPVC to the submitted draft.

• Any significant event or problem occurring during the DHPC dissemination which reveals a need to change the communication or a need for further communication to HCPs, this should be notified in a timely manner to or KPVC to be approved.

• In cases where a medicines authority in any country requests the dissemination of a DHPC for any authorized medicinal product in Kuwait, the MAH should notify KPVC.

• or KPVC may publish the final DHPC on its official link under the MOH website.

• A DHPC may be prepared in the following cases:

✓ New major warnings or precautions for use in the product

investigation is required.

2) Major case: requires fast response within 48 hours and further communication of additional information if further investigation is required.

3) Minor case: response is provided whenever requested after carrying out the necessary investigation.

Who disseminates the safety information?

The information may be disseminated by:

1) Official letters issued by the pharmacovigilance responsible entity.

2) Media (newspapers, news channels, social media, MOH official website…etc.)

Any safety update, which needs to be communicated to HCPs or the public should be approved by the relevant department according to the local regulations and guidelines.

Objectives of safety communication

1. Prevent patient from experiencing adverse reactions.

2. Facilitate changes to attitudes knowledge, perception and practices in relation to use of medicines including self–medications and rational prescribing.

3. Facilitate informed decisions that support risk minimization behavior and safe–use of medicines.

Principles of safety communication

1. The need for communicating safety information should be considered throughout the pharmacovigilance and risk management process, and has to be part of risk assessment.

2. The information in the safety communication must not be misleading and shall be presented objectively.

3. Safety information should not include any material or statement, which might constitute advertising.

4. Safety communication should be tailored to the appropriate audiences (e.g. patients and HCPs) by using appropriate language and taking account of the different levels of knowledge and information needs.

5. Information on risks should be presented in the context of the benefits of the medicine and include available and relevant information on the seriousness, severity, frequency, risk factors, time to onset, reversibility of potential adverse reactions and, if available, expected time to recovery.

6. Where relevant safety communication should be complemented at a later stage with follow–up communication.

7. The effectiveness of safety communication is expected to be as a subjected to regular evaluation.

8. Safety communications should comply with relevant requirements relating to individual data protection and confidentiality unless its public disclosure is necessary for the protection of public health.

9. Any safety update which needs to be communicated to HCPs or public should be approved by KPVC before it is communicated.

10. MAH will notify KPVC of any information which may impact the benefit–risk balance of a medicinal product announced or circulated by any other competent Authority.

11. The MAHwill ensure that information to the public is presented objectively and is not misleading.

12. Whenever a MAH becomes aware that a third party (e.g. scientific journals, learned societies, patients' organizations) intends to issue communication that could potentially impact the benefit–risk balance of a medicinal product authorised in Kuwait, the MAH should inform KPVC and make every effort to share the content of the communications with the relevant authorities.

• Where questions related to individual treatment advice, the patient should be advised to contact HCPs.

6. Risk minimisation measures such as patient alert cards or HCP safety guidance:

○ Any risk minimization measures to be communicated to HCPs or public should be approved by KPVC before it is communicated.

Patient alert card:

○ The aim of this tool should be to ensure that special information regarding the patient's current therapy and its important risks (e.g., potential life–threatening interactions with other therapies) is held by the patient at all times and reaches the relevant HCP when needed.

○ The information should be kept to the minimum necessary to convey the key minimization message(s) and the required action, in any circumstances, including emergency.

○ Ability to carry the patient alert card with ease (e.g. it can be fitted in a wallet) should be a key design feature of this tool.

HCP safety guidance:

○ This is defined as the provision of all the methods, tools and platforms to ensure that all HCPs have timely access to relevant information on safety issues or benefit/risk evaluations of human medicines.

MODULE THIRTEEN:

POST–AUTHORIZATION SAFETY/EFFICACY STUDIES (PASS/PAES)

POST–AUTHORISATION SAFETY/EFFICACY STUDIES (PASS/PAES)

Post–authorisation safety study (PASS) and post authorization efficacy studies (PAES) are studies that are carried out after a medicine has been authorized to obtain further information on a medicine's safety and/or efficacy profiles, or to measure the effectiveness of risk–management measures. Kuwait Pharmacovigilance Risk Assessment Committee (KuPRAC) is responsible for assessing the protocols of imposed PASSs and PAES and for assessing their results.

The purpose of the information in PASSs is to evaluate the safety and benefit–risk profile of a medicine and support regulatory decision–making. They aim to:

• Identify, characterize or quantify a safety hazard.

• Confirm the safety profile of a medicine.

• Measure the effectiveness of risk–management measures.

PASSs and PAESs can either be clinical trials or non–interventional studies, and they can be either voluntary or imposed.

This means that PASS and PAES may be initiated, managed and sponsored by a MAH voluntarily, or pursuant to an obligation imposed by KPVC.

PASS / PAES are clinical trials or non–interventional studies and does not address non–clinical safety studies. A PASS / PAES is non–interventional if the following requirements are cumulatively fulfilled:

• The medicinal product is prescribed in the usual manner in accordance with the terms of the marketing authorizations.

• The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study; and

• No additional diagnostic or monitoring procedures are applied to the patients and epidemiological methods are used for the information.

✓ New data identifying a previously unknown risk or a change in the frequency or severity of a known risk.

✓ Substantiated knowledge that the medicinal product is not as effective as previously considered.

✓ Other safety or efficacy relevant cases.

✓ Ongoing assessment of an important potential risk, for which data available at a particular point in time are insufficient to take regulatory action

○ Content of DHPCs:

✓ Draft DHPC

✓ The dissemination list (general practitioners, specialists, pharmacists, nurses; hospitals/ambulatory care/other institutions as appropriate)

✓ Timetable for disseminating the DHPC (maximum of 15 calendar days is considered appropriate)

✓ Dissemination mechanism

2. Media communications

a. Press communication

○ Press communication includes press releases and press briefings which are primarily intended for journalists.

○ KDFC may send press releases directly to journalists in addition to publishing them on their official website.

○ Press releases that have an impact on the medicine's benefit–risk balance may also be prepared and published by MAH after approval of KPVC.

○ Their press releases may reflect the position of the MAH on a safety topic but also should make reference to any regulatory action taken by the KPVC.

b. Website

○ KPVC and MAH ensure that important safety information published on websites under their control is easily accessible and understandable by the public.

○ Information on websites should be kept up to date, with any information that is out–of–date marked as such or removed.

c. other web–based communications

○ When using newer, more rapid communication channels, special attention should be paid to ensure that the accuracy of the information released is not compromised.

d. Bulletins and newsletter

○ KPVC publishes newsletter every two months to disseminate latest information on the safety and efficacy of pharmaceutical products to patients and HCPs.

e. social media

○ KPVC uses various forms of electronic social media to communicate some safety issues and is continuing to assess additional ways to communicate effectively with the public using these vehicles.

3. Inter–authority communication

• When a medicines authority takes regulatory action on a particular safety concern, KPVC may need to respond to enquiries or communicate on the same issue.

4. Intra–authority communication

○ When one medicinal administration within a sector takes action on a particular safety concern, other administrations may need to respond to enquiries or communicate on the same issue and communicate such safety concern effectively with KPVC.

5. Public enquiries

• Responses should take into account the information, which is in the public domain and include the relevant recommendations to patients and HCPs issued/approved by KPVC.

the total evidence stemming from the 'comparability exercise' and with adequate justification. In those cases, it is considered sufficient when only the most vulnerable patient population and the clinical endpoint is studied. The reason for this is to identify any product related differences. For studies using biosimilars with monoclonal antibodies, for example, it is not necessarily required to use 'overall survival or a 'progression-free survival as end point.

B. Interchangeability

Interchangeability of a medicine refers to a situation where a medicine can be exchanged for another equivalent product (with a proven equivalent efficacy and side-effect) at the patient level.

Robust post-marketing safety monitoring is an important component in ensuring the safety and effectiveness of biopharmaceutical products, including biosimilar and interchangeable products.

Post-marketing safety for interchangeable products should first take into consideration any particular safety or effectiveness concerns associated with the use of the reference product and its class, the proposed interchangeable product in its development and clinical use (if marketed outside Kuwait), the specific condition of use and patient population, and patient exposure in the interchangeability development program. Post-marketing safety monitoring for an interchangeable product should also have adequate PV mechanisms in place. Rare but potentially serious safety risks may not be detected during pre-approval clinical testing because the size of the population exposed likely will not be large enough to assess rare events. In particular cases, such risks may need to be evaluated through post-marketing surveillance or studies. In addition, as with other biopharmaceutical and biological products, KPVC may require a post-marketing study or a clinical trial to evaluate certain safety risks.

Because some aspects of post-marketing safety monitoring are product-specific and dependent upon the risk that is the focus of monitoring, KPVC encourages MAHs to submit a written proposal explaining their approach to post-marketing safety monitoring.

C. Traceability in Seriously or Chronically Ill Patients

Biopharmaceuticals are often used for seriously or chronically ill patients. Undesirable effects Arising from the switching between non-identical medicines should always be evaluated. Of course, biopharmaceuticals also have side effects, sometimes these appear while using the medicine. In other cases, they do not appear until after the treatment. Because of their specific properties biopharmaceuticals can lead to a response of the immune system of a patient. This can have consequences for the safety and efficacy of that medicine. Therefore, during the clinical trials of a biological medicine this is monitored very carefully.

But even after registration, companies are required to develop and implement a pharmacovigilance plan for their biopharmaceuticals. An aspect of this is traceability, so that it is absolutely clear which patient at what time received what medicine. In order to trace which medicine is responsible for the undesirable side effects (e.g. an immune response), the physician needs to know which biological medicine was given and when it was given to the patient. This traceability is an essential requirement for biopharmaceuticals.

The automatic exchanging of different medicines by pharmacists (automatic substitution, resulting from the preference policy) analysis of collected data.

Non-interventional studies are defined by the methodological approach used and not by its scientific objectives. Non-interventional studies include database research or review of records where all the events of interest have already happened (this may include case control, cross-sectional, cohort or other study designs making secondary use of data). Non-interventional studies also include those involving primary data collection (e.g. prospective observational studies and registries in which the data collected derive from routine clinical care), provided that the conditions set out above are met. In these studies, interviews, questionnaires and blood samples may be performed as part of normal clinical practice.

MODULE FOURTEEN: PHARMACOVIGILANCE OF BIOPHARMACEUTICAL PRODUCTS

PHARMACOVIGILANCE OF BIOPHARMACEUTICAL PRODUCTS

Biopharmaceutical products is any pharmaceutical drug product manufactured in, extracted from, or semi-synthesized from biological sources. They are different from totally synthesised pharmaceuticals. They include vaccines, blood, blood components, allergenics, somatic cells, gene therapies, tissues, recombinant therapeutic protein, and living cells used in cell therapy.

Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living cells or tissues. They (or their precursors or components) are isolated from living sources—human, animal, plant, fungal, or microbial. Biological products and biosimilars are registered in Kuwait with special focus on significant challenges with respect to PV.

A biosimilar is defined by the WHO as a bio-therapeutic product (or biopharmaceutical), which is similar in terms of quality, safety and efficacy to an already licensed reference bio-therapeutic (biopharmaceutical) product.

Putting the biopharmaceuticals, biosimilars and pharmacovigilance together has yielded a complex regulatory landscape with wide variations and inconsistencies across countries and markets. It is difficult enough to build and maintain a robust PV program to meet regulatory requirements for small molecule drugs — and yet such programs will not satisfy the requirements for biopharmaceuticals and biosimilars.

Challenges Facing Pharmacovigilance of Biopharmaceutical Products

A. Monoclonal Antibodies

Biosimilars and biopharmaceuticals need specific registration requirements, depending on the type of active substance/compound. Furthermore, in the registration dossier specific additional data need to be included to allow a 'comparability exercise'. For instance, specific requirements exist for biosimilars of biopharmaceuticals consisting of monoclonal antibodies (mAb). However, contrary to what one might expect, it is not necessary for a manufacturer of a biosimilar to demonstrate safety and efficacy in all cases. This is not necessary for every indication or for every phase of treatment (e.g. in oncology in the early stage of the disease as (neo) adjuvant treatment or in the metastatic stage of the disease). An extrapolation of the clinical efficacy and safety data to other indications of the reference antibody is sometimes possible on the basis of the assessment by the regulatory authority (RA) and of

product interchangeably, clinical studies must be provided to the KPVC for assessment. Any adverse events (AE) that may be reported as a results of an interchange shall be investigated by KPVC and recommendation are raised to KuPRAC about any resulting risk measures.

5. Post-approval surveillance for immunogenicity and rare adverse events may be needed and/or required over the long-term, once a biosimilar is on the market. Such monitoring is essential.

Requirements: Reports about immunogenicity and rare adverse effects must be regularly submitted to KPVC along as part of the PSUR. PASS is recommended as an additional evidence-based study.

6. PV Inspection. As guidelines for biopharmaceuticals and biosimilar approvals and PV are continuously evolving internationally. Pharmaceutical companies shall need to stay vigilant so that their PV systems can rapidly and successfully adapt to evolving regulatory criteria. Such system shall always be ready for inspection to ensure fulfillment of PV requirements for biopharmaceuticals and biosimilars.

Requirements: Pharmaceutical companies must always improve their PV systems for biopharmaceuticals and biosimilars. They should be ready for PV inspections by KPVC as per stated Guidelines for Good PV Practice in Kuwait.

Reporting of Undesirable Effects

HCPs will use the ADR reporting form in KuGVP Annex 1 and the quality defects form in KuGVP Annex 2 to report undesirable effects and pharmaceutical manufacturing defects respectively for medicinal and biopharmaceutical products.

Reports on side effects of biopharmaceuticals must always include the brand name, the manufacture's name and the batch number of the given medicine.

Vaccines have their own AE reporting form and HCPs shall use it separately to report suspected adverse reactions to KPVC. Such reports can be filled and submitted online to be evaluated by KPVC and the assessment outcomes shall be directed to the responsible committee at the Ministry of Health. KPVC will evaluate the reported adverse events and present the report with the recommendations to the Vaccine Adverse Event Monitoring committee and to make the appropriate decision (Refer to Annex 8 for VAER form).

Vaccine's pharmacovigilance guidelines have a separate detailed document published along with the Kuwait Pharmacovigilance Practice Guidelines.

Annex 7

: Vaccines ADR Reporting Form

complicates this traceability and because of this is medically undesirable.

D. Pharmacovigilance and Risk Management

Reports on side effects of biopharmaceuticals must always include the brand name, the manufacture's name and the batch number of the given medicine. Therefore, it is essential that all biopharmaceuticals be prescribed using the brand name and not the name of the compound/substance (international non-proprietary name (INN)). This holds true for biosimilars as well. Manufactures are also required to have a risk management plan in place for every biological medicine. Among the reasons for this is the fact that the immune systems of patients may respond differently to different biopharmaceuticals, even to those with the same compound/ substance name. Moreover, biological reference medicines and biosimilars may not be registered for the same indications and may have other dosing regimens or different side effects and, at the end of 2012, the European Commission issued a directive which requires biological products to be identified by brand-name and not by INN.

PV Requirements for Biopharmaceuticals and biosimilars

Companies developing biopharmaceuticals and biosimilars need to be aware of several key issues with respect to biosimilars that will impact their PV programs:

1. Manufacturing methods. The manufacturing process is more complex than for conventional small-molecule drugs. Small differences between manufacturing methods can significantly impact a product's biological properties, purity and clinical activity. Thus, there is no guarantee that the resulting biopharmaceuticals and biosimilar will be comparable or interchangeable.

Requirement: Manufacturing process shall be submitted by the MAH to KPVC and Medicines and Medical Product Registration and Regulatory Administration for every biopharmaceutical or biosimilar product.

2. Product names. Several distinct biosimilars may currently be under development—but because their names are not necessarily distinctive, this is likely to result in traceability issues in the event of an ADR, at least in the short term. Each biopharmaceutical and biosimilar product shall be referred to by their specific brand-names not by their INN or by the reference brand product. This is also particularly important when reporting ADRs.

Requirement: Each biopharmaceutical and biosimilar product shall have its own unique distinctive name and that names of reference biopharmaceutical product cannot be used to refer to their biosimilar counterpart.

3. Biosimilars vs Generic and brand/innovator products. Generic and brand name products can be prescribed interchangeably in most cases. Biosimilars—although comparable to the innovator drugs—cannot. "Automatic" interchangeability would require data showing that a biosimilar produces an equivalent clinical result in any given individual.

