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Inspection and Human Medicines Pharmacovigilance

The European Union regulatory network incident management plan for medicines for human use

1. Introduction

The continuous monitoring of medicinal products throughout their lifecycle represents one of the core activities performed by Regulatory Authorities. Union and national pharmaceutical legislation has provided the Competent Authorities in the European Union (EU) with the necessary legal tools to allow for such monitoring, hence contributing to the safe use of medicines and the protection of public health.

Although the management of the large majority of emerging public health concerns related to the use of medicines has been possible by applying so-called routine measures, in a limited number of cases, commonly described as “crisis” situations, specific measures had to be taken to allow for an efficient management. This has been possible through the availability of dedicated “crisis” management plans at national level.

Acknowledging the existence of the European Medicines Agency’s Crisis Management Plan for Centrally Authorised Products (CAPs)[1], which became effective in September 1997, the need was identified to not only revise such Crisis Management Plan to take into account experience gained over a time span of nearly 9 years, but also to broaden its scope to include medicinal products authorised through the mutual recognition and the decentralised licensing routes, and through national procedures. This was done to enable a more global approach at EU level in relation to the management of incidents to avoid them developing into “crisis” situations. Consequently an EU Regulatory Network Incident Management Plan for medicines for human use was developed. A pilot phase was started in September 2009 and extended in July 2012. The procedure is now fully established and can be triggered by the European Commission (EC), a National Competent Authority (NCA) or the European Medicines Agency (EMA) as appropriate. Lessons learned have been considered and incorporated in the current document.

* This revision includes an update of Annex 2 and Annex 3.

[1] Crisis Management Plan Regarding Centrally Authorised Products for Human Use (Doc. Ref. CPMP/388/97).

2. Objectives of the incident management plan

Throughout the lifecycle of a medicinal product various types of events can occur or new information can arise which could have a serious impact on public health. In order to ensure the most appropriate management of such events or new information whilst also aiming for an efficient operation of the EU Regulatory Network in this field, the objectives of the EU Regulatory Network Incident Management Plan are:

- To continuously monitor such events and new information (hereafter called “incidents”), to review their public health impact, and to take the necessary routine measures to remedy the situation. This activity is referred to in this document as proactive incident management, the main aim being to prevent an incident developing into a crisis.
- To request further analysis under the form of the Preliminary Risk Analysis when routine measures are not considered sufficient to address the incident. This PRA is requested by the Incident Review Network from the relevant party and constitutes the basis of the decision on whether or not a crisis management phase should be triggered.
- To undertake in case of a confirmed crisis the initiatives necessary to manage and control the situation, whereby urgent and coordinated action within the EU Regulatory Network is necessary. This activity is referred to in this document as reactive incident management and is led by the EU Executive Task Force and EU Operational Task Force.

3. Prerequisites

To meet the aforementioned objectives, a number of prerequisites need to be fulfilled:

- As a general principle, the EU Regulatory Network Incident Management Plan should be flexible enough to address the various situations which may arise in the complex EU regulatory framework and to take due account of its specificities. In all situations there should be a close collaboration between the NCAs, the EC and the EMA. In addition, the Incident Management Plan will have to comply with all provisions laid down in Union legislation, including aspects such as the right for Member States (MSs) to take pre-emptive action in accordance with the provisions of such Union legislation, the Union referral mechanisms at the disposal of the Regulatory Authorities, communication channels available within the EU Regulatory Network, etc.
- In order to avoid duplication of work, hence making the best use of available resources, it is of utmost importance that clear roles and responsibilities are allocated to the various involved parties. When assigning such roles and responsibilities, the legal provisions as described in Union legislation should be adhered to, and, in addition, due account should be taken of the need for a collaborative and coordinated approach within the context of the EU Regulatory Network.
- Irrespective of the nature of the incident and the licensing route of the concerned medicinal product(s), the Incident Management Plan should be able to address, in a coordinated manner and within the shortest possible timeframe, the public health concerns, regardless of whether they fall within the scope of proactive or reactive incident management. The availability of adequate mechanisms and structures to enable efficient decision-making is hereby of utmost importance.

- It is also of key importance to ensure that all measures taken guarantee the highest possible protection of public health and that any situation which could endanger confidence and trust in the Competent Authorities and the EU Regulatory Network is avoided. In this respect, due account should also be taken of the arrangements laid down in the Memorandum of Understanding (MoU) signed between each NCA and the EMA on the sharing of EudraVigilance data, and other safety and pharmacovigilance related documents, quality or manufacturing and inspection information and/or information relating to medicinal products for human use.

4. Key Principles of the incident management plan

4.1. Scope

The scope of the EU Regulatory Network Incident Management Plan is defined by both the source of events/new information and the type of medicinal products, as outlined below:

- Source of events/new information:
  - The event or the new information may be related to quality, efficacy or safety concerns. Sometimes the event or the new information can be related to both quality and safety concerns (e.g. problems of viral contamination with biological products). In situations characterised by purely pharmacovigilance issues or a combination of quality and safety concerns the Incident Management Plan will apply. However, other situations related solely to quality concerns, but without a safety component (e.g. non-compliance with previous approved product specifications, product contamination, etc.) occur. Product quality reports, defective product reports and all reported incidents that may be caused by product quality problems should be dealt with in accordance with the "Compilation of Union Procedures on Inspections and Exchange of Information"[2], and the Incident Management Plan involving the Incident Review Network will be triggered only in the cases when there is a major public health impact relating to the safety, efficacy and/or availability of medicinal products.
  - In addition, there may be other situations where the emerging issue, due to its (potential) major public health impact needs to be escalated in order to facilitate coordination at EU level, such as supply shortages caused by manufacturing/Good Manufacturing Practice (GMP) compliance problems. These situations may be dealt with in the context of this Incident Management Plan.
- Type of medicinal products:
  - The event or the new information may be related to a single medicinal product or to several medicinal products. The product(s) may have been authorised through the centralised procedure, the mutual recognition procedure, the decentralised procedure and/or (a) national procedure(s).

