Received: 14 May 2020 | Revised: 6 August 2020 | Accepted: 8 September 2020

DOI: 10.1002/pds.5133

REVIEW

WILEY

Navigating stormy waters: 10 years of operation of the European Union Regulatory Network Incident Management Plan for Medicines for Human Use

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Abstract

Purpose: The article provides an overview of the European Union Incident Management plan (EU-IMP) and reviews its first 10 years of operation. It outlines its scope, objectives, triggers, principles, and components.

Methods: Records were extracted from the European Pharmacovigilance Issues Tracking Tool and a separate tracking system for the period August 20, 2009 to August 19, 2019.

Results: During the 10 years of observation, 78 incidents were reviewed by the Incident Review Network and addressed through routine measures. Their number has varied throughout the years with a significant decrease after 2012. Incidents mainly covered safety (56%) and quality (34%) issues or a combination thereof (5%). The majority (70%) were notified by EU regulators and involved centrally and nationally authorized product in similar proportions. A referral was recommended as the assessment pathway for 47% of the issues while lines-to-take were the most frequent communication measure (the sole measure in 65% cases). Forty-six per cent of the issues resulted in a variation, whereas 22% resulted in maintenance of the marketing authorization.

Conclusion: The EU-IMP is underpinned by a robust regulatory framework with defined processes and clear roles and responsibilities and offers a platform to coordinate actions and communication at EU level, rapidly pool expertise, minimize duplications, and address public health incidents.

KEYWORDS

drug safety, EU incident management plan, EU regulatory network, incident review network, pharmacoepidemiology, pharmacovigilance, quality

1 | INTRODUCTION

Medicinal products are authorized once their quality, safety, and efficacy have been assessed and their benefit-risk balance judged to be positive. By supporting the development of new medicines and

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granting marketing authorizations, Regulatory Authorities (RAs) enable the availability of new therapeutic options to respond to unmet medical needs.[1] RAs are responsible for protecting public health by monitoring that the above requirements are met throughout the entire lifecycle of a medicinal product and by taking the necessary actions, when this is no longer the case.

Medicines are authorized mainly based on the supportive data coming from clinical trials that are typically of limited duration and sample size, exclude the most severely ill patients, and limit the number of comedications.[2] Those controlled conditions significantly differ from the ones encountered in real life and may consequently hamper the possibility of identifying in the pre-authorization period important serious adverse drug reactions. For instance, rare, delayed reactions or those that occur due to an interaction with other medicinal products or comorbidities might only emerge after a medicine is released on the market, when the exposure is significantly larger, for a longer duration and in less ideal settings.

Even in cases where a medicinal product has been authorized for many years, some new information might emerge at some point that may warrant to recall that medicine because it ceases to satisfy the quality requirements, as a result of, for example, unexpected identification of impurities, with possible consequent shortage of supply.

In the European Economic Area (EEA), the European Union (EU) Regulatory Network (hereafter referred to as "the Network") is composed of the RAs in the Member States (MSs) (hereafter referred to as National Competent Authorities [NCAs]), the European Commission (EC), and the European Medicines Agency (EMA).[3] The continuous collaboration among those partners ensures that individual efforts are coordinated and concerted toward the common goal of protecting public health, through an approach underpinned by the existence of clear roles and responsibilities.

The EC is the competent authority for centrally authorized products (CAPs), while NCAs are the competent authorities for nationally authorized products (NAPs). The EU regulatory model foresees that while NCAs retain responsibility for medicinal products authorized on their territory, the EMA provides coordination to support the scientific evaluation, supervision, and safety monitoring of all medicines on the EU market.[4]

In order to enable the network to rapidly and effectively manage incidents along the lifecycle of CAPs, the EMA established a crisis management plan in 1997.[5] Taking into account the experience gained with CAPs, as well as the need to have a more encompassing and coordinated approach in the EU, the initial plan was revised and widened in scope to include medicines authorized in the EU through any procedure. Additionally, the membership was revised to include a wider expertise and, in order to formalize the process, a module was created in the European Pharmacovigilance Issues Tracking Tool (EPITT)[6] to track the EU-IMP steps and support rapid communication on incidents between MSs and the EMA. Arising from these, the EU Regulatory Network Incident Management Plan (EU-IMP) was set up in 2009.[7] The EU-IMP is coordinated by the EMA and can be triggered by any member of the Network.

KEY POINTS

- The EU-IMP supports the EU Regulatory Network in protecting public health.
- It offers an opportunity to coordinate actions and communication at EU level.
- It deals with the full spectrum of important public health issues relating to medicinal products on the EU market.
- During 10 years, 78 incidents were reviewed by the IRN and all have been addressed through routine measures.

An incident is defined as an event or new information regarding one or more medicine(s) authorized in the EU, which could have a serious impact on public health.[7] This may include events that affect the known safety, quality, efficacy, or availability of the medicinal product, due to for example, manufacturing compliance or other supply chain issues. While some events initially might not seem to have major consequences on public health, they may trigger media attention and patients' concerns, and subsequently negatively impact on the use of a medicine.