Requirement: To use a biosimilar and a biopharmaceutical

information in order to obtain a wider view of the clinical safety profile of an investigational product (IP), and if necessary, to take action on important clinical safety information arising during clinical development. The sponsor is ultimately responsible for the ongoing safety evaluation of the IP, and timely communication of safety information to relevant stakeholders including regulators, institutional review boards (IRB) and other investigators.

In Kuwait, Clinical trials have been recently adopted for the evaluation of safety and efficacy of TPs/MPs and, henceforth, it was necessary to have local regulatory guidelines to locally control and regulate the conduct of clinical research. Sponsors are required, under such guidelines, to report SUSARs to KPVC as soon as possible and in any case, no later than timelines stipulated in the local pharmacovigilance guidelines. This means that sponsors of any clinical research, including regulated clinical trials, have an obligation to report to KPVC, all SUSARs related to IPs (TP/MP) used in the research.

This guidance is adapted from the ICH E6 (R2): Good Clinical Practice (GCP) Guidance which has been developed by the appropriate ICH Expert Working Group and subjected to consultation by the regulatory parties, in accordance with the ICH Process. It serves to clarify the local regulatory requirements in relation to the ICH GCP Guideline.

Scope

This guidance applies to the following types of clinical research conducted in Kuwait, which involves the use of TP/MP:

(a) Regulated Clinical Trials of:

(i) Approved clinical trials on TP

(ii) Approved clinical trials on MP (e.g. Cell, Tissue and Gene Therapy Products; or Complementary Health Products)

(b) Other clinical research not regulated by KDFC, involving the use of TP/MP.

This guidance addresses the type of documents to be submitted, the timelines and the requirements for reporting of safety information in clinical research involving the use of TP/MP. It covers the following:

- Definitions and terminology associated with clinical safety experience
- Standards for expedited reporting: what to report and how to report
- Timelines for expedited reporting;
- Minimum data set forreporting
- Managing blinded therapycases: The treatment in which certain information , such as the type of therapy provided is concealed from the patient or researchers to ensure the integrity of the clinical trial or research study .

This guidance does not cover safety reporting relating to TP/MP that do not have any ongoing clinical trials or other clinical research in Kuwait

Definitions and Terminologies Associated with Clinical Safety Experience

Adverse Event (AE)

Any untoward medical occurrence in a subject administered a TP/MP and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a TP/MP, whether or not considered related to the TP/MP.

وزارة الصحة
قطاع الرقابة الدوائية والغذائية
مكتب الكويت لرقابة اليقظة الدوائية
Ministry of Health
Drug & Food Control Sector
Kuwait Office For Pharmacovigilance Surveillance (KOPS)

Vaccines Adverse Event Reporting Form (VAER)

1. Patient Details:

Name:	Civil ID:		Nationality:
Date of birth:	Gender: ☐ Male ☐ Female		Age at vaccination: ☐ Year ☐ Months ☐ Days
Address:	Phone number:		E-mail:

Pregnant at time of vaccination? ☐ Yes ☐ No ☐ Unknown
If yes, describe the event, any congenital complications, and estimated due date (Trimester):

2. Health Facility (place of vaccination center):

Name:	Type: (Government / Private):	Address:	Phone Number:

3. Vaccine / Vaccination Program:

Name of vaccine	Type of vaccination program (Mandatory / Voluntary)	Date and time of vaccination	Route of administration	Dose (1st, 2nd, etc.)	Batch / Lot number	Expiry date

4. Description of adverse reaction:

Describe the adverse event(s), treatment, and outcome(s), if any: (symptoms, signs, time course, etc.)	Result or outcome of adverse event(s): ☐ Healthcare professional office/clinic visit ☐ Emergency room/department or urgent care ☐ Hospitalization ☐ Duration of hospital: ☐ Hospital name: ☐ Prolongation of hospitalization ☐ Was vaccine received during hospitalization? Yes No ☐ Life-threatening illness (immediate risk of death from the event) ☐ Disability or permanent damage ☐ Patient died ☐ Date of death: (.....) ☐ Congenital anomaly or birth defect ☐ Other:
Past medical history (including: history of similar reactions or other allergies), concomitant medication and other relevant information (e.g., other vaccs.):	
Medical tests and laboratory results related to the adverse event(s): (include dates)	
Has the patient recovered from the adverse event(s)? ☐ Yes ☐ No ☐ Unknown	
Date reaction started:	Date reaction stopped:

5. Reporter data: (All data will be kept confidential)

Name:	Profession/Specialty:	Site:	
Email:	Phone:	Signature:	

Please send this form by email to: ... Or by Whats App to: +965 2661 1616
Note: Identities of reporter, patient and institution will remain confidential

monitoring, consent forms). This is particularly true for reactions, which, in their most severe forms, threaten life or function. Such reactions should be reported promptly to the KPVC at KDFC, MOH, Kuwait.

Therefore, special medical or administrative criteria are needed to define reactions that, either due to their nature ("serious") or due to significant, unexpected information they provide, justify expedited reporting.

As stated in the definition, a serious' adverse event/reaction is one where the patient's outcome ,event out corn or action criteria are associated with events that pose a threat to a patient's life or cause severe harm.. Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardies the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Additionally, to ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe" which are not synonymous, the following note of clarification is provided:

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations

Serious Unexpected Adverse Drug Reaction (SUSAR)

A serious adverse drug reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved TP/MP, local product information leaflet or Investigator's Brochure for a TP/MP that has been approved for marketing).

Standards for Expedited Reporting

What Should Be Reported

Single Cases of SUSARs

All SUSARs for pre-marketed TP/MP (i.e., locally unregistered TP/MP) and marketed TP/MP (i.e., locally registered TP/MP) involved in ongoing clinical research in Kuwait are subjected to expedited reporting. Such expedited safety reports should be sent to the KPVC when the minimum criteria for expedited reporting are met (refer to Section 3.2.3). The source of these expedited safety reports should always be specified.

(a) Locally unregistered TP/MP used as investigational product (IP)

Clinical trials involving locally unregistered TP/MP as IP are regulated by KDFC. All SUSARs on locally unregistered TP/MP involved in such clinical trials are subject to expedited reporting. Safety reports from the following sources should be submitted:

- Any type of clinical investigation, independent of design or purpose (including other protocols with the same investigational TP/MP);
- Cases not reported directly to a sponsor or manufacturer, for example, those found in regulatory authority-generated ADR registries;

Adverse Drug Reaction (ADR)

Any untoward and unintended response in a subject to a TP/MP which is related to any dose of the TP/MP administered to that subject. In other words, a causal relationship between a TP/MP and an adverse event is at least a reasonable possibility.

Unexpected Adverse Drug Reaction

An adverse drug reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved TP/MP, local product information leaflet or Investigator's Brochure for a TP/MP that has been approved for marketing).

Expectedness of an Adverse Drug Reaction

The purpose of expedited reporting is to make regulators, investigators, and other appropriate people aware of new, important information on serious reactions. Therefore, such reporting will generally involve events previously unobserved or undocumented, and a guideline is needed on how to define an event as "unexpected" or "expected" (expected/unexpected from the perspective of previously observed, not on the basis of what might be anticipated from the pharmacological properties of a TP/MP).

As stated in the definition, an "unexpected" adverse reaction is one where the nature or severity of which is not consistent with information in the relevant source document(s). Until source documents are amended, expedited reporting is required for additional occurrences of the reaction.

The following documents or circumstances will be used to determine whether an adverse event/ reaction is expected:

(a) The Investigator's Brochure will serve as the source document for a TP/MP that is not yet approved for marketing in Kuwait.

(b) The local product information leaflet or the Investigator's Brochure for a TP/MP that has been approved for marketing in Kuwait.

(c) Reports which add significant information on specificity or severity of a known, already documented serious ADR constitute unexpected events.

For example, an event more specific or more severe than described in the Investigator's Brochure would be considered "unexpected". Specific examples would be acute renal failure as a labelled ADR with a subsequent new report of interstitial nephritis; or hepatitis with a first report of fulminant hepatitis.

Serious Adverse Event or Adverse Drug Reaction

A serious adverse event or adverse drug reaction is any untoward medical occurrence that at any dose:

(a) results in death,

(b) is life-threatening*,

(c) requires inpatient hospitalization or prolongation of existing hospitalization,

(d) results in persistent or significant disability/incapacity, or

(e) is a congenital anomaly/birth defect.

*Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it were more severe.

Seriousness of an Adverse Event or Adverse Drug Reaction

During clinical investigations, adverse events may occur which, if suspected to be TP/MP-related (adverse drug reactions), might be significant enough to lead to important changes in the way the TP/MP is developed (e.g., change in dose, population, needed

MODULE FIFTEEN:

EXPEDITED SAFETY REPORTING REQUIREMENTS FOR THERAPEUTIC PRODUCTS and MEDICINAL PRODUCTS USED IN CLINICAL TRIALS

This guidance also outlines the expedited safety reporting requirements for therapeutic products and medicinal products used as clinical research materials in clinical research that is not regulated by KDFC

EXPEDITED SAFETY REPORTING REQUIREMENTS FOR THERAPEUTIC PRODUCTS and MEDICINAL PRODUCTS USED IN CLINICAL TRIALS

Introduction

Purpose

The purpose of this document is to provide guidance to industry on the expedited reporting of serious, unexpected, adverse drug reactions (SUSARs) related to therapeutic products (TP) and medicinal products (MP) used as investigational products (IP) in clinical research, including regulated clinical trials.

An "investigational product" (IP) is defined as a TP/MP or a placebo that is to be tested or used as a reference in a clinical trial.

Background

When a TP/MP is under clinical development, there is limited safety data surrounding its use. This is particularly so in the early stages of clinical trials and prior any marketing experience of the product. It is essential to acquire well-timed and relevant safety

no standard are international nomenclature. The expression 'reasonable causal relationship' is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship.

Other Observations

There are situations in addition to single case reports of "serious" adverse events or reactions that may necessitate rapid communication to the KPVC ; appropriate medical and scientific judgement should be applied for each situation. In general, information that might materially influence the benefit–risk assessment of a TP/MP or that would be sufficient to consider changes in TP/MP administration or in the overall conduct of a clinical investigation represent such situations. Examples include:

(a) For an "expected," serious ADR, an increase in the rate of occurrence which is judged to be clinically important.

(b) A significant hazard to the patient population, such as lack of efficacy with a TP/MP used in treating life–threatening disease.

(c) A major safety finding from a newly completed animal study (such as carcinogenicity).

Reporting Time Frames

Fatal or Life–Threatening SUSARs

Certain ADRs can be alarming enough to warrant immediate notification to regulators , particularly in countries where the TP/MP , its indication , formulation , or target population are not yet approved for marketing . Such reports may prompt considerations of suspension or other restrictions on a clinical investigation program, particularly in cases involving fatal or life –threatening events. in

. , programme.

The KPVC should be notified as soon as possible but no later than 7 calendar days after first knowledge by the sponsor that a case qualifies, followed by as complete a report as possible within 8 additional calendar days. This report may include an assessment of the importance and implication of the findings, including relevant previous experience with the same or similar TP/MP. Subsequent follow–up reports should be submitted as it becomes available.

All Other SUSARs

SUSARs that are not fatal or life–threatening must be filed as soon as possible but no later than 15 calendar days after first knowledge by the sponsor that the case meets the minimum criteria for expedited reporting. Follow–up reports should be submitted as it becomes available.

Minimum Criteria for Reporting

Information for final description and evaluation of a case report may not be available within the required time frames for reporting outlined above. Nevertheless, for regulatory purposes, initial reports should be submitted as soon as possible and within the prescribed time, as long as the following minimum criteria are met:

- An identifiable patient.
- A suspect TP/MP.
- An identifiable reporting source.
- Event or outcome that can be identified as serious and unexpected.
- There is a reasonable suspected causal relationship.

Follow–up information should be actively sought and submitted

- Overseas spontaneous reports. Please refer to Section 3.2.3 to ensure that the minimum criteria are met for regulatory reporting.

(b) Locally registered TP/MP used as investigational product

For regulated clinical trials on locally registered TP/MP:

- If the locally registered TP/MP is used as a test product, local andoverseas reports of SUSARs arising from that same clinical trial protocol conducted in Kuwait should be submitted.
- If the locally registered TP/MP is used as a reference (i.e., comparator), only local reports of SUSARs arising from that same clinical trial protocol should be submitted.

Any additional information may be requested as needed.

For clinical research not regulated by KDFC but involves the use of locally registered TP/MP as IP, only local reports of SUSARs arising from that same clinical trial protocol conducted in Kuwait should be submitted.

(c) TP/MP used as auxiliary product

An "auxiliary product" (AP) is defined as a TP/MP used for the needs of a clinical trial as described in the protocol, but not as an investigational product. These Include, for example: rescue medication, challenge agents, MPs used to assess end–points in the clinical trials, and MPs used for background treatment.

For regulated clinical trials and other clinical research not over seen by the KDFC , sponsors are required to submit all local SUSARS related to the use of the auxiliary TP / MP to KPVC. This submission should be made irrespective of the registration status of the auxiliary TP / MP as specified in the research protocol .

Note: KDFC reserves the right to request SAE reports for overseas clinical trials if the same trials are to be conducted in Kuwait .

It should be noted that expedited reporting would not normally be required in the following situation :

- Adverse events or adverse drug reactions that are serious but expected
- Serious adverse events from clinical investigations that are determined to be underplayed to the study product, whether expected or not.
- Non–serious adverse drug reactions, regardless of whether they are expected or notwhether
- Adverse events associated with placebo

Causality Assessment

Causality assessment is required for clinical investigation cases. All cases judged by either the reporting HCP or the sponsor as having a reasonable suspected causal relationship to the TP/MP qualify as ADRs.

Adverse event reports associated with marketed TP/MP (spontaneous reports) usually imply causality. However, for the purposes of regulatory reporting, if a spontaneous report initially lacks sufficient detail to permit rational assessment of causality by the HCP or sponsor, the report (even if serious in nature), may be submitted to KPVC only after proper causality assessment has been made by a HCP or the sponsor based on updated information.

Many terms and scales are in use to describe the degree of causality (attributability) between a TP/MP and an event, such as certainly, definitely, probably, possibly or likely related or not related. Phrases such as "plausible relationship," "suspected causality," or "causal relationship cannot be ruled out" are also invoked to describe cause and effect. However, there is currently

efficacy endpoint in a

clinical investigation, the integrity of the clinical investigation may be compromised if the blind is broken. Under these and similar circumstances, it may be appropriate to reach agreement with the KPVC in advance concerning serious events that would be treated as disease–related and not subjected to routine expedited reporting.

Miscellaneous Issues

Products with More Than One Presentation or Use

To prevent ambiguities and uncertainties , any ADR that qualifies for expedited reporting associated with a specific product presentation(such as dosage form, formulation , or delivery system) . Or particular product use (e. g. For a specific indication or population) should be reported or referenced in regulatory filings across all related product presentations and uses. pr andIt is not uncommon for pharmacologically active compound to be studied or marketed in multiple dosage forms or delivery systems (e. g. ,oral, IM, IV, topical). These different formulations may exhibit significant differences in their clinical safety profiles. Similarly , the same product may be used for different indications or patient populations(such as single vs. Chronic administration) , which can also influence safety expectations . Therefore , the concept of "expectedness "may vary depending on the specific product or usage context. Separate investigator's Brochures may be warranted and used accordingly. However , such documents are expected to cover ADR informations that applies to all affected product presentations and uses. When relevant , separate discussions of pertinent product–specific or use specific safety information will also be included .

It is recommended that any ADRs that qualify for expedited reporting observed with one product dosage form or use be cross referenced to regulatory records for all other dosage forms and uses for that product. This may result in a certain amount of over–reporting or unnecessary reporting in obvious situations (for example, a report of phlebitis on IV injection sent to authorities in a country where only an oral dosage form is studied or marketed). However, underreporting is completely avoided.

Post–study Events

Although such information is not routinely sought or collected by the sponsor, serious adverse events that occur after the patient has completed a clinical study (including any protocol–required post–treatment follow–up) will possibly be reported by an investigator to the sponsor. Such cases should be regarded for expedited reporting purposes as though they were study reports. Therefore, causality assessment and determination of expectedness are needed for a decision on whether or not expedited reporting is required.

Informing Investigators and Ethics Committees (Ec)\

Institutional Review Boards (Irb) Of New Safety Information

In general, the sponsor of a study should amend the Investigator's Brochure as needed, so as to keep the description of safety information updated. Sponsors should refer to the current safety reporting requirements of the IRB.