4.2. An incident versus a crisis

4.2.1. Definition of an incident

In the context of this Incident Management Plan, an incident is defined as a situation where an

[2] The SOP "Dealing with Reports of Defective Medicinal Products" (SOP/INSP/2018) applies in this situation.

event occurs or new information arises, irrespective of whether this is in the public domain or not, in relation to (a) medicinal product(s), authorised in the EU, and irrespective of the licensing route, which could have a serious impact on public health.
Situations such as events that do not seem at a first glance to have a serious impact on public health, but are in the public domain, irrespective if they are subject of media attention or not, and may lead to serious public concerns about (a) product(s), may also need to be considered as incidents. Likewise, situations which might have a negative impact on the appropriate use of (a) medicinal product(s) (e.g. resulting in patients stop taking their medicine) or on the availability of medicinal product(s) fall within the definition of an incident.

4.2.2. Definition of a crisis

In the context of this Incident Management Plan, a crisis is defined as a situation where, after assessment of the incident's associated risks, routine measures are not considered sufficient and therefore urgent and coordinated action within the EU Regulatory Network is required to manage and control the situation.

4.3. Proactive versus reactive incident management

As outlined before, proactive incident management is the activity whereby the main aim is to prevent an incident developing into a crisis by taking the necessary routine measures to remedy the situation. Routine measures are defined in the context of this document as measures which can readily be applied to address the identified public health concerns. It should be emphasised that three types of measures are at the disposal of Regulatory Authorities in the EU: (1) pharmacovigilance and quality/manufacturing monitoring tools, (2) tools available in Union legislation to take regulatory action, and (3) communication tools to inform patients, healthcare professionals and the general public. The actions to be taken to address the public health concerns can either consist of one type of measure as outlined before, or a combination of measures. Anyway, the decision on the measures to be initiated will always have to take due account of two aspects: the severity of the problem as well as the level of urgency.
In practice this means that the introduction of changes to the product information, combined or not with communication to healthcare professionals (e.g. the circulation of a Direct Healthcare Professional Communication) should normally be considered as a routine measure. Likewise, even the recommendation of the Committee for Human Medicinal Products (CHMP) for a suspension of the marketing authorisation, combined with a Press Release and a Questions & Answers (Q&A) document, or the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMD(h))'s consensus view that the marketing authorisation of the concerned non-CAPs should be suspended, could be considered as a routine measure.
When the incident is thought to have a major impact and/or may lead to serious public concerns about (a) product(s), a dedicated structure established in the context of incident management, namely the Incident Review Network, is in charge of reviewing all the information available at the current time and advise on whether routine measures are sufficient to remedy the situation, or if it should be escalated to the crisis management phase.

Reactive incident management (or crisis management), is initiated when the use of routine measures is no longer adequate to address the situation and therefore urgent and coordinated action within the EU Regulatory Network is considered necessary. For example the suspension by a MS of the marketing of a medicinal product prior to any scientific review at EU level or regulatory action taken by NCAs following the recommendation by the Pharmacovigilance Risk Assessment Committee (PRAC) prior to consideration by the CHMP and CMD(h), may be judged

as a situation which would necessitate urgent and coordinated action within the EU Regulatory Network, hence falling within the scope of reactive incident management.
Although one should always aim for proactive handling of incidents, situations will occur, as experience has shown, where it is necessary to undertake reactive actions.

4.4. Operation of the EU regulatory network incident management plan

The two pillars of the EU Regulatory Network Incident Management Plan are (1) the availability of dedicated management structures at EU level, and (2) the availability of a dedicated EU-wide Incident Management Procedure.

4.4.1. Management structures

In order to provide for the aforementioned two step approach (consisting of proactive and reactive incident management), the following organisational structures are established:

4.4.1.1. Incident management structure

The Pharmacovigilance Rapid Alert (RA) and Non-Urgent Information (NUI) system allows for rapid exchange of information on safety concerns within the EU Regulatory Network. In parallel, the Quality Defect RA system has been established to ensure that information concerning the recall of medicinal products due to quality defects or which are falsified is notified rapidly between the NCAs, the EMA, the EC and other relevant partners, competent authorities outside the EU and international organisations (e.g. Council of Europe/ European Directorate for the Quality of Medicines & HealthCare, World Health Organization).
In addition, a dedicated structure in the context of incident management has been set-up within the EU Regulatory Network, i.e. the Incident Review Network (IRN). Its main role is to review, from a managerial perspective, incidents reported as a Pharmacovigilance RA in terms of their public health impact and if the identified concerns are likely to be addressed through routine measures (hereby also considering the consequences for on-going clinical trials). In addition, the IRN can provide advice to any request as regards an incident reported via NUI in terms of the public health impact and if the remedial action can be undertaken through routine measures. Likewise, other incidents (not reported via RA or NUI) or emerging issues with a (potential) major public health impact (such as certain Quality Defect RA, or supply shortages caused by manufacturing/GMP compliance problems) should be addressed to the IRN in order to obtain a steer from a managerial perspective on how to best address the situation. The IRN will decide on the preparation of a Preliminary Risk Analysis (PRA) for those incidents for which the IRN is of the view that the identified public health concerns may not be addressed by taking routine measures.

The IRN is a virtual network. Its composition is multidisciplinary and includes experienced staff members from the EMA, the EC and NCAs. It should be emphasised that its tasks are purely managerial and advisory. The IRN, therefore, has a distinct role which will not interfere with the tasks performed by the CHMP, the PRAC and the CMD(h), i.e. the scientific assessment of the identified concerns and the provision of recommendations for regulatory action. The rules of procedure necessary for the efficient operation of such a virtual network are attached (see Annex 1). The composition of the IRN is provided in Annex 2.

4.4.1.2. Crisis management structures

Two types of crisis management structures have been set-up:

- At EU level, EU crisis management structures, consisting of an EU Executive Task Force and an EU Operational Task Force.
- At Member State level, national crisis management structures.