Incidents are managed through "routine" measures, that is, those that are already established and immediately applicable, such as (1) pharmacovigilance and quality/manufacturing monitoring tools, for example, carrying out of inspections (2) regulatory tools enabling action, for example, variation, suspension, or revocation of the marketing authorization, and (3) communications aimed at patients and healthcare professionals, for example, press release, questions and answers (Q&A) documents, Direct Healthcare Professional Communication (DHPC), and so on.

The EU-IMP is therefore fully in line with the WHO manual for the assessment of pharmacovigilance systems,[8] that identifies crisis management and communication as two of the minimum requirements of functional pharmacovigilance systems. Through communication, the work of RAs in assessing and supervising medicinal products throughout their life cycle becomes visible to the public.[9]

The decision on the appropriate measure is informed by consideration of the impact, the level of urgency of the incident, as well as evidence coming from various sources. For instance, the results of a study conducted within the SCOPE initiative have shown that EU Health Care Professionals have high awareness of DHPCs.[10]

If routine measures are not considered sufficient to address the public health concern, due to its potential impact and/or urgency, an incident can be upgraded to a crisis. This has not been necessary for the 78 incidents that have been dealt with by the EU-IMP during the period of observation of this study.

Acknowledging that no previous publication is available in the scientific literature, the main objective of this descriptive analysis is to

provide a comprehensive overview of the experience during the first 10 years of operation of the EU-IMP, including concrete examples, as well as to support future research aimed at analyzing the system and its performance.

2 | PRINCIPLES OF THE EU-IMP

In line with the provisions of EU legislation, the modus operandi of the EU-IMP is based on achieving an appropriate balance between the prerogative of NCAs to take the pre-emptive actions they deem appropriate for their territory (eg, suspend a product, trigger the EU referral mechanisms,[11] and so on), and the need for coordination at EU level.

Clear roles, responsibilities, and established mechanisms to bring together expertise from the entire Network and share information are crucial to minimize the potential for duplication and perhaps divergent actions, shorten the time needed for decision making, and deliver a consistent message for the EU public, while effectively responding to the public health concern.

Flexibility is a key factor in managing very different issues that may range from safety to quality, efficacy, or a combination thereof, and may concern one or more medicinal products (eg, product class issues, products manufactured at the same facility) authorized through different procedures.

The approach followed by the EU-IMP builds on the realization that public health issues benefit from a common methodology with the objective to ensure that outcomes are proportional to the public health concern, based on robust evidence and supported by an agreed approach for informing stakeholders. Many factors contribute to the achievement of this and the associated decision making, including the estimation of the public health impact of the issue, the identification of knowledge gaps and the appropriate regulatory framework to address these and the definition of the communication strategy.

3 | EXCHANGE OF INFORMATION ON PUBLIC HEALTH CONCERNS

The EU-IMP may be triggered after new information on a public health concern is received from any source, but more frequently EU NCAs, non-EU RAs, Marketing Authorization Holders (MAHs), the Press, and so on. This may include new data shared with regulators, publications in scientific journals, actions taken by a non-EU RA, and so on.

Two instruments have been devised in the EU to facilitate exchange of information relating to serious safety and quality issues. These are EPITT and the rapid alert notification procedure aimed at members of the Rapid Alert Network.[12]

Through EPITT, MSs and the EMA exchange safety information on (1) concerns with potential major impact on the known risk-benefit balance of a medicine, possibly warranting prompt regulatory action and communication (in the form of Rapid Alerts) or (2) other less urgent concerns (in the form of Non-Urgent Information).

Through the Rapid Alert Network procedure, MSs, EMA, the EC, and other relevant partners (eg, international organizations and non-EU RAs) exchange quality information mainly on recalls of medicinal products, due to quality defects or falsification that may result in illness, suboptimal or inappropriate treatment, or threat to life.

4 | HOW THE EU-IMP WORKS

The EU-IMP facilitates the interaction between the incident management structures set up at EU-level and those established at national level.

The EU-IMP has a proactive and a reactive component. The proactive component has the objectives of: (1) continuously scanning the horizon and monitoring various sources of information (eg, newly published data, communications from other RAs, signals from safety databases, and so on) on incidents impacting medicinal products, (2) reviewing their public health impact, and (3) recommending the necessary routine measures to remedy the situation.

When a serious concern for a medicinal product with the potential of leading to major risks for public health is identified, the Incident Review Network (IRN) is involved within the shortest possible time. After reviewing the information available on a particular incident, the IRN Chair (or back-up) takes the decision on whether an IRN is needed. This is normally the case when discussion within the Network is needed as to the most appropriate assessment pathway for the issue and there is need for coordination at EU level in terms of actions and communication. The IRN then convenes by teleconference and is chaired by the EMA. It has a core of about 20 members (from the EMA, its scientific committees, EC and NCAs) with multidisciplinary expertise covering risk management, risk communication, regulatory affairs and pharmacovigilance (Figure 1). Additional members may be invited ad-hoc to participate, based on the specific expertise required. For example in case of quality and Good Manufacturing Practice (GMP) issues, participation from the European Directorate for the