Annex 8: CIOMS–I Format

as it becomes available.

How To Report

The CIOMS–I form (Appendix 1) is a widely accepted standard for expedited adverse event reporting. However, no matter what the form or format used, it is important that certain data elements described in Appendix 2, when available, be included in any expedited report (although some items may not be relevant depending on the circumstances).

It is recommended that the description for the SUSARs be reported using MedDRA (Medical Dictionary for Regulatory Activities), which is a standardized medical terminology developed by ICH to classify adverse event information associated with the use of biopharmaceuticals and other medical products.

All reports must be sent to the KPVC (KDFC), and other official parties requiring them (e.g., Investigators and Institutional Review Boards). Please refer to Appendix 3 for a summary of the safety reporting requirements for clinical trials of TP/MP.

For All clinical research whether regulated or not regulated by KDFC, the expedited safety reports should be submitted via email to adr_reporting@moh.gov.kw

Managing Blinded Therapy Cases

When the sponsor and investigator are blinded to individual patient treatment (as in a double–blind study), the occurrence of a serious event requires a decision on whether to open (break) the code for the specific patient. If the investigator breaks the blind, then it is assumed the sponsor will also know the assigned treatment for that patient. Although it is advantageous to retain the blind for all patients prior to final study analysis, when a serious adverse reaction is judged reportable on an expedited basis, it is recommended that the blind be broken only for that specific patient by the sponsor even if the investigator has not broken the blind. It is also recommended that, when possible and appropriate, the blind be maintained for those persons, such as biometrics personnel, responsible for analysis and interpretation of results at the study"s conclusion .

Maintaining blinding under the described circumstances presents several disadvantages that out weigh the potential benefits . Retaining the blinding , especially when using a placebo or comparator (typically a marketed product) , can lead to unnecessary case filings . m pr. When the blind is eventually opened, which may be many weeks or months after reporting to regulators, it must be ensured that company and regulatory databases are revised. If the event is serious, new, and possibly related to the TP/MP, then if the Investigator's Brochure is updated, notifying relevant parties of the new information in a blinded fashion is inappropriate and possibly misleading. Moreover, breaking the blind for a single patient usually has little or no significant implications for the conduct of the clinical investigation or on the analysis of the final clinical investigation data.

For events where the treatment blind has been broken and reveals placebo, and no expedited report has been filed to the KPVC yet, expedited safety reporting is not required. On the other hand, if a report has already been submitted and subsequently, the blind is broken, the KPVC must be updated on this new information by sending the safety report and highlighting this information for the database to be updated.

However, when a fatal or other "serious" outcome is the primary

Daily dose and regimen (specify units – e.g., mg, ml, mg/kg)
Route of administration
Starting date and time of day
Stopping date and time, or duration of treatment
Other Treatment(s)
For concomitant TP/MP (including non-prescription/OTC TP/MP) and non- TP/MP product therapies, provide the same information as for the suspected product.
Details of Suspected Adverse Drug Reaction(s)
Full description of reaction(s) including body site and severity, as well as the criterion (or criteria) for regarding the report as serious should be given. In addition to a description of the reported signs and symptoms, whenever possible, attempts should be made to establish a specific diagnosis for the reaction.
Start date (and time) of onset of reaction Stop date (and time) or duration of reaction Dechallenge and rechallenge information
Setting (e.g., hospital, out-patient clinic, home, nursing home)
Outcome: information on recovery and any sequelae; what specific tests and/or treatment may have been required and their results; for a fatal outcome, cause of death and a comment on its possible relationship to the suspected reaction should be provided. Any autopsy or other post-mortem findings (including a coroner's report) should also be provided when available. Other information: anything relevant to facilitate assessment of the case, such as medical history including allergy, drug or alcohol abuse; family history; findings from special investigations.
Details on Reporter of Event (Suspected ADR)
Name Address
Telephone number Profession (specialty)
Administrative and Sponsor/Company Details
Source of report: spontaneous, clinical investigation (to provide details), literature, or other
Date event report was first received by sponsor/manufacturer
Country in which event occurred
Type of report filed to authorities: initial or follow-up (first, second, etc.) Name and address of sponsor/manufacturer/company
Name, address, telephone number and fax number of contact person in reporting company or institution
• Clinical trial application/reference number – for KDFC
Sponsor/manufacturer's identification number for the case (this number must be the same for the initial and follow-up reports on the same case)
EXPEDITED SAFETY REPORTING REQUIREMENTS FOR THERAPEUTIC PRODUCTS and MEDICINAL PRODUCTS USED IN CLINICAL TRIALS
The information provided in this Appendix is only a summary. Please read the entire guidance.
Annex 10: Summary of Expedited Reporting Requirements (Clinical Trials)
Investigational TP/MP
1. Locally unregistered
2. Locally registered:
• Regulated clinical trials: (Used as test product) in Kuwait (Used as reference or comparator) in Kuwait
• Clinical research not regulated by KDFC: Local SUSARs arising from the protocol ongoing in Kuwait
Auxiliary TP/MP
Local SUSARs arising from the protocol ongoing in Kuwait


CIOMS FORM
SUSPECT ADVERSE REACTION REPORT
I. REACTION INFORMATION
II. SUSPECT DRUG(S) INFORMATION
III. CONCOMITANT DRUG(S) AND HISTORY
IV. MANUFACTURER INFORMATION

Annex 9: Data Elements for Inclusion in Expedited Reports of Serious Adverse Drug Reactions

The following list of items has its foundation in several established precedents, including those of CIOMS-I, the WHO International Drug Monitoring Centre, and various regulatory authority forms and guidelines. Some items may not be relevant depending on the circumstances. The minimum information required for expedited reporting purposes is: an identifiable patient, the name of a suspect TP/MP, an identifiable reporting source, and an event or outcome that can be identified as serious and unexpected, and for which there is a reasonable suspected causal relationship. Attempts should be made to obtain follow-up information on as many other listed items pertinent to the case.

Patient Details
Initials
Other relevant identifier (clinical investigation number, for example) Gender
Age and/or date of birth Weight
Height
Suspected TP/MP(s)
Brand name as reported
International Non-Proprietary Name (INN) Batch number
Indication(s) for which suspect TP/MP was prescribed or tested
Dosage form and strength

Nature of Report	Expedited Reporting?	Timeframe of Report	Preferred Format	Other Documents	Party Responsible for Reporting to KDFC
Serious and Unrelated to TP/MP	NO	Not Applicable			
Serious and Related and Expected	NO	Not Applicable			
Serious and Related and Unexpected			CIOMS-I	Where applicable: • Dear HCP Letter • Company's comments	Sponsor
(i) Death* /Life-threatening events	YES	• Initial report by 7 calendar days • Follow-up report as complete a possible within 8 additional calendar days • Subsequent follow-up reports Adhey become available			
(ii) All other events		• Initial report 15 calendar days • Follow-up reports As they become available			

* Note: The investigator should supply KDFC as well as the IRB and Sponsor with any additional requested information

will be well coordinated and vaccines will be effectively monitored for safety. This will contribute to assessing risks, benefits and effectiveness of vaccines thus minimizing harm and risks while maximizing known benefits.

An effective and well-functioning AEFI surveillance system will eventually boost trust, public confidence and will also help improve the quality of the immunization programme in the long run. It is therefore essential that all stakeholders like PHA, DRA, vaccine manufacturers, laboratories and healthcare providers make concerted efforts to provide documented evidence through an effective AEFI surveillance system. This will ensure that the best immunization services are being provided to the community including effective monitoring and response to AEFIs.

This manual was developed in line with the strategic objective 4 of the Global Vaccine Action Plan (GVAP) 2011 – 2020 (Strong immunization systems that are an integral part of a well-functioning health system) to ensure capacity for vaccine safety activities, including capacity to collect and interpret safety data, with enhanced capacity in countries that introduce newly developed vaccines.

It is envisaged that this document will guide stakeholders at all levels to be involved in and take part in the strengthening of the AEFI surveillance system in Kuwait.

Acknowledgements

"Kuwait Ministry of Health acknowledge the World Health Organization for the technical support and guidance offered for developing this work".

Glossary

Immunity	The ability of the human body to tolerate the presence of material 'indigenous' to the human 'body' (self) and to eliminate 'foreign' (non-self) material. This discriminatory ability provides protection from infectious diseases, since most microbes are identified as foreign by the immune system.
Immunization anxiety-related reaction	An AEFI arising from anxiety about the immunization.
Immunization error-related reaction	An AEFI that is caused by inappropriate vaccine handling, prescribing or administration and thus by its nature is preventable.
Immunization safety	The process of ensuring the safety of all aspects of immunization, including vaccine quality, adverse events surveillance, vaccine storage and handling, vaccine administration, disposal of sharps and management of waste.
Immunization safety Surveillance	A system for ensuring immunization safety through detecting, reporting, investigating, and responding to AEFI.
Injection safety	The public health practices and policies dealing with various aspects of the use of injections (including adequate supply, administration and waste disposal) so that the provider and recipient are not exposed to avoidable risks of adverse events (e.g. transmission of infective pathogens) and creation of dangerous waste is prevented. All injections, irrespective of their purpose, are covered by this term (see definition of safe injection practices).
Non-serious AEFI	An event that is not 'serious' and does not pose a potential risk to the health of the recipient. Non-serious AEFIs also should be carefully monitored because they may signal a potentially larger problem with the vaccine or immunization or have an impact on the acceptability of immunization in general.
Safe injection practice	Practices which ensure that the process of injection carries the minimum of risk, regardless of the reason for the injection or the product injected.

KPVC-KDFC-MOH-Kuwait
MODULE SIXTEEN:
GUIDANCE ON VACCINE SAFETY MONITORING and SURVEILLANCE OF ADVERSE EVENTS FOLLOWING IMMUNIZATION

Overview

Vaccines are largely used to protect individuals particularly children from acquiring deadly infectious diseases which are preventable. Such products are relatively safe and can rarely cause adverse events following immunization (AEFI). A proportion of these may occur during immunization campaigns. Therefore, monitoring vaccine safety is of paramount importance in a healthcare system of any country.

AEFI surveillance system focuses on vaccine safety and it utilizes tools, guidelines and procedures geared to assure public health protection through the use of vaccines with proven safety profile. Kuwait envisions a vaccine safety system with national dedicated vaccine pharmacovigilance capacity, with designated staff, with clear mandates and well- defined structures and roles.

By establishing coordinating mechanisms between Public Health Administration (PHA) and Drug Regulatory Authority (DRA), and KPVC for sharing vaccine safety data, as well as engaging healthcare providers at all levels, the AEFI surveillance system

intended effect

Vaccine reaction	An event caused or precipitated by the active component or one of the other components of the vaccine. It may also relate to a vaccine quality defect.
Vaccine safety	The process, which maintains the highest efficacy of and lowest adverse reaction to a vaccine by addressing its production, storage and handling. Vaccine safety is a part of immunization safety.

Abbreviations

KPVC		Kuwait Office for Pharmacovigilance Surveillance
ADRs	–	Adverse Drug Reactions
AEFI	–	Adverse Events Following Immunization
AESI	–	Adverse event of special interest
BCG	–	Bacillus Calmette–Guerin CSF – Cerebrospinal fluid
DIO	–	District Immunization Officer DT–Diphtheria Tetanus
DTaP	–	Diphtheria Tetanus Acellular Pertussis vaccine
DTwP	–	Diphtheria Tetanus Whole Cell Pertussis vaccine
DTPa–HepB–Hib	–	Diphtheria Tetanus Acellular Pertussis, Hepatitis B Hemophilus influenza vaccine
EPI	–	Expanded Programme on Immunization
GVAP	–	Global Vaccine Action Plan
DRA	–	Drug Regulatory Authority Administration
Hep B	–	Hepatitis B Vaccine
Hib	–	Hemophilus influenza type b vaccine IPV–Inactivated Polio Vaccine
MMR	–	Measles Mumps Rubella
MOH	–	Ministry of Health
NIP	–	National Immunization Program
NITAG	–	National Immunization Technical Advisory Group
OPV	–	Oral Polio Vaccine
PHA	–	Public Health Administration
SIO	–	State Immunization Officer
VAPP	–	Vaccine Associated Paralytic Poliomyelitis
VPD	–	Vaccine Preventable Disease
WHO	–	World Health Organization

Introduction

Vaccines are biological substances that are administered to individuals to elicit immunity (protection) against specific diseases. Such products are formulated together with adjuvants and/or excipients, and like all medical products, may cause adverse events following their administration to some individuals. Despite the fact that such adverse events following immunization (AEFIs) are mostly mild and very rarely severe, measures still need to be put in place to monitor and prevent their occurrence and take appropriate regulatory action(s) on the products themselves if needed.

A good vaccine is one that provides the best protection and gives rise to minimum adverse events. AEFIs can arise through a variety of reasons: these include events that could be inherent to the vaccine product, or related to the quality, or immunization error or immunization anxiety or could be coincidental. A robust AEFI surveillance system in a country will help authorities to detect, manage and prevent AEFIs.

In Kuwait, the Ministry of Health (MOH) operates the National Immunization Program (NIP) through the Public Health Administration (PHA). PHA is responsible for setting up policy guidelines and standards for selection, supply and utilization of vaccines in the country.

Likewise, the National Drug Regulatory Authority – DRA in cooperation with KPVC, monitor the safety of all medical products including vaccines. The DRA uses spontaneous pharmacovigilance system to collect any suspected adverse drug reactions experienced by patients. The DRA is also responsible for authorization of marketing all medicines in Kuwait. All vaccine manufacturers are required by law to register their products before supplying and distributing them in the country.

Reporting of AEFI and subsequent investigation may trigger regulatory action including withdrawing the marketing authorization of a vaccine, instructing vaccine manufacturers to change their product labels, restricting the use of vaccines to specific patient groups or recalling defective vaccine batches from the market.

The overall goal of this manual is the protection of the health and wellbeing of the population particularly infants, children and pregnant women and the general population who depend on vaccines to protect them from serious vaccine preventable diseases (VPD). This manual outlines the processes and procedures to be followed by healthcare providers in reporting, documenting and preventing AEFIs, as well as the roles and responsibilities of stakeholders responsible for the planning and delivery of immunization programs in Kuwait in close partnership. The manual also outlines the surveillance system and provide tools and procedures needed to report and manage AEFIs. An understanding of the types of AEFIs, investigation techniques, specimen collection, managing AEFIs and communication including communicating with the media, are also described in this document.

It is anticipated that healthcare providers will read and use this manual and thus appropriately manage, report, and prevent AEFIs in the country. The manual will also bring together stakeholders and allow for networking and improved collaboration in the process of detecting, analyzing and preventing AEFIs.

Basic Concepts of Vaccines and Adverse Events Following Immunization

Vaccines

A vaccine is a biological product that stimulates and strengthens the immune response against specific vaccine –preventable disease (VPD) produces and enhances immunity to the particular Vaccine Preventable Disease (VPD) for which it is targeted. A vaccine contains the disease–causing microorganism or virus, or a portion of it, in a form that is incapable of causing

Adverse Event Following Immunization (AEFI)	Any unwanted medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavorable or unintended sign, abnormal laboratory finding, symptom or disease.
Adverse Events of Special Interest (AESI)	A pre–identified and predefined medically–significant event that has the potential to be causally associated with a vaccine product that needs to be carefully monitored and confirmed by further specific studies.
Causal association	A cause–and–effect relationship between a causative (risk) factor and an outcome. Causally associated events are also temporally associated (i.e. they occur after vaccine administration), but events which are temporally associated may not necessarily be causally associated.
Causality assessment	In the context of AEFI surveillance, it is a systematic review of data about AEFI case(s) to determine the likelihood of a causal association between the event and the vaccine(s) received.
Cluster	Two or more cases of the same or similar events related in time, geography (place), and/or vaccine administered. AEFI clusters are usually associated with a particular supplier/provider, health facility, and/or a vial of vaccine or a batch of vaccines.
Coincidental events	An AEFI that is caused by something other than the vaccine product, immunization error or immunization anxiety.
Contraindications	A situation where a particular treatment or procedure, such as vaccination with a particular vaccine, must not be administered for safety reasons. Contraindications can be permanent (absolute), such as known severe allergies to a vaccine component, or temporary (relative), such as an acute/ severe febrile illness.
Serious AEFI	An event that results in death, is life–threatening, requires in–patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. Any medical event that requires intervention to prevent one of the outcomes above may also be considered as serious.
Severe vaccine reaction	It refers to the intensity of vaccine reactions. A severe reaction refers to the high grade intensity of its grading such as mild, moderate and severe. Severe reactions may include both serious and non–serious reactions.
Signal (safety signal)	Information (from one or multiple sources) which suggests a new and potentially causal association, or a new aspect of an own association, between an intervention and an adverse event or set of related adverse events, that is judged to be of sufficient likelihood to justify the verification process.
Surveillance	The continuing, systematic collection of data those are analyzed and disseminated to enable decision–making and action to protect the health of populations.
Trigger event	A medical incident following immunization that stimulates a response, usually a case investigation.
Vaccine	A biological preparation that improves immunity to a particular disease. In addition to the antigen, it contains multiple components (excipients) and each component may have unique safety implications.
Vaccine pharmacovigilance	The science and activities relating to the detection, assessment, understanding and communication of AEFI and other vaccine– or immunization–related issues, and to the prevention of untoward effects of the vaccine or immunization.
Vaccine product–related reaction	An AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product, whether the active component or one of the other components of the vaccine (e.g., adjuvant, preservative or stabilizer).
Vaccine quality defect related reaction	An AEFI that is caused or precipitated by a vaccine that is due to one or more quality defects of the vaccine product, including its administration device as provided by the manufacturer (e.g., manufacturing errors).
Vaccination failure	Vaccination failure may be defined on the basis of clinical endpoints or immunological criteria where correlates or surrogate markers for disease protection exist. Primary failure (e.g., lack of sero–conversion or sero–protection) needs to be distinguished from secondary failure (waning immunity). Vaccination failure can be due to: (i) failure to vaccinate, i.e., an indicated vaccine was not administered appropriately for any reason; or (ii) because the vaccine did not produce its

the actual disease. It is usually made from either live attenuated or inactivated (killed) forms of the microbe, or from its toxin or one of its surface proteins. New technologies include viral vectors, RNA, DNA and recombinant proteins.