The composition, the roles and the responsibilities of the EU crisis management structures are as follows:

- EU Executive Task Force:
  - Core composition includes senior management representatives of the European Commission (2), the EMA (3) and the NCAs (2). As regards the NCAs, this refers to appointed Heads of Medicines Agencies (HMA). The EU Executive Task Force is chaired by the EC. In addition, depending on the situation, the CHMP Chair and/or the PRAC Chair, and/or the CMD(h) Chair may be invited to participate at EU Executive Task Force meetings. It should be emphasised that the composition of this group is fixed and its size is limited. The composition of the EU Executive Task Force is provided in Annex 3.
  - Its role is strategic and its responsibilities are to (1) confirm the crisis, (2) initiate the crisis management steps of the Incident Management Plan (or the relevant steps, where appropriate), including the communication strategy, and (3) agree on the closure of the crisis.
- EU Operational Task Force:
  - Core composition includes staff member appointed at the level of the EMA, the EC, as well as depending on the situation, the CHMP (Co)-Rapporteur(s), the PRAC (Co)-Rapporteurs, the Reference Member State (RMS) representatives, the lead MS representatives (the latter for nationally authorised products), the Supervisory Authority representatives. The composition of this group will therefore vary depending on the situation. In order to allow the EU Operational Task Force to efficiently operate the crisis management steps of the Incident Management Plan, various fields of expertise need to be represented in such group.
  - Its role is operational, acting as a support to the EU Executive Task Force by providing the required administrative and scientific input, and its responsibilities are to (1) implement the decisions taken by the EU Executive Task Force in a timely manner, (2) operate the crisis management steps of the Incident Management Plan (or the relevant steps, where appropriate), including communication aspects, (3) follow-up on the implementation, including communication aspects, (4) propose to the EU Executive Task Force any necessary remedial action forsubsequent implementation, and (5) propose to the EU Executive Task Force to close the crisis.

It is the responsibility of each NCA to establish a national crisis management structure which allows for adequate interaction with the management structures set-up at EU level. Such national structure should operate in accordance with a national crisis management procedure.

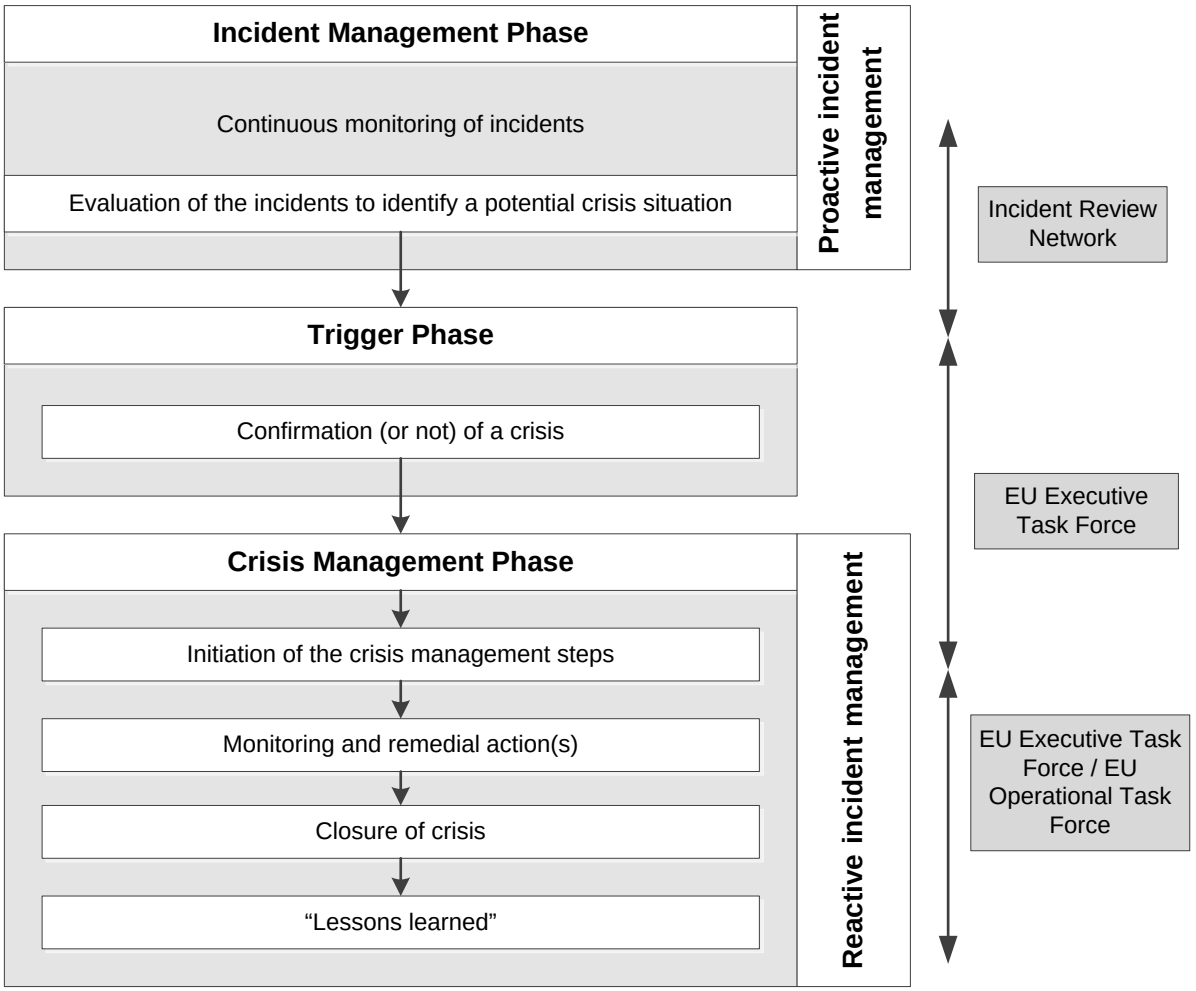
The availability of different levels of management structures will require an excellent collaboration in order to deal in the most efficient way, and with full respect of the time constraints, with a (potential) crisis situation. This will necessitate features such as adequate communication channels, availability of back-ups, etc. in order to facilitate efficient decision-making.

4.4.2. Incident management procedure

The EU-wide Incident Management Plan consists of the following key steps:

- Continuous monitoring of incidents (i.e. occurrence of events or receipt of new information) which could have a serious impact on public health.
- Evaluation of the incidents to identify a potential crisis situation (including the need to prepare for any (media) queries and the identification of the most appropriate legal / regulatory framework to be used to address the situation).
- Confirmation (or not) of a crisis.
- Initiation of the crisis management steps of the Incident Management Plan (or the relevant steps, where appropriate), including the communication strategy.
- Monitoring of the initiatives taken and identification of the need for remedial action(s), where necessary.
- Closure of the crisis.
- Conduct of a “lessons learned” exercise.

This is summarised in the following flowchart:



A more detailed description of the aforementioned key steps is provided in Annex 4.