Primary components of vaccines

Vaccines may be monovalent or multivalent (polyvalent). A monovalent vaccine contains a single strain of a single antigen/immunogen (e.g., measles vaccine), whereas a polyvalent vaccine contains two or more strains/serotypes of the same antigen/immunogen (e.g., t OPV and IPV each of which contain three attenuated polio virus types).

Combination (or combined) vaccines contain two or more different antigens (e.g., DTwP, DTPa–HepB–Hib). The potential advantages of combination vaccines include reduction in the cost and difficulty of shipping and storing and administering multiple vaccines, avoiding multiple injections, reducing the cost of extra health–care visits, improving timeliness of vaccination, and facilitating the addition of new vaccines into immunization programmes.

There is no evidence that the administration of several antigens in combined vaccines increases the burden on the immune system, which is capable of responding to millions of antigens at a time. Combining antigens usually does not increase the risk of adverse reactions and can lead to an overall reduction in adverse reactions. For instance, it can decrease the number of anxiety–related reactions and the chances of immunization error–related reactions.

Other components of vaccines

In addition to the primary antigen(s), vaccines contain small quantities of other substances. Sometimes AEFI can result from one of the other substances. They include,

Adjuvants: Substances added to a vaccine to enhance the immune response, thus making it possible, in some cases, to reduce the amount of antigen (immunogen) per dose or the total number of doses needed to achieve immunity.

Antibiotics: Antibiotics are used during the manufacturing phase to prevent bacterial contamination of the tissue culture cells in which the viruses are grown.

Preservatives: These are chemicals (e.g., thiomersal, phenol derivatives) that are added to killed or subunit vaccines in order to inactivate viruses, detoxify bacterial toxins, and remain in the vial to prevent serious secondary infections in multi–dose vials as a result of bacterial or fungal contamination after they are opened.

Stabilizers: Stabilizers are used to help the vaccine maintain its effectiveness during storage.

Contraindications and precautions to vaccination

A contraindication to vaccination is a rare characteristic in a recipient that increases the risk of a serious adverse reaction if the vaccine is given. Ignoring contraindications can lead to avoidable vaccine reactions. One of the most serious reactions following vaccination is anaphylaxis which is the only contraindication applicable to subsequent doses of the same vaccine. Most contraindications such as severe acute illnesses (e.g., acute respiratory tract infection) or treatment with steroids are temporary and the vaccination can be administered later. These are called temporary or relative contraindications.

Precautions, in contrast, are events or conditions that should be considered in determining if the benefits of the vaccine outweigh the risks (especially if they would– be recipient is immunocompromised or pregnant). Precaution mentioned in

on an individual's response and thus increase the risk of adverse vaccine reactions. Insufficient inactivation of wild-type vaccine agent (e.g. wild polio virus) during the manufacturing process or contamination introduced during the manufacturing process could cause the vaccine quality defect-related reactions.

B. Vaccine reactions by seriousness and frequency

Most vaccine reactions are minor and subside on their own. Serious reactions are very rare and, in general, do not result in death or long-term disability. Table 2.2 describes the frequency of occurrence of reported adverse events.

Table 2.2 Frequency of occurrence of reported adverse reactions

Frequency category	Frequency in rate	Frequency in %
Very common	≥ 1/10	≥ 10%
Common (frequent)	≥ 1/100 and < 1/10	≥ 1% and < 10%
Uncommon (infrequent)	≥ 1/1000 and < 1/100	≥ 0.1% and < 1%
Rare	≥ 1/10 000 and <1/1000	≥ 0.01% and < 0.1%
Very rare	< 1/10 000	< 0.01%

Common, minor vaccine reactions

They are caused when recipient's immune system reacts to antigens or the vaccine's components (e.g., aluminum adjuvant, stabilizers or preservatives) contained in the vaccine. Most AEFI are minor and settle on their own. Minor AEFI could be local or systemic. Local reactions include pain, swelling and redness at injection site.

Systemic reactions include fever irritability and malaise. A successful vaccine reduces these reactions to a minimum while producing the best possible immunity.

Rare, more severe (and serious) vaccine reactions

They are caused by the body's reaction to a particular component in a vaccine. The term "severe" is used to describe the intensity of a specific event (as in mild, moderate or severe); the event itself, however, may be of relatively minor medical significance. Severe AEFI can be disabling but are rarely life threatening. Some examples are seizures, thrombocytopenia, Hypotonic Hyporesponsive Episodes (HHE) and prolonged crying etc.

Severe AEFI are considered serious by definition if they:

- Result in death
- are life-threatening
- require in-patient hospitalization or prolongation of existing hospitalization
- result in persistent or significant disability/incapacity
- are a congenital anomaly/birth defect

All serious AEFI should be reported, investigated and the causality assessed.

Febrile seizures are uncommon in children younger than six months or older than six years. If such seizures occur with in these age groups, a comprehensive evaluation is warranted to identify any underlying causesNote that children less than six months or over six years of age are unlikely to have febrile seizures. If this happens, a thorough investigation should be conducted to determine the underlying cause(s).

C. Immunization error-related reactions

The term "Immunization" as used here means the "use" of a vaccine for the purpose of immunizing individuals. "Use" includes all processes that occur after a vaccine product has left the manufacturing/packaging site – i.e. handling, prescribing and administration of the vaccine.

Immunization error-related reactions are usually preventable, and they divert attention from the benefit of the immunization

product labeling are sometimes mistakenly interpreted as contraindication, leading to missed opportunities for vaccination. Precautions stated in the product labelling may sometimes be inappropriately interpreted as contraindications, resulting in missed opportunities to vaccinate.

Adverse Events Following Immunization (AEFI)

An adverse event following immunization is any untoward medical occurrence (unfavorable or unintended sign, abnormal laboratory finding, symptoms or disease) which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. Reported adverse events can either be true adverse events – i.e., resulting from the vaccine or immunization process – or coincidental events that are not due to the vaccine or immunization process but are temporally associated with immunization. The five categories of AEFI as defined by CIOMS and WHO are described in table 2.1

Table 2.1 Cause-specific categorization of AEFI

Cause-specific type of AEFI	Definition
Vaccine product-related reaction	An AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product.
Vaccine quality defect-related reaction	An AEFI that is caused or precipitated by a vaccine that is due to one or more quality defects of the vaccine product, including its administration device as provided by the manufacturer. (e.g., Manufacturing error)
Immunization error-related reaction	An AEFI that is caused by inappropriate vaccine handling, prescribing or administration and thus by its nature is preventable.
Immunization anxiety-related reaction	An AEFI arising from anxiety about the immunization.
Coincidental event	An AEFI that is caused by something other than the vaccine product, immunization error or immunization anxiety, but a temporal association with immunization exists.

Vaccine reactions

Based specifically on cause, seriousness and frequency, vaccine reactions may be grouped into two broad categories:

A. Cause-specific vaccine reactions:

- vaccine product-related reaction and
- vaccine quality defect-related reaction

B. Vaccine reactions by seriousness and frequency:

- common or minor reactions.
- rare or serious reactions.

C. Immunization error-related reaction.

D. Immunization anxiety-related reaction.

E. Coincidental Events

A. Cause-specific vaccine reactions

Vaccine product-related reaction: This is an individual's reaction to the inherent properties of the vaccine, even when the vaccine has been prepared, handled and administered correctly. Most often the exact mechanism of a vaccine product-related reaction is poorly understood. The reaction may be due to an idiosyncratic immune mediate reaction (e.g. anaphylaxis) or to replication of the vaccine-associated microbial agent (e.g. vaccine-associated poliomyelitis following OPV which contains attenuated live virus).

Vaccine quality defect-related reaction: This is a due to a defect in a vaccine (or its administration device) that occurred during the manufacturing process. Such a defect may have an impact

	Incorrectly sterile technique or inappropriate procedure with a multi-dose vial	Infection at/beyond the site of Injection

Coincidental events

An event may occur coincidentally with immunization and sometimes be falsely attributed to the vaccine i.e. a chance temporal association is falsely attributed to immunization. Such temporal associations are inevitable especially in a mass immunization campaign.

Vaccines are normally administered early in life when infections and other illnesses are common, including manifestations of underlying congenital or neurological conditions. It is, therefore, possible to encounter many events, including deaths that can be falsely attributed to vaccine through a chance association.

For example, incidence of sudden infant death syndrome (SIDS or "cot death") peaks around the age of early childhood immunization. Consequently, many SIDS cases will occur in children who have recently been immunized. However, several well designed studies have shown that the association of SIDS and immunization is coincidental and not causal.

Coincidental adverse events may be predictable. The number of events to be expected depends upon the size of the population and the incidence of disease or death in the community. Knowledge of these background rates of disease and deaths, particularly age-specific disease incidence rates, allows estimation of the expected numbers of coincidental events.

Key AEFI teminology

Cluster of AEFI

A cluster is defined as two or more cases of the same or similar event, which is related in time and has occurred within the same district or geographical unit or associated with the same vaccine, same batch number administered or same vaccinator.

Signal

Information that arises from one or multiple sources which suggests a new potentially causal association or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verification process

Prevention and management of AEFI

General principles of prevention and management of AEFI

Vaccines are very rarely contraindicated. However, it is important to check for contraindications to avoid serious reactions. For example, a vaccine is contraindicated if there is a history of anaphylaxis to a given vaccine or its components in previous vaccinations.

Vaccine anaphylaxis is very rare. However, it is recommended that preparedness to provide emergency treatment for anaphylaxis is necessary in all clinic settings. All immunization providers need to be trained and develop competence in recognizing and managing anaphylaxis and have epinephrine (adrenaline) available.

For parents, advice should be given on managing the common minor reactions, in addition to instructions on seeking proper medical care if there are more severe symptoms. Such action will help to reassure parents about immunization and prepare them for common reactions.

Antipyretic drugs, in a recommended dosage and schedule, can be given as recommended by the prescriber (or manufacturer) to

programme. Some of them are described in Table 2.3. The identification and correction of these errors in a timely manner are, therefore, of great importance.

D. Immunization anxiety-related reactions

Individuals and groups can become stressed and may react in anticipation to, and as a result of, any kind of injection. This reaction is unrelated to the constituents of the vaccine product. Fainting (vasovagal syncope or syncope) is relatively common, particularly in children over five years of age and among adolescents. Some children who faint may have a syncopal hypoxic convulsion. Hyperventilation as a result of anxiety about the immunization leads to specific symptoms such as light-headedness, dizziness, tingling around the mouth and in the hands. This is also common in mass vaccination campaigns.

Younger children may have breath-holding and vomiting as a common symptom of anxiety. Young children may also scream or run away to avoid the injection.

Some individuals may have needle-phobia. In group immunization, mass hysteria is possible, especially if one or more of the vaccinees is observed by others to faint or have some other reaction such as itching, weakness of limbs and so on.

Sometimes a fainting episode can be misdiagnosed as anaphylaxis. Careful observation and clinical judgement is necessary to differentiate.

An immunization error-related reaction may sometimes lead to a cluster of events associated with immunization. These clusters are usually linked to a particular provider or health facility, or even to single or multiple vials of vaccine that have been contaminated or inappropriately prepared. For instance, freezing vaccine during transport may lead to an increase in local reactions. The details of an approach to investigating AEFI clusters are described later.

Table 2.3 Immunization error-related reactions

Immunization error		Related reaction
Error in vaccine handling	Exposure to excess heat or cold as a result of inappropriate transport, storage or handling of the vaccine (and its diluents where applicable)	Systemic or local reactions due to changes in the physical nature of the vaccine, such as agglutination of aluminium-based excipients in freeze-sensitive vaccines
	Use of a product after the expiry date	Failure to protect against, or loss of potency or/and viability of an attenuated product
Error in vaccine prescribing or	Failure to adhere to a contraindication	Anaphylaxis, disseminated infection with anLAV
non-adherence to recommendations for use	Failure to adhere to vaccine indications or prescription (dose or schedule)	Systemic and/or local reactions, neurological, muscular, vascular or bony injury due to incorrect injection site, equipment or technique
Error in administration	Use of an incorrect diluent or injection of a product other than the intended vaccine	Failure to vaccinate due to incorrect diluent, reaction due to inherent properties of whatever was administered other than the intended vaccine or diluent

requires a case–based assessment where the risk of the vaccine is balanced against the potential benefits. The use of live vaccines in pregnancy is a good example of this.

To avoid/minimize immunization error, the following should be observed.

- It is both important and necessary to maintain the cold chain at all levels.
- Vaccines must be reconstituted only with the diluents supplied by the manufacturer.
- Reconstituted vaccine should be maintained in the recommended cold chain and used within six hours after reconstitution (or as directed by the manufacturer); it must be discarded at the end of each immunization session and should never be retained.
- Other than vaccines, no other drugs or substances should be stored in the refrigerator of the immunization center.
- Immunization workers must be adequately trained and closely supervised to ensure that proper procedures are followed.
- Careful epidemiological investigation of an AEFI is needed to pinpoint the cause and to correct immunization practices.
- Prior to immunization, adequate attention must be given to contraindications.

Follow–up and corrective actions following immunization error–related reactions should be based on the findings of the investigation. Depending on the nature of the immunization error, these actions can be both general (e.g. training and awareness) and specific (e.g. strengthening cold chain maintenance if the problem found to be related to cold chain issues). Continued monitoring and supportive supervision can help to minimize these adverse events.

Prevention and management of immunization anxiety–related reactions

Training and awareness to enable health staff to identify and manage medical emergencies appropriately is important. Fainting does not require any clinical management beyond placing the patient in a recumbent position.

Syncopal hypoxic convulsions are short–lived generalized tonic–clonic seizures which can be managed by keeping the patient lying down and securing the airway by placing the patient on one side to prevent aspiration should the patient vomit. The seizure will end spontaneously but, if prolonged or focal, further investigations may be required.

The likelihood of fainting should be anticipated when immunizing older children. It can be reduced by minimizing stress among those awaiting injection, through short waiting times, comfortable room temperatures, preparation of the vaccine outside the recipient's line of vision, and privacy during the procedure.

Sometime, cases with hysteria may even require hospitalization and can cause public concern. Clear explanations about the immunization and a calm, confident delivery will decrease the level of anxiety about the injections and thus reduce the likelihood of an occurrence.

Careful observation and clinical judgement to differentiate between anaphylaxis and syncope is necessary. However, an accidental administration of a single intramuscular dose of adrenaline to a person experiencing only syncope (fainting) following vaccination dose not compromise the effectiveness or safety of the vaccine. dose of adrenaline (intramuscularly) to a vaccine with only syncope does not harm the vaccine.

ease pain and reduce fever (when fever occur). However, it is important to advice against overuse of paracetamol or any other antipyretic drug as overdosing may harm the vaccine. Extra fluids need to be given to children with fever. For a local reaction, a cold cloth applied to the site may ease the pain.

Using local remedies for any serious vaccine reaction can risk the health and life of the vaccines and is strongly discouraged. Early medical care by a qualified clinician will minimize any unwanted outcome and ensure early recovery, and may also save lives.

Prevention and management immunization error–related reactions

Immunization error–related reactions are preventable and identification and correction of these errors in a timely manner are important.

Prior to the introduction of auto–disable (AD) syringes, the most common immunization error was an infection as a result of a non–sterile injection because of contamination of the vaccine or diluent vial or the injecting device (syringe and/or needle). The infection could manifest as a local reaction (e.g. suppuration, abscess) or a severe systemic reaction (e.g. sepsis, toxic shock syndrome). In addition, there was the perception of a risk linking immunization with blood borne infections. Nevertheless, one needs to consider infection that can occur in cases of mass vaccination or in disaster situations, particularly if there is a shortage of supplies or problems with logistics. This can be avoided by proper planning and preparedness of programme managers.

The symptoms arising from an immunization error may help to identify the likely cause. For instance, children immunized with contaminated vaccine (usually the bacterium Staphylococcus aureus) become sick within a few hours with an injection site reaction (local tenderness, redness and swelling) and then develop systemic symptoms (vomiting, diarrhea, high temperature, rigors and circulatory collapse). Bacteriological examination of the vial, if still available, can confirm the source and type of infection.

Sterile abscesses, while rare (~1 per 100 000 doses) are local reactions from aluminum–containing vaccines, especially DTP. They, along with other local reactions, are more likely to occur if there is inadequate shaking of the vaccine before use, superficial injection and use of vaccine that had been frozen. Contamination of vaccine or injection equipment can lead to a bacterial abscess. For BCG vaccine, injection abscess can result from improper technique of injection (subcutaneous rather than intradermal injection).

Subcutaneous used for vaccines , insulin , or blood thinners , goes deeper and needle is inserted at a slightly deeper angle (45–90) degrees. Intradermal used for allergy tests and tuberculosis test, the needle is inserted at very shallow angle (10 –15) degrees.

Ignoring contraindications may lead to serious vaccine reactions and is considered an immunization error. The immunization teams should be clearly aware of such contraindications and any precautions. Any uncertainty should be referred to a higher level – a programme manager, pediatrician or physician. However, it is equally important not to overreact to concerns of false contraindications as this may lead to missed opportunities for vaccination, reducing coverage and thereby increasing the risk of disease in both individuals and the community.

Health–care workers also need a clear understanding of contraindications and precautions. Precautions are not contraindications, but a decision on whether to vaccinate

The objectives of AEFI surveillance are to:

- Rapidly detect and respond on time to the occurrence of an AEFI
- Identify, correct and prevent immunization error related reactions.
- Facilitate AEFI causality assessment.
- Recognize clustering or unusually high rates of AEFI, including those that are mild and/or "expected".
- Identify potential safety signals (including previously unknown vaccine reactions), and generate hypotheses that may require further investigation.

Figure 5 AEFI surveillance cycle

Generate information with which to effectively communicate with vaccine recipients /parents, the community, media and other stake holders, regarding the safety of vaccines used in Kuwait.

Vaccine recipients themselves and/ or parents of immunized infants/children, health care providers at immunization facilities and staff in immunization facilities are most likely to recognize or detect AEFIs when they first occur. Any AEFI case that is therefore notified to any health care provider working within the health care system, should be reported to the District Immunization Officer (DIO) using the standard reporting form (Annex 8) through the fastest means possible. The DIO should in fact be informed of any Serious AEFI cases by telephone and this should be followed up by completion and submission of the reporting form.

The reportable AEFI include serious AEFI, AEFI as a result of potential immunization errors, clusters, AEFI causing parental or community concern, those that are unexpected, and any that are known but occur with unexpected frequency. Table 4.1 below provides case definitions of commonly reportable AEFI. However, it needs to be stressed that health workers should report all cases that are notified to them.

All vaccination staff must be able to recognize AEFIs and report them. However, accurate diagnosis of AEFIs requires staff training and education. HCPs also have the additional responsibility to manage AEFI and, if necessary, refer such patients for any required treatment.

Stakeholders in AEFI reporting and investigation; their roles and responsibilities

A. Subnational Stakeholders

In Kuwait, the subnational stakeholders in AEFI reporting and investigation are

1. Vaccine recipients' /parents'/ guardian
2. Health workers

Management of suspected anaphylaxis or collapse after vaccination

Sudden and severe events occurring post–vaccination, especially syncope, are frequently reported as anaphylaxis. However, anaphylaxis following vaccination is very rare and the risk (in general) is 1 2 cases per million vaccine doses.

The onset of anaphylaxis can occur after several minutes (> 5 minutes) but rarely up to two hours following vaccination. The progression of symptoms is rapid and usually involves multiple body systems, almost always with skin involvement (generalized erythema and/or urticaria), as well as signs of upper and/or lower respiratory tract obstruction and/or circulatory collapse. In young children (though anaphylaxis occurs at any age) limpness, pallor or loss of consciousness may reflect hypotension. In general, the more rapid the onset, the more severe is the reaction. Events happen without warning. Emergency equipment must be immediately at hand whenever immunizations are given. All vaccinators must be familiar with the practical steps necessary to save life following anaphylaxis. Each vaccinating center must have an emergency kit with adrenaline. The expiry date of the adrenaline should be written on the outside of the emergency kit and the whole kit should be checked three or four times a year. It is important to note that health–care workers may misdiagnose syncope attack as anaphylaxis and administer adrenaline as a part of the emergency care. If the correct dose of adrenaline according to age and weight is administered via the intramuscular route, no harm is likely to occur. However, an overdose, by administering intravenous or intracardiac adrenaline or by repeated administration, may cause harm.

Table 3 Conditions that may be mistaken for anaphylaxis post–immunization

Diagnosis	Onset, symptoms and signs
Vasovagal event	Symptoms are usually immediate (< 5minutes) and commence during the injection process. No skin rash, bradycardia not tachycardia, no respiratory involvement, spontaneous resolution when prone.
Hypotonic hyporesponsive episode	Onset 2 4 hours post–immunization, sudden pallor, hypotonia and unresponsiveness, usually in an infant. No skin rash, respiratory or cardiovascular compromise.
Seizure	Onset usually at least 6 8 hours post–vaccination with a killed vaccine. Sudden unresponsiveness usually with tonic–clonic movement, usually febrile, no cardiovascular compromise, no respiratory compromise unless apnea or aspiration.
Aspiration of oral vaccine (e.g. OPV or rotaviral vaccine)	Immediate respiratory symptoms (cough, gagging, stridor or wheeze) during administration, usually in infant. No skin rash or cardiovascular compromise.
Somatic conversion symptoms	Immediate or delayed respiratory symptoms, syncope, neurological symptoms without objective respiratory or neurological signs.
Severe coincidental diseases	Usually due to coincidental – unrecognized congenital heart disease or occult infections. May have respiratory or cardiovascular compromise but there are usually symptoms, signs or investigations to indicate alternate cause.
Iatrogenic – error related	Immediate toxic drug reaction with symptoms and signs due to drug toxicity. Reported with immunization related errors which have resulted from inadvertent administration of a muscle relaxant or insulin.

AEFI surveillance in Kuwait

Surveillance for adverse events following immunization (AEFI) is an integral part of the National Immunization Program (NIP), and reinforces the safe use of all vaccines in the country while also helping to rmaintain public confidence in its immunization program. As shown in figure 4.1, this is done systematically

Hypotonic, Hyporesponsive Episode (HHE or shock-collapse)	Event of sudden onset occurring within 48 [usually less than 12] hours of vaccination and lasting from one minute to several hours, in children younger than 10 years of age. All of the following must be present: • limpness (hypotonic) • reduced responsiveness (hypo responsive) • pallor or cyanosis – or failure to observe/ recall	Mainly DPT, rarely others
Injection site abscess	Fluctuant or draining fluid-filled lesion at the site of injection. Bacterial if evidence of infection (e.g. purulent, inflammatory signs, fever, positive bacterial culture), Sterile abscess if no evidence of bacterial infection on culture. Sterile abscesses are usually due to the inherent properties of the vaccine.	All injectable vaccines
Lymphadenitis (includes suppurative lymphadenitis)	Either at least one lymph nodes enlarged to >1.5 cm in size (one adult finger width) or a draining sinus over a lymph node. Almost exclusively caused by BCG and then occurring within 2 to 6 months after receipt of BCG vaccine, on the same side as inoculation (mostly axillary).	BCG
Persistent inconsolable screaming	Inconsolable and continuous crying lasting 3 hours or longer accompanied by high-pitched screaming.	DPT, Pertussis
Seizures	Occurrence of generalized convulsions that are not accompanied by focal neurological signs or symptoms. Febrile seizures: if temperature elevated >100.4 ^{0}F or 38 ^{0}C (rectal) Afebrile seizures: if temperature is normal	All, especially Pertussis, Measles
Sepsis	Acute onset of severe generalized illness due to bacterial infection and confirmed, if possible by positive blood culture.	All injectable vaccines
Severe local reaction	Redness and/or swelling centered at the site of injection and one or more of the following: Swelling beyond the nearest joint Pain, redness and swelling of more than 3 days and interfering with daily activities Requires hospitalization. Local reactions of milder intensity occurring commonly, which and trivial and do not need to be reported	All injectable vaccines
Toxic shock syndrome (TSS)	Abrupt onset of fever, vomiting and watery diarrhea within a few hours of immunization. Often leading to death within 24 to 48 hours.	All injectable vaccines
Vaccine Associated Paralytic Poliomyelitis (presenting as AF	Acute onset of flaccid paralysis and neurological deficits, compatible with diagnosis of poliomyelitis, with isolation of vaccine virus and absence of wild virus in stool	OPV

Serious AEFI: Any AEFI causing
Death
Hospitalization
Disability, congenital anomaly

3. The District Immunization Officer (DIO)

B. National stakeholders in AEFI investigation

In Kuwait, the national stakeholders are

1. Kuwait Public Health Administration, Medicines and Medical Product Registration and Regulatory Administration, and KPVC

2. National AEFI committee

Field investigation of AEFI

The ultimate goal of an AEFI field investigation is to find the cause of the reported AEFI(s) and prevent recurrence. Remedial action needs to be taken promptly for immunization error related AEFI. Even if the cause cannot be identified or the cause of the event was due to some other reason, the fact that staff had investigated the incident itself will increase public confidence in the immunization programs.

The purpose of investigating AEFI cases is

• clarify the outcome of the medical incident comprising the AEFI.

• To ascertain the particulars, circumstances and procedures around the vaccine used to immunize the affected recipient. Most importantly, identify any potential vaccine related link to the given AEFI.

• To examine the operational aspects of the programme. Even if an event seems to be vaccine product induced or coincidental.

• To determine whether a reported event was a single incident or one of a cluster and if it is a cluster, confirm that the suspected immunizations were indeed given and the individual vaccines that were used.

• To determine whether unimmunized people are experiencing the same medical incidents.

• To confirm the reported diagnosis and/or propose other possible diagnoses as well as.

Table 4 Case definitions of the reportable adverse events.

AEFI	Case definition	Vaccine
Anaphylaxis	A clinical syndrome characterized by sudden onset (within one hour), rapid progression of signs and symptoms involving multiple (more than two) organ systems – Skin – urticaria (Hives), angioedema (swelling of face/body), Respiratory – persistent cough, wheeze, stridor, Cardiovascular – low blood pressure (hypotension) or reduced circulation (fast weak pulses), Gastrointestinal – vomiting, abdominal pain.	All
BCG Omitis/ Osteomyelitis	Inflammation of the bone with isolation of Mycobacterium bovis BCG strain.	BCG
Disseminated BCG infections	Widespread infection occurring within 1 to 12 months after BCG vaccination and confirmed by isolation of Mycobacterium bovis BCG strain. Usually in immuno-compromised individuals.	BCG
Encephalopathy	Acute onset of major illness characterized by • Depressed or altered level of consciousness and/or distinct change in behaviour lasting for one day or more	Measles, Pertussis
Fever	The fever can be classified (based on rectal temperature) such as • Mild fever: 38 to 38.9 ^{0}C • Moderate fever: 39 to 40.4^{0}C • Severe fever: >40.5^{0}C	All

and send the same to the following National levels

a. The Public Health Administration (PHA)

b. The Medicines and Medical Product Registration and Regulatory Administration

c. Kuwait Office for Pharmacovigilance Surveillance (KPVC)

2. Warranting a detailed investigation if it is a Serious AEFI (death, hospitalization, significant disability, life threatening, or congenital anomaly/ birth defect)
or is a part of a cluster, or
a part of a group of events above expected rate/ severity, or
a suspected signal,
He should discuss the same with the local experts (or technical expert committee if available) and plan for a detailed field investigation. Prior to initiating an investigation, he should e-mail or send the report (Annex 8) to the national levels as described above

If the DIO and the experts feel that the investigation can be done locally, they can visit the patient and locality and initiate the detailed investigation along with appropriate members of the local health care team. If however assistance is required for investigation from the national level, the PHA/ Medicines and Medical Product Registration and Regulatory / KPVC should be contacted and assistance for an investigation solicited. National investigations should be led by a team from the national AEFI committee, supported by the PHA, and KDFC. During field investigations, the AEFI investigation form (Annex 10) should be used as a guide to collect suitable information.

The investigators should seek to document any deficiencies found in a generic way and suggest corrective measures, and not single out any individuals to blame. While an individual may have been at fault, it is more effective to focus on identifying the problems in the system and procedures leading to the event. This is more effective in avoiding similar errors in the future, than blaming or punishing individuals. Such an approach is essential to ensure that AEFI reporting is encouraged for the ultimate benefit of all patients and the immunization program as a whole. It is also much more likely to improve system performance.

The specific activities conducted at this point will include the following

• Confirm the AEFI, assign a unique report identifying number, complete All details in the AEFI reporting form (in case any of them were missing when reporting) and initiate AEFI investigation.

• Convene a local expert (or technical expert task force if available) planning meeting prior to the investigation.

• With the experts, the DIO should visit as required the patient, the care provider(s) and the hospital; interview relevant stakeholders (parents, health worker, treating doctor, vaccine supply focal person); and conduct the investigation of the AEFI case.

• Complete the AEFI investigation form (Annex 10).

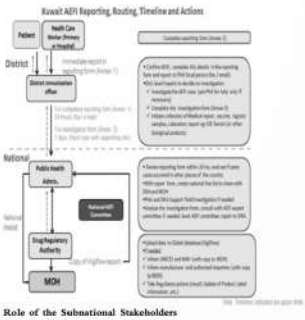
• Initiate collection of medical reports, a post-mortem report (if available), vaccine vials (if necessary, and kept under cold chain conditions), logistic samples, and laboratory reports e.g., CSF, Serum (or other biological products).

Generally, before the AEFI is attributed to any vaccine product related problems, the investigator should rule out any potential immunization errors and obvious coincidental events, as these

Other severe and unusual events

No time limit, if they are thought by health workers or the public to be related to immunization

Figure 6 Kuwait AEFI Reporting routing, timeline and actions



Role of the Subnational Stakeholders

Role of the Vaccine recipients /Parents

At the time of immunization, it is important for health workers to sensitize the vaccine recipients/ parents about expected events such as fever and pain at injection site etc. following immunization. Parents should be advised about simple home remedies (e.g. correct positioning of the child when sleeping, increasing intake of fluids, sponging, breast feeding, antipyretics etc.) should such events occur; however, at the same time, Vaccine recipients /Parents should also be instructed to report severe expected events (e.g. very high fever, not responding to anti pyretic) or other unusual events to the health worker if they occur.

Role of the health worker

If home remedies do not work, vaccine recipients themselves and/ or parents or guardians of immunized infants/children usually report the event to HCPs at immunization or other health care facilities. Sometimes staff in these facilities recognize or detect AEFIs when they first occur. All such AEFI cases brought to the notice of the health care worker or detected by the worker should be reported to the District Immunization Officer (DIO) using the standard reporting form (Annex 8).

Thus, the main role of the health worker is to provide primary medical care and report the basic details about the notified adverse event to the district by completing the AEFI reporting form (preceded if appropriate with a preliminary report by telephone if it is a serious event).

Role of stakeholders at the district and the state level

When an AEFI report (Annex 8) is received by the DIO, he should review the report and determine if the reported AEFI case meets the criteria required for a detailed investigation. If necessary, he should contact the primary reporter and visit the locality of the event and interview relevant stakeholders for additional information. The case may be considered

1. Not warranting detailed investigation if it is a minor AEFI and NOT serious AEFI, he should indicate this on the reporting form

after program errors etc.) and ensuring that they are implemented.