In summary, the Incident Management Plan follows a two-step approach, i.e.:

- Proactive incident management: the daily management of incidents in terms of their identification and monitoring, the review of their public health impact, and the initiation of the remedial action(s) to address the situation. In case of serious concerns about (a) product(s) potentially leading to major risks for public health, this set of activities involves the IRN, which based on the existing evidence, will decide on the possibility to address the incident through routine measures, or alternatively will request a PRA from the lead party before deciding on the need to escalate the incident to the EU Executive task Force for consideration and confirmation (or not) of a crisis.
- Reactive incident management: the initiation, in exceptional circumstances, i.e. in case of a confirmed crisis, of the crisis management steps of the Incident Management Plan, the subsequent operation of such crisis management steps, up to the closure of a crisis.

In concreto this means that it is in only a few situations that the complete Incident Management Plan (including the crisis management steps) will have to be followed, whilst in the large majority of situations only the incident management steps will need to be followed.
It should, once again, be emphasised that any application of the Incident Management Plan fully acknowledges the rights of the NCAs to take pre-emptive action at national level in accordance with the provisions of Union legislation.

Annex 1

Incident Review Network - Rules of procedure

1. Mandate

The mandate of the IRN is to:

- actively review, from a managerial point of view, incidents reported as a Pharmacovigilance RA in terms of their public health impact and if the identified concerns are likely to be addressed through routine measures (hereby also considering the consequences for on-going clinical trials), consider the need to prepare for any (media) queries, and identify the most appropriate legal/regulatory framework to be used to address the situation;
- likewise provide advice, upon request, for incidents reported via NUI, to the person initiating the NUI, in terms of the public health impact and if the remedial action can be undertaken through routine measures;
- likewise review other incidents (not reported via Pharmacovigilance RA or NUI) brought to the attention of the IRN Chair such as quality problems (reported in the frame of the "Compilation of Union Procedures on Inspections and Exchange of Information") accompanied by a safety concern, newly published data in scientific journals, coverage in the lay press, action taken by a non-EU Regulatory Authority, etc., in terms of the public health impact and the possibility to apply routine measures to address the identified concerns;
- likewise provide advice on emerging issues with a (potential) major public health impact (such as supply shortages caused by manufacturing/GMP compliance problems);
- decide, after review of an incident, on the need to prepare a PRA, (for those incidents for which the IRN is of the view that the identified public health concerns may not be addressed by taking routine measures), to subsequently request the lead party to prepare such PRA, and to finally discuss it, and in particular the various options available as regards the managerial handling of the incident/crisis, with the party responsible for drafting the PRA.

It should be emphasised that the activities performed by the IRN do not interfere with the work undertaken by the CHMP, the PRAC or the CMD(h), i.e. the scientific assessment of the identified concerns and the provision of recommendations for regulatory action.

The mandate of the IRN will be reviewed at regular intervals in the context of the regular review of the operational aspects of the incident management handling at EU level.

2. Composition

The IRN is a virtual multidisciplinary network of experienced staff members (working at the EMA and the NCAs of the MSs), set up within the EU Regulatory Network.

It is composed of a core group of 8 persons, 6 of whom are jointly appointed by HMA and the EMA, for a period of 3 years, which can be renewed.

The following disciplines are represented in the core group: risk management, risk communication and regulatory affairs. In addition European Commission representatives (2) are part of the core composition.

Additional members will be invited to participate in the IRN depending on the situation. The disciplines represented in the additional membership are pharmacovigilance / pharmacoepidemiology and GMP / quality.
To ensure a link between the IRN and the EMA scientific committees or working group, the chairs of the CHMP, PRAC and CMDh will also be invited as appropriate, as well as other EMA staff members working across the relevant Divisions to provide advisory and administrative supports, as per its role as coordinator of the EU Pharmacovigilance System. The EMA will chair the IRN.

3. Renewal of membership

Three months before the end of the mandate, existing members will be invited to express an interest in continuing membership for another term of 3 years.

Subsequently a call for expression of interest will be made at HMA and EMA level.
The final appointments will be jointly made by the EMA and HMA.

4. Operational aspects

Upon receipt of a Pharmacovigilance RA, or NUI for which the advice of the IRN has been sought, or any other incident (not reported via Pharmacovigilance RA or NUI), the IRN (either the core group or the extended group with additional members depending on the situation) will review within 24 hours of receipt, from a managerial perspective, the reported incident in terms of their public health impact and if the identified concerns are likely to be addressed through routine measures. Their conclusion should be by consensus. The IRN Chair will organise a teleconference with IRN members to discuss the issue at stake. The outcome of the IRN discussions will be recorded by the EMA into the European Pharmacovigilance Issues Tracking Tool (EPITT). In addition, such outcome will be circulated to CHMP, PRAC, CMD(h) as appropriate, cc. HMA. If the conclusion is that routine measures are likely not to be sufficient to address the situation, the IRN Chair will ask the lead party to draft a PRA within a defined timeframe agreed by the IRN. Upon receipt, the IRN will discuss the PRA, and in particular the various options available to manage the incident/crisis, with the party responsible for drafting the PRA. Subsequently the PRA (including the preferred option) will be provided by the EMA to the EU Executive Task Force.

Annex 2

Incident review network – Composition

The composition of the Incident Review Network is as follows:

IRN core composition (covering the following areas of expertise: regulatory, risk management, risk communication)	
European Medicines Agency	Fergus Sweeney (Chair), Peter Arlett (back-up Chair), Monica Dias
European Commission	Olga Solomon
Member States	Maria Luisa Casini, Amelia Cupelli, Brigitte Keller-Stanislawski, Almath Spooner
As applicable Pharmacovigilance / Pharmacoepidemiology experts	Dolores Montero Corominas, Sabine Straus
As applicable, when the incident impacts on the products' quality or relates to a GMP compliance issue (a); representative of Official Medicines Control Laboratory (OMCL) Networks (b)	a) Brendan Cuddy, Anne Hayes, Diana van Riet-Nales b) Corinne Civade
EMA committees / Working group	Chairs of the CHMP, PRAC and CMDh as applicable
Other representatives participating in the IRN meetings	
Member States	Representative of the Member States raising the incident, lead Member States of the product(s) concerned depending on its marketing authorisation type (e.g. CHMP/PRAC rapporteurs, Reference Member State(s), or lead Member State(s) for signal detection in EudraVigilance as appropriate
Supervisory Authorities	Of the product(s) concerned where applicable
EMA staff members representatives of various areas such as	Scientific expertise (e.g. Safety and/or Quality including the EMA Product Lead), Communication, Regulatory and International Affairs and other as appropriate.