The DRA or the national pharmacovigilance center is responsible to share the information with the global community by uploading the information into the Global pharmacovigilance database – VigiBase®, maintained by the Uppsala Monitoring Centre under the WHO International Drug Monitoring Program – using information available in the completed case investigation form (Annex 10). The DRA can also provide information on the vaccines, and lots distributed in the country when requested by the AEFI committee, PHA and MOH. The DRA can also provide additional information on AEFI from other sources.

Table 5 Steps in an AEFI investigation

Step	Description	Actions
1	Confirm information in report	☐ Obtain patient's medical file (or other clinical record) ☐ Check patient details and event from medical file and document the information. ☐ Obtain any details missing from AEFI Report Form.
2	Investigate and collect data. About the patient:	☐ Immunization history ☐ Previous medical history, including prior history of similar reaction or other allergies ☐ Family history of similar events.
	About the event:	☐ History, clinical description, any relevant laboratory results about the AEFI and diagnosis of the event ☐ Treatment, whether hospitalized and outcome.
	About the suspected vaccine(s):	☐ Conditions under which the vaccine was shipped, its present storage condition, state of vaccine vial monitor and temperature record of cold chain, etc. ☐ Storage conditions of vaccine at all levels before it arrived at health facility (Vaccine Vial Monitor) ☐ The date of manufacture, lot and batch numbers of vaccine and diluent
	About other people:	☐ Whether others received the same vaccine and developed illness and whether they need to be included in the investigation. ☐ Whether others had similar illness (may need working case definition); if so exposure of cases to suspect vaccine(s) ☐ Discuss with other immunization service providers to obtain an idea of the local standard practices
3	Assess the service provided	☐ Vaccine storage (including open vials), distribution and disposal
	By asking about	Diluents storage and distribution Reconstitution (process and time kept) Use and sterilization of syringes and needles

are more common. Therefore, the investigation should first try to rule out immunization errors related to the storage, handling, reconstitution or administration of vaccines.

Attention can then focus on other events. Details of coincidental events can be determined by reviewing hospital admissions for similar conditions during the same period and verifying their vaccination status. A quick review of the morbidity pattern of similar conditions in the previous years can also indicate if the event is a part of a similar pattern observed in the previous years. The medical literature can also help, as the estimated background incidence of various conditions may be available in the published domain.

Once the investigation is initiated, the district investigator should inform the PHA and the KDFC on the status and progress of the investigation. This is necessary, as a national level officer should be the spokesperson of the government to the media and the public about the investigation. The completed case investigation form (Annex 10) along with the supporting documents such as the medical report, vaccine, logistic samples, laboratory reports e.g., CSF, Serum (or other biological products) should be sent to the PHA/ KDFC within 7 days of initial case notification. If this is not possible, at least a progress report should be made with details on when the completed report can be expected.

It is important to remember that in case national assistance for an investigation is requested, more accurate information can be obtained by a single coordinated investigation rather than a piecemeal investigation. Table 5 summarizes the key steps in an AEFI investigation.

Role of the National stakeholders

When the national AEFI focal point of the PHA receives the AEFI reporting form, it is essential to review it in the context of other reported AEFI received from all parts of the country, particularly in the same period of time, to see if this report may constitute a signal. This can be done by appending data into a national AEFI linelist (Annex 9) with information from the reporting form and reviewing the data or running analyses as needed. If similar cases were reported earlier, it is essential to determine if an epidemiological linkage or other pattern can be identified if there is one. The need for technical or operational assistance for the investigation has to be assessed. Expert advice can be sought from the National AEFI Committee at this point.

The KDFC,, PHA and the National AEFI Committee play a key role in supporting the immunization program for AEFI investigation and causality assessment. They also provide recommendations to the MOH on vaccines based on their causality assessment findings. The KDFC and the PHA together coordinate and provide technical/logistical support to conduct the meetings of the National AEFI Committee (Figure 6). Based on causality assessment and National AEFI Committee recommendations, KDFC along with KPVC shall take the appropriate regulatory actions including but not limited to recall of the vaccine or the affected batches, update of product labelling information (addition of precaution, contraindication, restriction of use to special population or other sections), withdrawal of product authorization or registration.

National AEFI Committee assigns the responsible entity for providing all feedback to the relevant stakeholders within 7 days of causality assessment or potential signals determined by data review/analysis at the national level. National AEFI Committee also responsible on following up on the actions recommended at the national level (e.g. change in logistics, cold chain, training

Common exposures among the cases can be identified by reviewing:

- all data on vaccine(s) used (name, lot number, etc.),
- data on other people in the area (also non-exposed); and
- any potentially coincident factors in the community.

When an AEFI cluster has been identified, the cause-specific definitions provide a framework for investigation and causality assessment. Usually, the key considerations will be to investigate the possibility of an immunization error vaccine or a quality defect. The possibility of immunization error must be considered when events cluster in one setting without a similar change in frequency in other settings using the same vaccine. On the other hand, if an increased frequency of events is reported from multiple settings the possibility of a quality defect must be considered more strongly. Clusters of fainting after immunization are well-recognized immunization anxiety-related reactions during immunization programmes targeting adolescent girls.

For relatively new vaccines or established vaccines used in new target populations, a cluster may represent a previously unrecognized vaccine product-related reaction. Knowledge of the background incidence of events which may occur in causal relationship with a vaccine is therefore essential for assessing a cluster in terms of the strength of the signal it may provide.

Interpretation of results from AEFI clusters

If all cases received vaccines from the same health worker/facility and there are no other cases, an immunization error is likely. If all cases received the same vaccine or lot, and there are no similar cases in the community, a problem with the vaccine or the respective lot is likely. If the event is a known vaccine reaction but is found to occur at an increased rate, an immunization error or a vaccine problem are likely causes. Finally, if cases in the unvaccinated population are occurring at about the same rate/proportion as among the vaccinated from the same area in the same age group, the adverse event was probably coincidental (Figure 7).

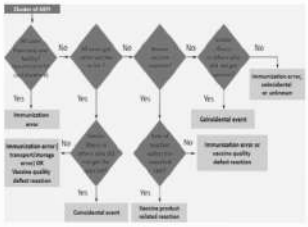


Figure 7Identifying cause of AEFI cluster

Laboratory testing of specimens

Laboratories have an important role in AEFI case diagnosis and case management. They also have a key role in testing the quality of the samples of vaccines and the logistics used.

Laboratory tests for the purpose of AEFI case diagnosis and case management conducted on the patient (eg blood, urine, radiology, ECG etc) are based on the provisional case diagnosis and recommendations of the treating physician. These tests are

		Number of immunizations (greater than normal?) Details of training in immunization practice, supervision and vaccinator(s)
	Observing the service in action:	Refrigerator – what else is stored (note if similar containers stored next to vaccine vials which could be confused); which vaccines/diluents stored with other drugs; whether any vials have lost their label Immunization procedures (reconstitution, drawing up vaccine into the syringe, injection technique, safety of needles and syringes; disposal of opened vials) If any open vials look contaminated
4	Formulate a working hypothesis:	On the likely possible cause(s) of the event.
5	Test working hypothesis:	Does case distribution match working hypothesis? Laboratory tests may help (see text).
6	Conclude investigation	Reach a conclusion on the cause. Complete AEFI Investigation Form Take corrective action and recommend further action

Investigation of AEFI with fatal outcome

In the event of an identified death following immunization, the field investigation has to be initiated immediately. Within 24 hours the death should be notified to all administrative levels concerned, including the District immunization officers, the PHA and the DRA. Investigation of the case should be carried out by a team of experts from relevant areas, including clinicians. As a death causally linked to immunization is extremely rare (anaphylactic reactions being one of the only 2–3 known events), major programmatic errors may be involved and thus an investigation to rule those out has to be conducted without any delay to prevent additional cases. As any fatality temporally linked to a vaccination can cause panic, the public will also demand an immediate explanation.

A post-mortem is preferred and recommended following all deaths suspected to be caused by a vaccine / immunization. However, the decision to conduct a post- mortem should be within the religious, cultural acceptance and legal framework of the local population.

Investigating AEFI clusters

A cluster of AEFI is defined as two or more cases of the same adverse event related in time, place or vaccine administration. Apart from checking on these three factors, the investigator should look for AEFI occurring in similar age groups and populations with genetic predisposition or disease.

Cluster investigation begins by establishing a case definition for the AEFI and related circumstances and by identifying all cases that meet the case definition. The investigator should demarcate the cluster and identify common exposure factors within the cluster.

Cluster identification (i.e. cases with common characteristics) is done by gathering details (when and where) of vaccines administered. This can be achieved by collecting and recording

- detailed data on each patient,
- programme-related data (storage and handling, etc.); and
- immunization practices and the relevant health workers' practices.

diagnosis. Samples for both toxicology and pathological examination should be sent to the reference laboratories identified by NIP as early as possible to avoid loss of biological samples due to decomposition. It is essential to ensure that a detailed patient's history is included in the autopsy form and submitted to the autopsy team to help them look for any underlying pathologies.

Guide to human specimen sample collection

The details of the type of AEFI, the tests to be performed, the specimens to be collected, the process of storage and shipment and the labs are outlined in Table 6

Table 6 Type of AEFI, the tests to be performed, the specimens to be collected, storage and shipment procedures and the labs conducting tests

Suspected AEFI	Diagnosti c Method	Specimen	When collect	Preparation, Storage and shipment
Injectionite abscesses	Microsco py and Culture sensitivity	Pus Swab	At contact	Use Transport media to transport Pus swabs to the next level
BCG lymphadeni tis	Microsco py, Culture and serology	Blood, LN Aspirate or Biopsy and Suspected Vial Batch	At Contact	Wrap in leak proof and water proof container transport. Vaccine sample should be transported in reverse cold chain
Collapse/ shock-like state	Microsco py, Culture and serology	Blood and Suspected Vial Batch	At Contact	* Blood smear * Blood sugar tests at site * Ensure aseptic for blood collection for culture
Convulsion s/or Seizures	Microsco py, Culture and antigen detection	Collect CSF From affected cases	At Contact	* Ensure aseptic techniques of lumbar puncture * Never use vials that contained antibiotics * Sugar and cell counts should be done at site * Transport to referral laboratory immediately
Encephalitis	Microsco py, Culture and antigen detection	Collect CSF From affected cases	At Contact	* Ensure aseptic techniques of LP * Never use vials that contained antibiotics * Sugar and cell counts should be done at site Transport to referral laboratory immediately
Death	Serology	(1) Blood (2) Vial Batch	Immediat e	* Never use vials that contained antibiotics * Ensure aseptic retrieval [illegible] * Transport suspected vial batch in reverse cold chain

Vaccines and logistics

Vaccines and logistics samples from the site and the distribution point(s) should be collected as soon as possible and kept in cold chain. They should be sent to the laboratory for testing only on the recommendation of the local experts.

Testing of vaccines and logistics should be requested on a clear suspicion and not as routine and never before the working hypothesis has been formulated (Table 5.2). Determining which samples to send for testing (if any) depends on the working hypothesis for the cause of the event(s). If the used vial of suspect vaccine is available, it should be separately labelled and sent along with unused vials of the same lot.

The DIO will be responsible for the packaging, cold chain maintenance and shipment of samples in the correct temperature to the national laboratory at Medicines and Medical Product Registration and Regulatory laboratory. ALL specimens sent to the lab should be accompanied by a laboratory request form (Annex 11).

The laboratory will process the specimens and send the laboratory results to National NIP Manager and DRA Director General. Laboratories will also send a copy of the laboratory

considered "routine" and should be performed in clinical laboratories. The results of these tests are important to confirm the case diagnosis and arrive at the "valid diagnosis" for assessing causality as described in section 7.2.

Laboratory testing of samples of vaccines and logistics are rarely necessary. It is not mandatory following an AEFI, particularly if the cause is evident such as a coincidental event or a program error. However, laboratory testing of vaccines and logistics are at times required to confirm or rule out the suspected cause.

In the context of AEFI, sometimes additional specific tests on the patient, vaccines and logistics as outlined below may also be necessary to confirm the cause. The testing of additional specimens includes:

Human specimens

- Histopathology, body fluids etc. can be done at laboratories identified and approved by the MOH
- Autopsy specimens at approved and accredited government forensic laboratories as identified by MOH

Vaccines and logistics

- Vaccines and diluents for sterility and chemical composition.
- Syringes and needles for sterility.

Only the appropriate specimen in the correct quantity required for the investigation should be collected. Laboratory specimens should be stored and transported as recommended and accompanied by clear supporting documents, reasons for specimen collection and any additional information required by the investigators. In case laboratory investigation is required, AEFI laboratory request form (Annex 11) should be completed and sent with any specimen collected.

- Laboratory testing is not a routine requirement but may be a part of an investigation.
- Laboratory testing is costly and is recommended only when it is necessary.
- However, securing samples (vaccine vials, syringes, blood etc.) and storing them correctly is important because later investigation may require them.

Therefore, proper storage and transport of suspected samples is recommended.

Human Specimens

It is difficult to generalize what specimens will be required in a given situation as it will depend on the symptoms and signs of the patient and the clinical decisions made by the doctor in charge of the case. Table 5.1 gives a general outline of some of the specimens that could be collected. The list is not exhaustive. It is necessary to record the type date and time of collection of each and every sample collected.

Documents of clinical investigations and medical records related to the incident will support correct lab investigations. It is advised to consult the treating clinician(s) to make a decision on samples to be tested.

For biochemical, histo-pathological and microbiological examination, specimens should be handled at the district hospital and forwarded to the nearest laboratory, where facilities are available to carry out requested laboratory testing. If facilities for essential laboratory testing are not available at intermediate level (State/District) institutions, sending samples to national laboratory or an accredited laboratory abroad need to be considered after discussing with NIP.

In case of death suspected to be due to an AEFI, an autopsy needs to be performed as soon as possible (within 72 hours) to avoid tissue lysis (for e.g. in the adrenal glands), which can alter

- at the district level by DIO and relevant staff
- at national level by the PHA and DRA.

Analysis of data at district level is important to identify the programme errors. This helps to carry out corrective action in a timely manner. Table 6.1 describes the type of analysis and the purpose.

Table 8 Types and purpose of data analysis at different levels

Programme implementation level	Suggested Analysis	Purpose of analysis at this level
Local level E.g., district	• Number of reports by clinics, hospitals, by a given time • Reported AEFIs by Place (clinics, hospitals), Persons and time • Reported AEFIs by antigen	• These are programme operation indicators such as timeliness and completeness • Identify immunization errors and thereby will lead to corrective action • Will identify vaccine reactions and coincidence
National level	• Number of reports by intermediate levels • Reported AEFIs by Place (clinics, hospitals), Persons and time • Cluster analysis • Reported AEFIs by antigen	• These are programme operation indicators (timeliness, completeness) at intermediate level • Identify immunization (programme) errors and thereby will lead to corrective action. • Cluster analysis too lead to identify immunization errors, but also coincidental events and vaccine reactions. • Will identify vaccine reactions including signal detection • Lead to take operational and policy decisions in the country

Process of data analysis

Before analysis of the line list at the national level, it is important to re-check the case definitions adopted by the reporting sources. The case should fit into a case definition such as the Brighton collaboration case definitions (www.brightoncollaboration.org) or any definition selected by the National AEFI Committee.

Line lists should be used to sort data by place, person and time. Analysis should be done by antigens by type of reported adverse events (e.g. high fever, abscess) after stratifying data. Number of doses administered for each antigen is the best denominator for calculating reported AEFI rates for each antigen in a given time period (by month, quarter or year). Various denominators and their limitations are described in table 6.2. Analysis can be expanded to AEFI rates by first or second or third dose, when the antigen is administered more than once. For this, the number of doses administered of the given antigen by first, second or third need to be used as the denominator.

Table 9 Selection of denominators and their limitations

Denominator	Limitations
Administered doses of vaccines	Most reliable, but not often available
Distributed doses	Greater than administered doses, thus may reduce rate (underestimate)
Coverage x Population	May be less accurate because of variability in coverage estimates
Target population	Proxy measure for vaccine population (may also underestimate)

Multiplier: Use of proper multiplier in data analysis is important and also varied by purpose and level of analysis. At local level, percentage (x100= %) is the best choice, whereas at state and national levels, one may use 1000, 100,000 or million as

results to all persons with contact details (complete address with postal code, phone and fax numbers and email address) mentioned in the lab request form

Table 7 Laboratory testing to investigate AEFI by working hypothesis

Working hypothesis	Specimens to send	Laboratory test
Vaccine transportation or storage	Vaccine vial	Visual test for clarity, presence of foreign matter, turbulence, discoloration or flocculation (examine under magnification)
Reconstitution error	Vaccine vial and/or diluents	Chemical composition analysis for abnormal components (e.g. suspect drug used instead of vaccine or diluent), or microbiological culture for bacterial
Non-sterile injection	Needle, syringe, vaccine vial and diluents	Sterility, if an infectious cause is suspected
Vaccine problem	Vaccine vial	Chemical compositio n analysis: preservatives, adjuvant level, etc. (e.g. aluminium content) or biological tests for foreign substances or toxins if abnormal toxicity is suspected

Data and performance analysis

Sources of AEFI data

Information on vaccine safety and the possible occurrence of AEFIs can be obtained from clinical examinations, interviews of health workers, parents and community leaders, review of registers, Vaccine and Injection logbooks, observation of immunization administration, vaccine handling and storage and laboratory reports. Analysis of data on AEFIs consists of reviewing data from the following sources

- Data collated into a linelist
- Case investigation forms for each reported AEFI case,
- Laboratory information (Human and vaccine related)
- Records about similar events in the community
- Records of the implicated vaccine

Analysis of AEFI reports

It is essential that all notified cases are reported (serious and non-serious AEFI) using the AEFI reporting form (Annex 8). All reported AEFI cases should be line listed at all levels using the AEFI line list (Annex 9). This is the first step of data management. Before the analysis, verify and reassure the data for accuracy. The surveillance system should include,

Timeliness and completeness of receiving AEFI forms.

- Identifying health institutions where AEFIs are not reported by checking on "zero reporting" or "nil reporting". Determine whether it is due to failure of reporting or whether there are no AEFIs to be reported.
- Assessing AEFI case reports received during stipulated time period.
- Assessing number of events and reporting rate per 1,000 or 10,000 or 100,000 doses of vaccine used.
- Analyses by the type of AEFI
- Analyzing programme errors by number and rates per 100 or 1,000 doses of relevant vaccines used.
- Compare the rates with available or known background rates.

Data analysis at different levels

Data analysis could be carried out by the responsible focal persons at different levels in the immunization safety surveillance system.

• excluding coincidental events.
• detection of signals for potential follow-up, testing of hypothesis and research; and
• validation of pre-licensure safety data with comparison of post-marketing surveillance safety data.

Case selection for causality assessment

The cases for which causality is ascertained include

• Serious AEFI
• Clusters and events above expected rate/ severity
• Evaluation of suspected Signals
• Other AEFI (if required)as decided by reviewing team / committee including
  ○ If immunization error is suspected
  ○ Significant events of unexplained cause within 30 days of vaccination
  ○ Events causing significant parental or community concern (e.g. Hypotonic Hyporesponsive Episode (HHE), febrile seizures etc.)

Preparation for causality assessment

Prior to causality assessment,

• The AEFI case investigation should have been completed
• All details of the case such as case report form, case investigation form (Annex 10), completed clinical case record, lab reports, autopsy report, details of field investigations etc. should be available at the time of assessment
• There must be a "valid diagnosis" which is which the extent to which the unfavorable or unintended sign, abnormal laboratory finding, symptom or disease is defined.

With inadequate or incomplete case information, an adequate causality assessment cannot be performed or if attempted, the AEFI may be deemed unclassifiable or not assessable due to lack of information. On the other hand, even with complete information the AEFI may be categorized indeterminate due to the lack of clear evidence of a causal link, or conflicting external evidence or other inconsistencies. Nevertheless, these assessments should be recorded because the reporting of more cases may lead to a stronger signal and a plausible hypothesis, or stronger refutation of any link.

Figure 8 Final classification of cases after determining causality

Causality assessment team

Causality assessment in Kuwait is done by a national reviewing teams/ committee

In summary, causality assessment of serious cases needs high levels of expertise and will be done by an expert committee only at the national level. An assessment usually will not prove or multiplier. For common, minor vaccine reactions, percentage is recommended and for rare serious reactions, 10,000, 100,000 or 1,000,000 (million) can be used.

Interpretation of data

Available expected rates for each type of AEFI for a given antigen is provided at http://www.who.int/vaccine_safety/initiative/tools/vaccinfosheets/en/index.html. This can help to make decision on corrective action to be taken on reported AEFIs. It is also important to know about background rates of reported medical events in the country. Comparison of background rates with reported rates of AEFI will guide to a possible hypothesis of a coincidental event. For example, febrile seizures with bacterial or viral infection aetiologies are common among young children and may also occur following some vaccines such as DTwP. Therefore, it is important to know the rate of febrile seizures due to other reasons and expected rates following a given antigen.

If the values exceed the expected background rates, then one should consider true increase or coincidence due to ongoing other diseases.

Monitoring and Evaluating the performance of the AEFI surveillance system

The AEFI surveillance system performance needs to be regularly reviewed at all levels to ensure that the system is sensitive enough to identify and respond to AEFI rapidly.

Some of the key indicators that help to monitor the performance of the system include

○ Timeliness and completeness of AEFI reporting
○ Percentage of AEFI cases reported on time (< 24 hours of notification) to the national level
○ Percentage of serious AEFI cases investigated on time (< 48 hours of onset) using standard formats.
○ Number (%) of AEFI investigation conclusions supported by findings of special tests (clinical specimens, Post-mortem findings (among AEFI deaths), lab findings for vaccine samples)
○ Number (%) AEFI cases where final classification including causality assessment by AEFI committee is completed within 30 days of receipt of all documentation from districts
○ Number (%) AEFI cases reviewed by National AEFI committee following receipt of reported AEFI cases from region at National level.
○ Number (%) AEFI cases reviewed by National AEFI committee and not assessable due to lack of information.
○ Response to AEFI by the program particularly those related to programme error

Brief Overview of AEFI Causality Assessment

This section is a short introduction and practical overview of the purpose, process and classification of AEFI cases after causality assessment

Causality assessment is the systematic evaluation of the information obtained about an AEFI to determine the likelihood that the event might have been caused by the vaccine/s received. Causality assessment does not necessarily establish whether or not a definite relationship exists, but generally ascertains a degree of association between the reported adverse events and the vaccine/vaccination. Nevertheless, causality assessment is a critical part of AEFI monitoring and enhances confidence in the national immunization programme. Causality assessment is important for:

• Identification of vaccine-related problems
• identification of immunization error-related problems.

vaccines on novel platforms followed by its rapid deployment on a mass scale poses unique challenges in monitoring vaccine safety. Timely detection and reporting of adverse events following COVID-19 vaccination is the first step in ensuring the continued safety of the vaccine, immunization safety surveillance and response.

In the COVID-19 vaccination context, surveillance systems need to be prepared for identifying and responding to both adverse events following immunization (AEFIs) and adverse event of special interest (AESIs) as well as other safety events that may cause public concern. Although both AEFIs and AESIs can be detected through passive and active surveillance, if active surveillance is not implemented for AESIs, all AESI-like adverse events occurring following COVID-19 immunization should be considered as AEFIs and the standard procedure for AEFI response should be adopted. The WHO 'Guidance on AESI in preparation for COVID-19 vaccine introduction' provides detailed information on AESIs including a list of potential AESIs, their case definitions, study protocols, training requirements, data collection tools (including AESI confirmation forms), processing, transmission, analysis and response: https://www.who.int/vaccine_safety/committee/reports/May_2020/en/

Communication and Media Management

Risk Communication

Communication makes stakeholders aware of the process at each stage of the Investigation. The identification of particular interest groups and their representatives should comprise a part of an overall communication strategy. Decisions including what, whom and how, should be part of an overall communication strategy.

Need for Improved Communication

Concerns are frequently raised about vaccines and immunization programs by members of the general public and in the media. These concerns can be serious and are often misplaced. The graphic below (Figure 9) illustrates some of the factors that may trigger public concerns; hence the need for improved quantity, quality and targeted communication about vaccine safety.

Figure 9 Factors triggering public concerns to immunization

Challenges to Effective Communication

Challenges that need to be overcome with effective communication include among others:

• Communicating the decline of childhood infections and deaths from VPD
• Introduction of new vaccines and related information gaps
• Mass campaigns or Supplemental Immunization Activities (SIAs)

disprove an association between an adverse event and the immunization. It is meant to assist in determining the level of certainty of such an association. A definite causal association or absence of association often cannot be established for an individual event.

Action and Response to AEFI

Responding to AEFI may involve immediate short-term activities or/and long-term follow-up activities. Follow-up activities should be based on findings of investigations, causality assessments and recommendations by the National AEFI Committee

Proper and early treatment should be provided to patients regardless of the diagnosis. Case management and referral will vary depending on the seriousness. Mild symptoms such as mild fever and pain are likely to be of short duration and can be managed by assuring and educating parents during immunization. If parents return to seek medical attention, these cases should be documented and reported in the standard form. In case patients need hospitalization, a clear system for referral should be in place.

Depending on the nature of the event(s), the number of people affected, and community perceptions, an investigation may be conducted. In general, it is not advisable to discontinue the immunization programme while awaiting the completion of the investigation. If AEFI causality is not established – depending on the nature of the event, its extent and whether it is ongoing – a further investigation or epidemiological study may be warranted. However, it must be accepted that in some cases the relationship to vaccine will never be clear.

Communication and training are two important follow-up actions that have long term implications.

Table 10 Actions to be taken upon completion of the investigation/causality assessment

Type of AEFI	Follow-up action
Vaccine-related reaction	If there is a higher reaction rate than expected from a specific vaccine or lot, obtain information from the manufacturer and consider: ■ withdrawing that lot; ■ investigating with the manufacturer; ■ obtaining vaccine from a different manufacturer.
Immunization error related	Correct the cause of the error. This may mean one or more of the following: ■ changing logistics for supplying the vaccine; ■ changing procedures at the health facility; ■ training of health workers; ■ intensifying supervision. Whatever action is taken, it is important to review at a later date to check that the immunization error related events have been corrected.
Coincidental	The main objective is to present the evidence showing that there is no indication that the AEFI is a vaccine-related reaction or immunization-related error and, that the most likely explanation is a temporal association between the event and vaccine/vaccination. This communication can be challenging when there is widespread belief that the event was caused by immunization. Sometimes, it may be useful to enlist further expert investigation to ensure that the event was truly coincidental. The potential for coincidental events to harm the immunization programme through false attribution is immense.

Responding To Adverse Events Following COVID-19Immunization (Aefis)

The unprecedented rapid development of the COVID-19

Communication with Other Healthcare Staff
• Communicate among all level of health authorities involved.
• Reinforce their knowledge, ability, skills and performances.
• Update them on investigation process, progress and findings.
• Reassure the staff of ongoing confidence in the immunization programme; quality of the vaccine and their services provided
• Do not blame health care worker, instead focus on the correction and quality of the NIP program.
Communicating with stakeholders
Vaccine safety information needs to be shared with other stakeholders in order to ensure dissemination of correct information and thereby ensuring the smooth functioning of national immunization programme. Depending on the need, stakeholders mentioned below will be given preliminary information at initial stage and final report after completion of investigation and causality assessment at a later stage.
• Kuwait Office for Pharmacovigilance Surveillance (KPVC)
• Medicines and Medical Product Registration and Regulatory Administration
• AEFI Committees at all levels
• Politicians
• Professional associations
• Universities and hospitals
• International agencies and development partners
• Manufacturers
Communicating with Media
The media is an important gateway to inform the public and shapes their view and attitudes towards vaccines and immunization, especially including the occasional mass campaign. In the long-term, building partnerships with the media is key to keep the public regularly informed about immunization, its benefits and to motivate families and communities to make use of immunization services.
Advance preparedness
Effective communication with the media includes efficient coordination with the field staff, a plan, trained personnel, budget and practiced responses to potential issues around AEFI. Effective communication should be in place before an immunization campaign starts and as part of the on-going communication to support routine immunization programmes.
A database of journalists
It is essential to maintain a database of print and electronic media journalists covering health (local, national, international) with contact information. They need to be contacted and informed about the circumstances of the AEFI.
Information packages:
Keep media informed through email or hardcopy by sending regular updates on any plans, programs and decisions. Sensitize media about health benefits of immunization and its impact globally and nationally. Prepare monthly or quarterly updates. Provide an updated information package with documents including Frequently Asked Questions (FAQs) on immunization in general, for specific disease and AEFI (Factsheet or a technical brief on a specific vaccine preventable disease etc.).
Draft media release:
The draft media release must specifically answer the 6 W's for journalists:
• Who is affected/is responsible?
• What has happened?
• What is being done?
• Where has it happened?
• When did it happen?
• Why did it happen?
• Will it happen again?
• Need for transparency and accountability
Communication with Clients, Parents or Guardian and Community
Communication with parents, other members of the community, health staff and media need to be carried out under all circumstances. They should be kept informed about the investigation, results and action taken already or going to be taken regarding the AEFI. It is crucial to highlight the benefits of immunization while communicating on AEFI with the public and stakeholders.
Key points to consider when communicating with the vaccine recipient (patient or client) or parents and guardians of the patient, community and health staff are;
• Listen to the client, parents or guardian and their concerns empathetically.
• Reassure and support the client, parent or guardian but do not make false promises.
• Assist the client, parents and guardian for hospitalization if necessary.
• Frequent communication with the client, parents or guardian regarding the progress of the patient.
• Prepare a fact sheet on adverse event for the client, parents or guardian, community, health staff and media.
• Build up and maintain relationship among health staff, community and media.
• Inform the individual client, parent or guardian about possible common adverse events and how to handle them.
• Continuously communicate with the client, parent or guardian and community during the investigation period to assure understanding the risk- benefit of vaccination.
Role of Healthcare Workers in Communicating AEFI
AEFI can have repercussions on the entire routine immunization programme as well as campaigns. Where medical interventions are necessary, they should be carried out as rapidly as possible. Suppressing reports of AEFI or slow reaction can cause considerable damage to the immunization programme in the long-term. Messages relating to adverse events must be disseminated rapidly to prevent rumors spreading.
Once an AEFI has occurred, responses should include the following communication elements:
• Communicate immediately with the MOH, and other high officials.
• Provide the vaccine recipient/parents with factual information. Remember that some vaccine recipients /parents may seek information elsewhere and you may lose credibility if you do not provide a trustworthy and technically sound response. The public and the other stakeholders have a right to know exactly what happened.
• Reassure parents, caregivers and adults that necessary measures are being taken so that the members of the community and caregivers are informed of what is happening.
• Communicate the results of the investigation to the National Immunization Program managers and to the District Immunization officers at all levels.
• If the AEFI was caused by immunization error, tell the public what steps are being taken to prevent similar events in the future.
• Broadcast an official statement about the event on radio and television and publish a statement in newspapers or social media

• Repeat the message to dispel all fears.
• Constantly reassure the public of the safety of vaccines.

that has been said.
• Have a media kit ready and share it with journalists. The media kit may consist of a media release with all the essential information, supplementary background information, benefits and a set of frequently asked questions about immunization.
Media Management Post AEFI
Keeping Promises to the Media
If it has been promised that media will be kept updated about the investigation findings, make sure the media is updated by the promised date. If the findings have been delayed, ensure the media is informed because they would be expecting answers.
Providing Answers to Unanswered Questions
During media conferences, if a question could not be answered for any reason – for example due to absence of data or if you were unprepared to answer the questions – get back to the media with the answers as soon as possible.
Keeping Media Informed About Subsequent Developments
If any decision or action is taken at the highest levels following AEFI investigations or during the investigations and the public must know about it, keep the media informed though a press release or hard copy document.
Dealing With Rumours and Misinformation
In the context of immunization, rumor is defined as an unverifiable assertion that is circulating, or a statement without facts to confirm its truth. Rumors and misinformation about immunization are amongst the most serious threats to the success of any immunization programme. Once rumors start, they can be very hard to stop. Some examples of rumors:
• "Vaccines are a contraceptive to control population or to limit the size of a certain ethnic group."
• "Vaccines are contaminated by the AIDS virus or mad cow disease."
• "Children are dying after receiving vaccines."
• "RNA vaccines will get into people's nuclei and modify their genes"
Unless the rumor can very easily be contained and addressed you must refer the matter to your supervisors as quickly as possible. You will need to work under their direction – action may even need to be taken at the national level. The consequences of rumors can be serious and, if unchecked, they can travel quickly beyond your local area.
Common causes of Rumors
• Inadequate information sharing by HCPs or
• Failure to communicate correct information about vaccine effects and schedules;
• Failure to check whether caregivers know and understand information;
• Failure to give clients opportunities to ask questions
• Parents/caregivers' negative attitudes about immunization services
What you can do at the health facility?
Under the direction of your supervisor:
• Meet with key opinion leaders (politicians, traditional and religious leaders, community leaders, other health workers).
• Organize meetings at sites where the individuals/groups are comfortable and feel at ease to ask questions.
• If there is a national mass media response, encourage your community members to watch and talk about it.
Words of Advice
• React swiftly and adapt your ongoing activities to give a quick response.
• Develop strong relationships and trust with your community in advance (religious, social and media groups).
• Give clear and consistent messages.
Annex 8 STANDARD AEFI REPORTING FORM
REPORTING FORM FOR ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFI)