Annex 3

EU executive task force – Composition

The composition of the EU Executive Task Force is as follows:

EU Executive Task Force core composition	
European Commission	Andrzej Rys (Chair), Olga Solomon
HMA	Dominique Martin, Lorraine Nolan
EMA	Guido Rasi (Executive Director), Noël Wathion, Fergus Sweeney

In addition, depending on the situation, the CHMP Chair and/or the PRAC Chair, and/or the CMD(h) Chair may be invited to participate at EU Executive Task Force meetings.

Annex 4

Outline of the incident management procedure

As described in Section 4.4. "Operation of the EU Regulatory Network Incident Management Plan", the Incident Management Plan consists of a number of key steps, as described below. Such information is summarised in the attached flowcharts (Attachments 1-4):

1. Continuous monitoring of incidents

1.1. Sources of information

Various sources of information suggesting an incident exist. Such information can be in the public domain or not. In addition, the information can be subject of media attention. In the latter case, the immediate assessment and handling of communication may become crucial especially when public confidence is at risk. Examples of such sources of information are new safety data provided to a Competent Authority, newly published data in scientific journals, coverage in the lay press, action taken by a non-EU Regulatory Authority, safety signal from a database, etc.

1.2. Exchange of information

Taking into account the characteristics of the EU Regulatory Network, it is of utmost importance that any information suggesting an incident is shared without delay between the NCAs, the EMA and the EC. To support a rapid exchange of information in this field, a Pharmacovigilance RA and NUI system has been established. The operation of this Pharmacovigilance RA and NUI system, whereby a clear distinction is made between the criteria for the use of a RA vis-à-vis the use of a NUI, is currently as follows:

- A RA should be used when a MS/the EMA has a safety concern which potentially has a major impact on the known risk-benefit balance of a medicinal product and which could warrant prompt regulatory action and communication to patients and healthcare professionals.
- A NUI should be used for information exchange in relation to safety concerns not fulfilling the criteria for a RA.
  In addition, in order to increase the efficiency of operation, a dedicated tool has been developed, i.e. EPITT, allowing the MSs, the EMA and the EC to have online access within the secure EudraNet network to and share information on the safety of medicinal products, including the Pharmacovigilance RAs and NUIs.

In parallel the "Compilation of Union Procedures on Inspections and Exchange of Information" provides for additional platforms for exchange of information suggesting an incident (e.g. Quality Defect RA system).

1.3. Filtering mechanism

There is a need to carefully screen an ever increasing amount of information and to actively search for any new important information in order to be able to conduct proactive incident management. The availability of a robust filtering mechanism, therefore, is crucial.

Any party within the EU Regulatory Network (e.g. MSs, EMA, and EC) can report incidents using the available tools (including the Pharmacovigilance or Quality Defect RA and NUI systems). Upon receipt, the IRN Chair should consider the relevance for involvement of the IRN taking due account of the apparent severity of the problem as well as its level of urgency.

2. Evaluation of the incidents to identify a potential crisis situation, resulting in the preparation of a preliminary risk analysis

2.1. Involvement of the incident review network

The main role of the IRN (cfr. IRN mandate as reflected in Annex 1) is to act as an advisory group in the frame of incident management to the EU Regulatory Network, primarily by actively reviewing, from a managerial point of view, certain incidents in terms of their public health impact and if the identified concerns are likely to be addressed through routine measures (hereby also considering the consequences for on-going clinical trials). Such review does not interfere with the work undertaken by the CHMP, the PRAC and the CMD(h), i.e. the scientific assessment of the identified concerns and the provision of recommendations for regulatory action. The IRN will also identify the most appropriate legal/regulatory framework to be used and will have to consider the need to prepare for any (media) queries. To allow for replies to such queries the IRN Chair will either ask the EMA (for Centrally Authorised products - CAPs) or the lead MS (for non-CAPs) to consider the preparation of “lines to take”. In situations where both CAPs and non-CAPs are involved, the EMA will take the lead in relation to the preparation of “lines totake”, in close collaboration with the involved MS(s).

Only the agreed identification by the IRN of a potential crisis on the basis of the information available at that moment (i.e. the IRN being of the view that the public health concerns are likely not to be addressed through routine measures) will trigger the involvement of the EU Executive Task Force. As regards the need to involve the EU Executive Task Force the IRN should also take into account when reviewing information, aspects such as new and major scientific findings of general public health relevance which may affect the EC’s policy in the pharmaceutical area and may require Union action (e.g. influenza pandemics).

2.2. Preparation of a preliminary risk analysis

In order to decide if the crisis management steps of the Incident Management Plan should be initiated, the situation should be carefully assessed on the basis of a PRA to be drafted by the CHMP (Co)-Rapporteur(s), PRAC (Co)- Rapporteurs, in collaboration with the EMA for CAPs, and the RMS(s) for products authorised via Mutual Recognition and Decentralised procedures. When only nationally authorised products are involved a lead MS needs to be identified, taking into account the lead MS for signal detection and, if applicable, Periodic Safety Update Report (PSUR) assessment. In case of situations characterised by involvement of both CAPs and non-CAPs the PRA needs to be drafted by the CHMP/PRAC (Co)-Rapporteurs in collaboration with the EMA.

The PRA will elaborate on a number of elements such as risk identification, risk analysis and analysis of the main options available to address the situation. In particular, the following needs to be undertaken:

- Risk identification: collection of the information; identification of the information sources; checking of the accuracy; elaboration of the characteristics of the risk(s) associated with the new findings in as quantitative a way as possible.
- Risk analysis: preliminary analysis of the wider impact of the risks and of the main options available to address the situation; review of previous/already existing risk assessments on the same issue.

It is important to emphasise that such analysis of the situation needs to be conducted in a very tight timeframe, which in no way can form the basis for regulatory action. The decision to request the preparation of a PRA is taken by the IRN. The IRN will set a timeframe for the preparation of the PRA and the aforementioned “lines to take”. In order to allow for efficient decision-making it is important for the PRA to clearly state the various options to manage the incident/crisis. Once available, the PRA, in particular the various options available as regards the managerial aspects of the handling of theincident/crisis, will be discussed between the IRN and the party responsible for drafting the PRA (preferably via teleconference). Once an agreement has been reached the PRA (including the preferred option) will be provided by the EMA to the EU Executive Task Force.

3. Confirmation (or not) of the crisis on the basis of the PRA and initiation of the crisis management steps of the Incident Management Plan (or parts of it, where relevant), including the communication aspects

On the basis of the PRA the EU Executive Task Force will decide if the crisis management steps of the Incident Management Plan (or parts of it, where relevant) should be initiated. In addition, the EU Executive Task Force will elaborate on the communication aspects, resulting in the availability of a communication strategy. Involvement of patients’ and healthcare professionals’ representatives may be considered in communication aspects and should be favoured, whenever possible. The overall aim is to convey a unified and targeted message to the outside world within the shortest possible timeframe. The EU Operational Task Force will subsequently implement the decisions taken by the EU Executive Task Force, in accordance with the agreed timeframes, and will operate the crisis management steps of the Incident Management Plan.

4. Monitoring of the initiatives taken and identification of the need for remedial action, where necessary

The EU Operational Task Force will also, as part of the operation of the IMP, monitor the implementation of the actions taken, including communication aspects. In case there is a need for remedial action, the EU Operational Task Force will propose the necessary initiatives to the EU Executive Task Force for subsequent implementation, once agreed by the EU Executive Task Force.

5. Closure of the incident or the crisis as appropriate

Should the IRN consider that routine measures are sufficient to address the situation upon review of the incident and its impact on public health, a close out communication will be sent by the EMA on behalf of the IRN to all involved parties, leading to the end of the IRN involvement. This will be done once the agreed (regulatory) actions will have been triggered (e.g. the notification letter from the triggering party for the launch of a Union referral procedure has been received by EMA, and/or the adequate communication has been issued to inform the marketing authorisation holders, healthcare professionals and the general public as applicable).

Should the crisis management have been triggered, the crisis situation will be considered closed once the EU Executive Task Force on the basis of advice provided by the EU Operational Task Force has agreed upon such closure. A close out letter will then be sent by the EMA on behalf of the EU Executive Task Force to all involved parties.

6. Conduct of a “lessons learned” exercise

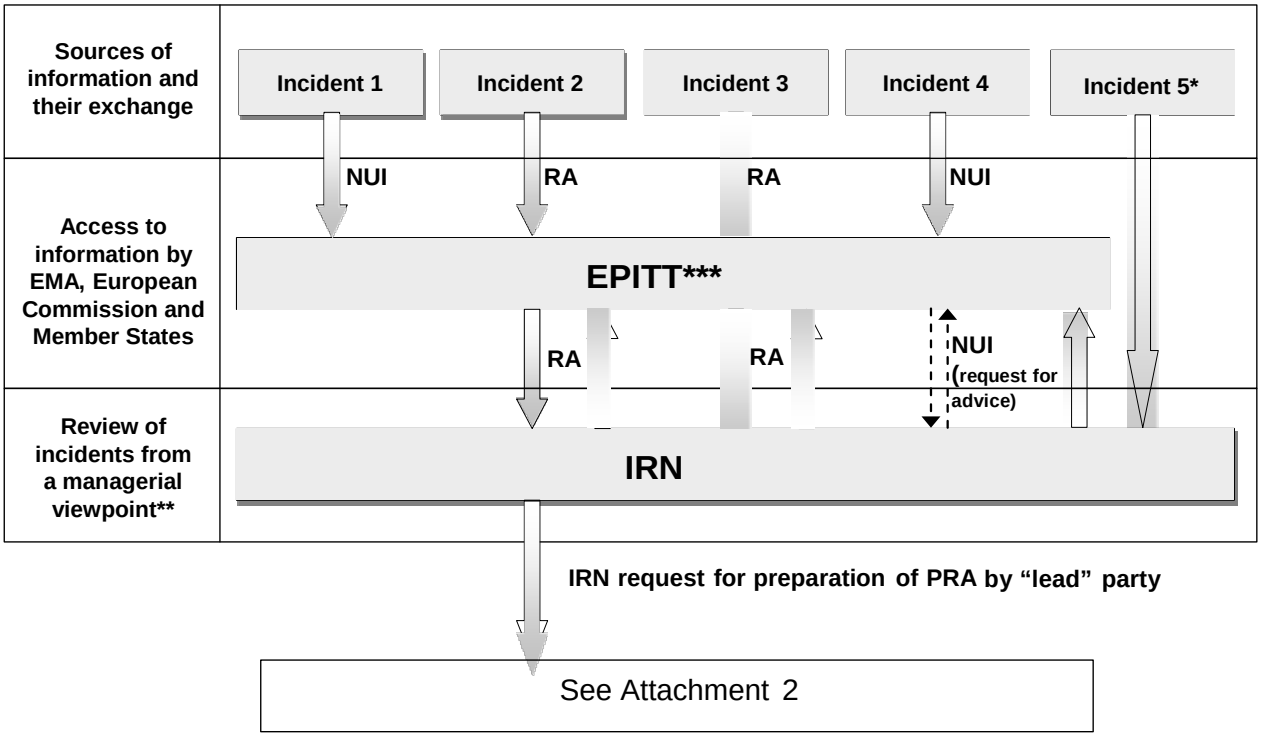
It is of utmost importance to carefully monitor the adequacy of the various elements of the Incident Management Plan. To this effect, the closure notice sent to all involved parties at the end of each incident reviewed by the IRN and each crisis initiated by the EU Executive Task Force will include the lessons learnt during the particular situations, if any.

In addition, there is a need to review at regular intervals (e.g. on a yearly basis) the operational aspects of the incident management handling at EU level, including experience obtained with the preparatory steps leading to the decision to confirm (or not) the crisis, in order to further increase the efficiency of operation.
The outcome of the regular “lessons learned” exercise performed by the IRN and EU Executive Task Force may lead to a revision of the Incident Management Plan.

Attachment 1

Incident management phase

Flowchart



* Refers to other sources of information (not reported via Pharmacovigilance RA or NUI) such as quality problems (reported in the frame of the "Compilation of Union Procedures on Inspections and Exchange of Information") accompanied by a safety concern, newly published data in scientific journals, coverage in the lay press, action taken by a non-EU Regulatory Authority, etc.