In the media release, mention the name and contact details of the AEFI focal person(s) and the name and contact details of the official spokesperson for further details should journalists have additional questions (at the end).
A spokesperson system:
The National AEFI committee shall assign after the approval of MOH a spokesperson who will be responsible for communicating the AEFI to media, public and stakeholders. This limits the possibility of conflicting messages coming from different sources. Ensure spokesperson has the important information.
Orientation workshops and field visits for media:
Regular orientation workshops and field visits for journalists will help them achieve a better understanding of immunization advantages as well as the complexities of an immunization programme. This will also help to identify in advance the kind of questions or concerns that journalists specifically have.
Media Management during an AEFI crisis
While every single AEFI must be investigated in detail, all AEFI cases may not be a crisis situation. A crisis often occurs from inaction rather than from taking appropriate action on AEFI.
Monitoring of media:
When an AEFI occurs, media should be monitored for authenticity of their reporting. The AEFI Committee should move very quickly to correct any inaccuracies. The AEFI Committee could take the following immediate actions:
• Analyze rumor, its level and potential to cause damage.
• Anticipate how situations might evolve following response; prepare before responding.
• Deal with a simple mistake in reporting with a simple solution. If it is an isolated error, make a polite call to the reporter and offer to help the reporter with correct data and facts then and in the future.
• If the rumor is confined to a small audience, correct it within that group only. If the error is widely reported, it may be necessary to call a media conference to present the correct facts before it leads to further damage.
• Plan how to prevent future rumors.
Prepare a media release:
An effective media release should include a complete account of the event, framed in its context (e.g. an isolated event or a cluster of AEFI or coincidental event). The media release should have:
• An outline of actions taken or planned (such as the AEFI investigation).
• An assurance that corrective action has been taken or will be taken.
• Reference to any relevant publication, video material or web site.
• Sender's name and spokesperson's details.
• Limited to one page of matter (400–500 words max).
• Short sentences (not exceeding two lines).
Quotes from key officials may be used after seeking their permission. The quotes must be positive and carry the key messages.
Call a media conference:
Media conferences may need to be conducted if AEFI is being reported extensively and widely and there is a need to provide accurate facts and de-sensationalize the story. A media conference enables all journalists to have the same information, thus there is then less likely of event being 'sensationalized'. Consider the following steps when preparing for the media conference:
• AEFI Committee takes the lead but identifies who facilitates the press conference.
• If there are several members on the panel, agree beforehand on the key message(s) in response to the AEFI.
• Agree on roles of each panel member beforehand, including the type of questions (media, political etc.) each panel member may best handle.
• Panel members must avoid contradicting each other in the press conference unless it is critical to clarify something incorrect

*Patient Name:	*Reporter's Name:
*Patient's full Address:	Institution:
	Designation and Department:
Telephone:	Address:
Sex: • M • F	Telephone and E-mail:
	Date patient notified event to health system:
*Date of birth: __ / __ / __	__ / __ / __
OR Age at onset:	Today's date: __ / __ / __

Vaccination Centre or Place of Vaccination – name and address:

Vaccine						Diluent (if applicable)			
Brand name of vaccine inc. name of manufacturer	Date of vaccination	Time of vaccination	Dose (1st, 2nd etc.)	Batch /Lot number	Expiry date	Name of diluent	Batch /Lot number	Expiry date	Date and time of reconstitution

*Adverse event(s):	Date AEFI started: __ / __ / __
local reaction • <3days • >3days • beyond nearest joint	Time
• Pain at Inj site • Erythema • Swelling • Itching • Seizures	Describe AEFI (Signs and Symptoms):
• febrile • afebrile	
• Abscess Sepsis	
• Encephalopathy	
• Toxic shock syndrome	
• Thrombocytopenia Anaphylaxis	
• Fever ≥38°C	
• Other (specify):	
*Serious: Yes / No; If Yes: • Death • Life Threatening • Persistent or significant disability • Hospitalization • Congenital anomaly	
• Another important medical event (specify):	
*Outcome: • Recovering • Recovered • Recovered with sequelae • Not Recovered • Unknown • Died	
If Died, date of death: __ /__ /__ Autopsy done: • Yes • No • Unknown	
Past medical history (including history of similar reaction or other allergies), concomitant medication and other relevant information (e.g., other cases). Use additional sheets if needed:	

*Compulsory field

Annex 9 AEFI LINELIST

	Name/ID
	District/ Area
	Date of birth (dd/mm/yyyy) and age
	Date of immunization(dd/mm/yyyy)
	Reaction type (code) [1] Minor [2] Severe/Serious
	Outcome (Recovered /disability/Died)
	Suspect vaccine (name and dose, e.g. Penta -2)
	Vaccine batch/Lot number
	Diluent batch number
	Onset time interval (hours, days, weeks)
	Date reporting (dd/mm/yyyy)
	Investigated? (If yes, date)
	Final Diagnosis
	Cause (code)

➢ Establishing codes for area, reaction type, cause of AEFI, and certainty of cause will facilitate recording, data entry and analysis. Because of the potential for coding errors, the code should be double-checked.

➢ Coding for cause of AEFI:

[A1]	[A2]	[A3]	[B]	[C]	[D]
Vaccine-related	Immunization error-related	Immunization anxiety-related	Indeterminate	Coincidental	Inadequate information to classify

Annex 10 AEFI INVESTIGATION FORM

AEFI INVESTIGATION FORM

(Only for Serious Adverse Events Following Immunization Death / Disability / Hospitalization / Cluster)

Section A	Basic details	
District / Area	Case ID:	
Place of vaccination ( ):		
☐ Govt. health facility		
☐ Private health facility		
☐ Other (specify)		
Vaccination in ( ):		
☐ Campaign		
☐ Routine		
☐ Other (specify)		
Address of vaccination site:		
Name of Reporting Officer:		Date of investigation: / /
		Date of filling this form: / /
Designation / Position:		This report is: ☐ First ☐ Interim ☐ Final
Telephone #landline Mobile:		
Email:		
Patient Name		Sex: • M • F

(use a separate form for each case in a cluster)

Date of birth (DD/MM/YYYY): / /

OR Age at onset: years months days

OR Age group: • < 1-year • 1-5 years • >5 years

Patient's full address with landmarks (Street name, house number, phone number etc.):

Brand Name of Vaccines (including manufacturer); diluent received by patient	Date of Vaccination	Time of vaccination	Dose (e.g. 1st, 2nd, etc.)	Batch/Lot Number	Expiry date
				Vaccine	Vaccine
				Diluent	Diluent
				Vaccine	Vaccine
				Diluent	Diluent
				Vaccine	Vaccine
				Diluent	Diluent
				Vaccine	Vaccine
				Diluent	Diluent
				Vaccine	Vaccine
				Diluent	Diluent

Type of site ( ) • Fixed • Mobile • Other

Date of first/key symptom (DD/MM/YYYY): / / _____Time of first symptom (hh:mm): ___/___

___ ___

Date of hospitalization (DD/MM/YYYY): / /

Date first reported to the health authority (DD/MM/YYYY): / /

Status on the date of investigation ( ): • Died • Disabled • Recovering • Recovered Completely • Unknown

If died, date and time of death (DD/MM/YYYY): / / (hh:mm):

Autopsy done? ( ) • Yes (date) • No

• Planned on (date) Time

Attach report (if available)

Criteria	Finding	Remarks (If yes provide details)
Past history of similar event	Yes / No / Unkn	
Adverse event after previous vaccination(s)	Yes / No / Unkn	
History of allergy to vaccine, drug or food	Yes / No / Unkn	
Pre-existing acute illness (30 days) prior to vaccination	Yes / No / Unkn	
Pre-existing comorbidity/ congenital disorder?	Yes / No / Unkn	
History of hospitalization in last 30 days, with cause	Yes / No / Unkn	
Has the patient tested COVID-19 vaccination positive prior to	Yes / No / Unkn	
Patient currently on concomitant medication? (If yes, name the drug, indication, doses and treatment dates)	Yes / No / Unkn	
Family history of any disease (relevant to AEFI) or allergy	Yes / No / Unkn	
For adult women		
• Currently pregnant? Yes (weeks)	/ No / Unknown	
• Currently breastfeeding? Yes / No		
For infants P1 Birth Weight:		
The birth was		
☐ Full-term		

☐ Pre-term

☐ 1st-term

Delivery procedure was

☐ Normal

☐ Caesarean

☐ Assisted

(forceps, vacuum, etc)

☐ With

complications (specify)

Section C	Details of first examination** of serious AEFI case

Source of information (all that apply):

☐ Examination by the investigator

☐ Documents

☐ Verbal autopsy Other

If from verbal autopsy, please mention source

Name of the person who first examined/treated the patient: Name of other persons treating the patient:

Other sources who provided information (specify):

Signs and symptoms in chronological order from the time of vaccination:

Name and contact information of person completing these clinical details: Designation: Date/time:

**Instructions – Attach copies of ALL available documents (including case sheet, discharge summary, case notes, laboratory reports and autopsy reports) and then complete additional information NOT AVAILABLE in existing documents, i.e.

- If patient has received medical care – attach copies of all available documents (including case sheet, discharge summary, laboratory reports and autopsy reports, if available) and write only the information that is not available in the attached documents below
- If patient has not received medical care – obtain history, examine the patient and write down your findings below (add additional sheets if necessary)

Provisional / Final diagnosis:

Section D	Details of vaccines provided at the site linked to AEFI on the corresponding day	
Number immunized for each antigen at session site. Attach record if available.	Vaccine name	
	Number of Doses	

When was the patient immunized (Record in ALL questions)

☐ Within the first vaccinations of the session

☐ Within the last vaccinations of the session

☐ Unknown

In case of multidose vials, was the vaccine given

☐ within the first few doses of the vial administered?

☐ within the last doses of the vial administered?

☐ unknown?

b) Was there an error in prescribing or non-adherence to recommendations for use of this vaccine?	Yes / No
c) Based on your investigation, do you feel that the vaccine (ingredients) administered could have been unsterile?	Yes / No / Unable to assess
d) Based on your investigation, do you feel that the vaccine's physical condition (e.g., color, turbidity, foreign substances etc.) was abnormal at the time of administration?	Yes / No / Unable to assess
e) Based on your investigation, do you feel that there was an error in vaccine reconstitution/preparation by the vaccinator (e.g. wrong product, wrong diluent, improper mixing, improper syringe filling etc.)?	Yes/ No / Unable to assess
f) Based on your investigation, do you feel that there was an error in vaccine handling (e.g., break in cold chain during transport, storage and/or immunization session etc.)?	Yes / No / Unable to assess
g) Based on your investigation, do you feel that the vaccine was administered incorrectly (e.g., wrong dose, site or route of administration, wrong needle size, not following good injection practice etc.)?	Yes / No / Unable to assess
h) Number immunized from the concerned vaccine vial/ampoule	
i) Number immunized with the concerned vaccine in the same session	
j) Number immunized with the concerned vaccine having the same batch number in other locations. Specify locations:	
k) Is this case a part of a cluster?	Yes / No / Unkn
If yes, how many other cases have been detected in the cluster?	
a) Did all the cases in the cluster receive vaccine from the same vial?	Yes / No / Unkn

b) If no, number of vials used in the cluster (enter details separately)	

It is compulsory for you to provide explanations for these answers separately

Section E	Immunization practices at the place(s) where concerned vaccine was used
(Complete this section by asking and/or observing practice)	
Syringes and needles used:	
• Are AD syringes used for immunization?	Yes / No / Unkn
If no, specify the type of syringes used: ☐ Glass ☐ Disposable ☐ Recycled Disposable ☐ Other	
Specific key findings/additional observations and comments:	

Reconstitution: (complete only if applicable, NA if not applicable)			
• Reconstitution procedure ( )	Status		
Same reconstitution syringe used for multiple vials of same vaccine?	Yes	No	NA
Same reconstitution syringe used for reconstituting different vaccines?			
Separate reconstitution syringe for each vaccine vial?	Yes	No	NA
Separate reconstitution syringe for each vaccination?	Yes	No	NA
	Yes	No	NA
• Are the vaccines and diluents being used the same as those recommended by the manufacturer?	Yes	No	NA
Specific key findings/additional observations and comments:			

Section F	Cold chain and transport
(Complete this section by asking and/or observing practice)	
Last vaccine storage point:	
• Is the temperature of the vaccine storage refrigerator monitored?	Yes / No
○ If "yes", was there any deviation outside of 2 8° C after the vaccine was placed inside?	Yes / No
○ If "yes", provide details of monitoring separately	
• Was the correct procedure for storing vaccines, diluents and syringes followed?	Yes / No / Unkn
• Was any other item (other than vaccines and diluents) in the refrigerator or freezer?	Yes / No / Unkn
• Were any partially used reconstituted vaccines in the refrigerator?	Yes / No / Unkn
• Were any unusable vaccines (expired, no label, frozen) in the refrigerator?	Yes / No / Unkn
• Were any unusable diluents (expired, manufacturer not matched, cracked, dirty ampoule) in the store?	Yes / No / Unkn
Specific key findings/additional observations and comments:	
Vaccine transportation:	
• Type of vaccine carrier used:	
• Was the vaccine carrier sent to the site on the same day as vaccination?	Yes / No / Unkn
• Was the vaccine carrier returned from the site on the same day as vaccination?	Yes / No / Unkn
• Was a conditioned ice-pack used?	Yes / No / Unkn
Specific key findings/additional observations and comments:	

Section G	Community investigation (Please visit locality and interview parents/others)
Were any similar events reported within a time period similar to when the adverse event occurred and in the same locality? Yes / No / Unknown If yes, describe:	
If yes, how many events/episodes?	
Of those effected, how many are:	
• Vaccinated:	
• Not vaccinated:	
• Unknown:	
Other comments:	

Annex 11 AEFI LABORATORY REQUEST FORM

AEFI – LABORATORY REQUEST FORM (LRF)
(For Serious Adverse Events Following Immunization)
AEFI category (Encircle): Death / Hospitalized / Cluster / Disability

District/Area		Case ID		
Name of person sending the specimen: Designation: Phone Number:		Date of filling LRF:		
Case Name				
Date of Birth		Sex	M	F

Vaccine Name /Diluent	Quantity Sent	Name of Manufacturer (in BLOCK Letters)	Batch No.	Manufacturing Date	Expiry Date

Complete Address of the patient with landmarks (Street name, house number, village, block, Tehsil, PIN No., Telephone No. etc.)			
Date of vaccination		Date of Onset	
Date of collection of specimen		Time of collection of specimen	

Precise description of samples:

a) For vaccine/diluents specimens: (to be transported in reverse cold chain)

b) For logistics specimens: (AD, Reconstitution, Disposable syringes)

Mention Logistics	Quantity Sent	Name of Manufacturer (in BLOCK Letters)	Batch No.	Manufacturing Date	Expiry Date

For Biological product specimen: (CSF, Blood, Urine, etc)

1. Specimen Type: (CSF, Blood, Urine, etc.)
2. Test requested:
3. Preliminary clinical diagnosis (working hypotheses):
4.Name and complete address of officials to whom laboratory results should be sent:

Send to	Complete address	Phone	Mobile	Email-ID
National Level				
District / Area level				
Others (specify)				

To be completed by lab officials after receiving the specimen								
Date of receipt of specimen at laboratory	D	D	M	M	Y	Y	Y	Y
Name of person receiving specimen(s) at laboratory								
Condition of specimen upon receipt at lab (encircle)	Good		Poor		Unknown			
Comments by pathologist, virologist or bacteriologist								
Date specimen results sent from this lab	D	D	M	M	Y	Y	Y	Y
Name of laboratory professional								
Signature								
Phone number:	Email							