** Including identification of the most appropriate legal/regulatory framework to be used and consideration of the need to prepare for any (media) queries.

*** In addition to information being put in EPITT, outcome of IRN discussions also to be circulated to CHMP, PRAC, CMD(h) as appropriate, cc. HMA.

EPITT: European Pharmacovigilance Issues Tracking Tool.

IRN: Incident Review Network.

NUI: Incident reported as a Non-Urgent Information.

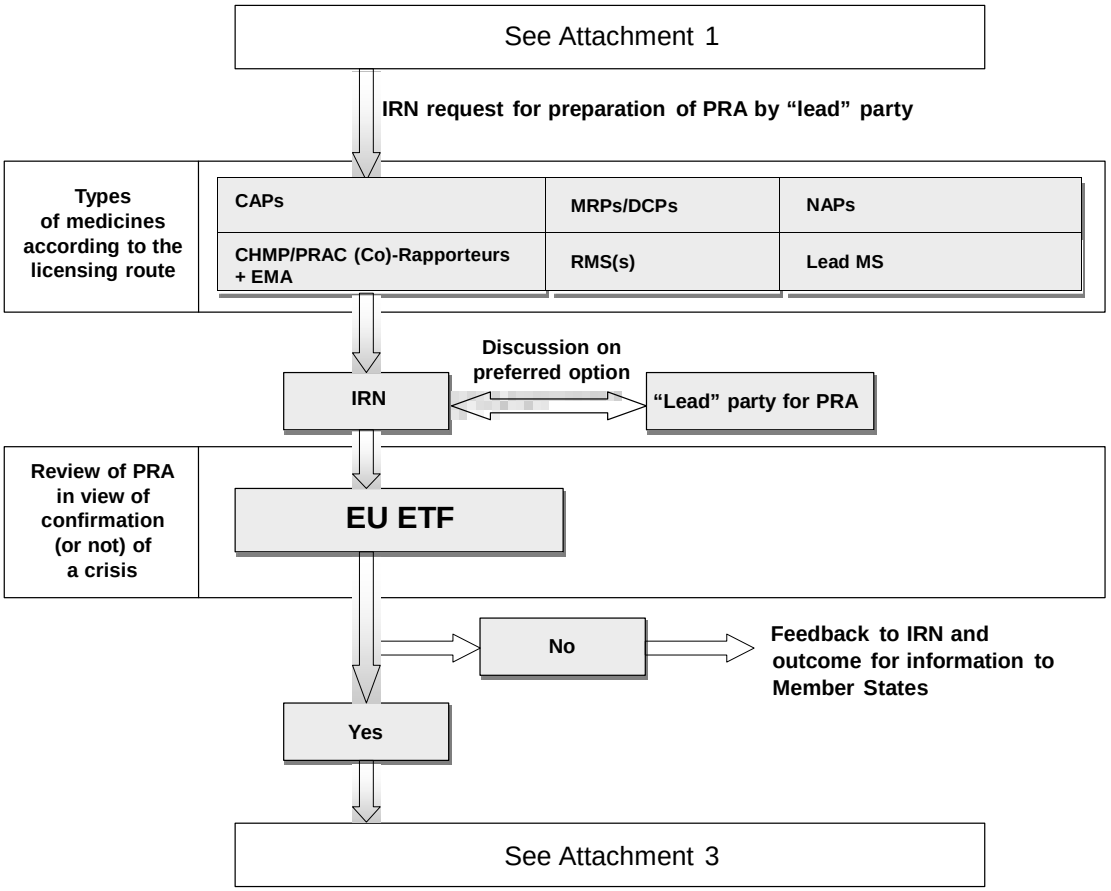
PRA: Preliminary Risk Analysis.

RA: Incident reported as a Rapid Alert.

Attachment 2

Trigger phase

Flowchart



CAPs: Centrally Authorised Products.

CHMP: Committee for Human Medicinal Products.

DCPs: Decentralised Products.

EU ETF: EU Executive Task Force. IRN: Incident Review Network.

MRPs: Mutually Recognised Products.

NAPs: Nationally Authorised Products.

PhVWP: Pharmacovigilance Working Party.

PRA: Preliminary Risk Analysis.

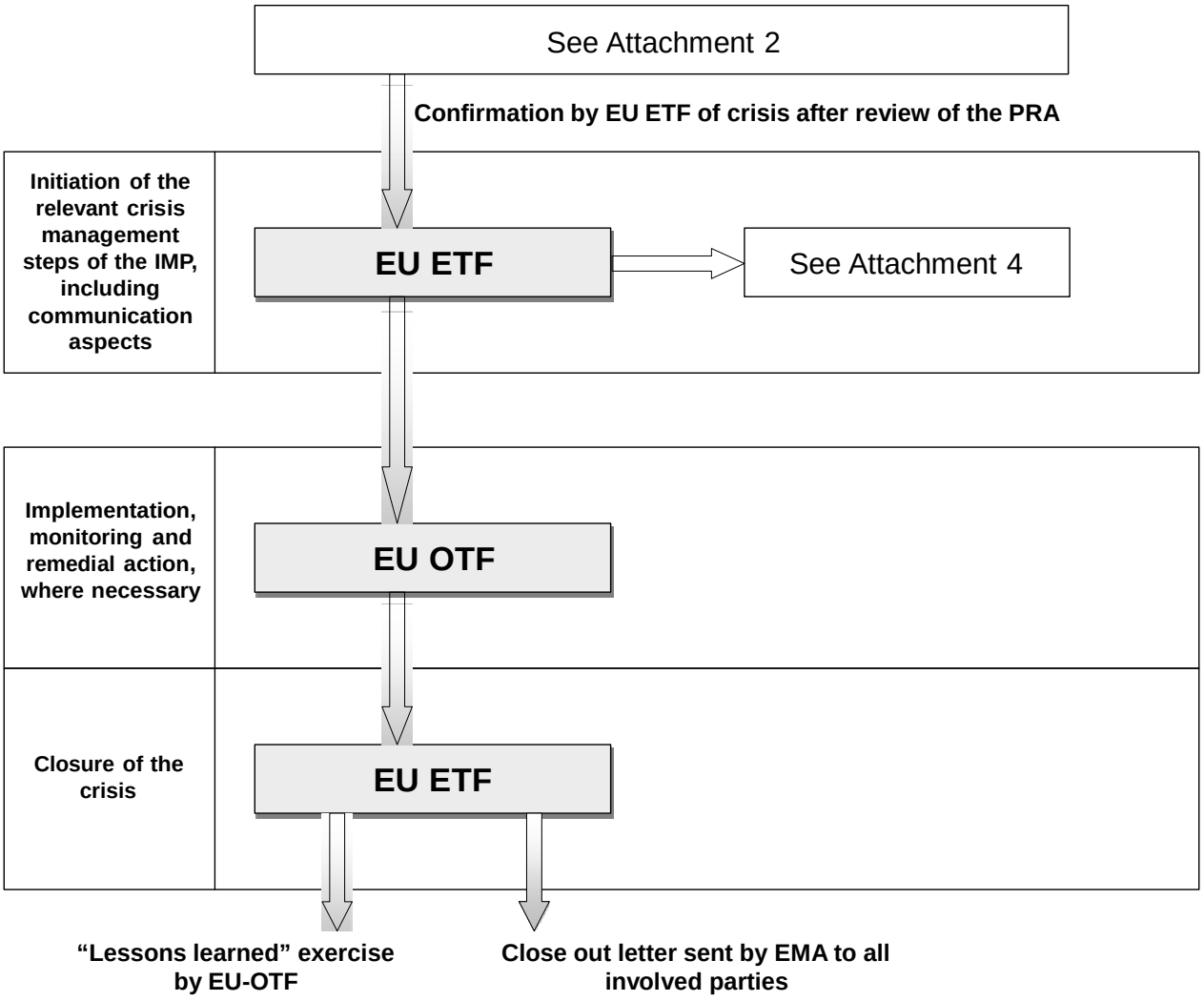
PRAC: Pharmacovigilance Risk Assessment Committee.

RMS(s): Reference Member State(s).

Attachment 3

Crisis management phase (1/2)

Flowchart



EU ETF: EU Executive Task Force.

EU OTF: EU Operational Task Force.

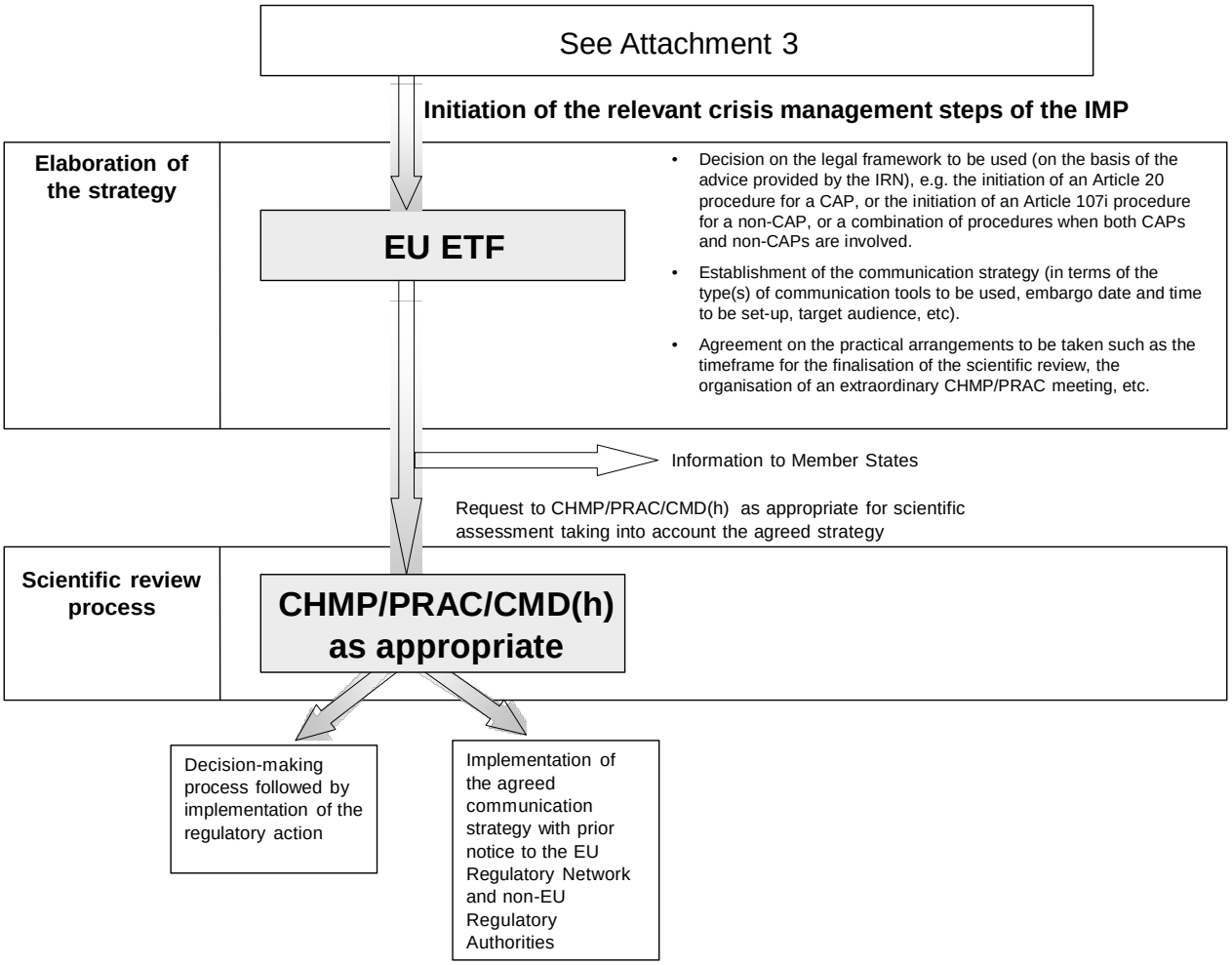
IMP: Incident Management Procedure.

PRA: Preliminary Risk Analysis.

Attachment 4

Crisis management phase (2/2)

Flowchart



CHMP: Committee for Human Medicinal Products.

CMD(h): Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human.

EC: European Commission.

EU ETF: EU Executive Task Force.

IMP: Incident Management Plan.

IRN: Incident Review Network.

PRAC: Pharmacovigilance Risk Assessment Committee.