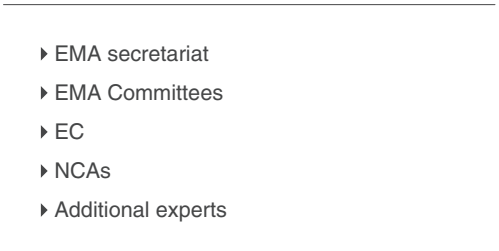

FIGURE 1 Composition of the IRN. EMA, European Medicines Agency; EC, European Commission; NCA, National Competent Authority

Quality of Medicines (EDQM),[13] the network of official medicines control laboratories (OMCL),[14] and so on may be required. The Chairs of the Committee for Medicinal Products for Human Use (CHMP), the Pharmacovigilance Risk Assessment Committee (PRAC) and the co-ordination group for mutual recognition and decentralized procedures—human (CMDh) are also invited, as applicable, to link the IRN and the scientific committees, which may subsequently be called on to conduct a detailed scientific assessment. This ensures that the right expertise and leadership are available to rapidly provide perspective and direction on how to best address an incident.

The main tasks of the IRN are to: (1) review the public health impact of incidents from a management and coordination perspective, (2) appraise whether routine measures are likely to satisfactorily address the incident, (3) recommend the assessment pathway (including possible actions to gather further information on the issue) to conclude on the appropriate regulatory measure, and (4) recommend the relevant communication tools. Its mandate does not include the scientific assessment of the issue, or the adoption of the final appropriate regulatory action, which are under the remit of the PRAC, CHMP, or the CMDh, as applicable.

Figures 2 and 3 reflect the experience in terms of assessment pathways and communication tools that have been recommended by IRN over the past 10 years of operations.

A referral[11] is a review procedure used to resolve issues such as concerns over the safety, or risk benefit balance of a medicine (or class of medicines). During a referral, the EMA, through its scientific committees and/or the CMDh, conducts a thorough scientific assessment on the issue and makes a recommendation on behalf of the EU. For most of referrals, the EC issues a decision to all MSs to reflect the measures to take to implement the recommendation.

A signal procedure is the framework through which the PRAC assesses information and makes a recommendation on a new or known adverse event that may be caused by a medicine authorized in the EU and requires further investigation.

Some communication measures, for example, Lines-to-Take (LTTs) are not public but are documents that are prepared by the agency and disseminated to the network to assist its staff in responding with a consistent message to possible media and public queries on issues of high public health interest.[15]

Depending on the type, severity, and urgency of the issue, the approach recommended by IRN to address an incident may include one of more of the options in Figures 2 and 3, as illustrated by the examples provided in section 7.

The IRN conclusions are tracked by the EMA and circulated to CHMP, PRAC, CMDh, and the Heads of Medicines Agencies for awareness.

The EU-IMP has also a reactive component, which would ensue in cases where the IRN concludes that routine measures are not sufficient to address the incident, but the latter risks escalating into a crisis. In this scenario, the IRN Chair may ask a lead party (Rapporteur for CAPs or appointed EU MS for NAPs) to prepare within a defined timeframe a Preliminary Risk Analysis, with the objective to elaborate on the risk and on the options available to handle (from an operational point of view) the incident. Based on the preliminary risk analysis, the main EU crisis management structure, that is, the EU Executive Task Force (EU-ETF), decides on whether the incident constitutes a crisis.

The EU-ETF is chaired by the EC and includes senior management representatives of the EC, EMA, and NCAs, with ad-hoc participation of scientific committee and CMDh Chairs. The role of the EU-ETF is strategic, and its main responsibilities are to: (1) confirm the crisis, (2) initiate the crisis management steps of the EU-IMP, including the communication strategy, and (3) agree on the closure of the crisis. The EU-ETF is supported by the EU Operational Task Force, which has a variable composition, with participants from the EMA, EC, MSs, and

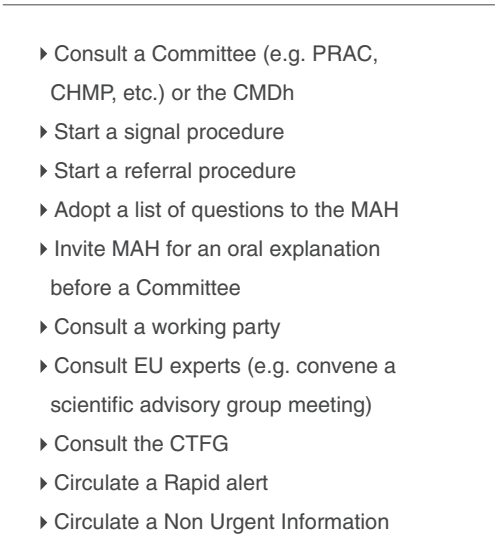

FIGURE 2 Assessment pathways toolbox. CHMP, Committee for Medicinal Products for Human Use; CMDh, Coordination Group for Mutual Recognition and Decentralized Procedures-human; CTFG, Clinical Trial Facilitation Group; EU, European Union; MAH, Marketing Authorization Holder; PRAC, Pharmacovigilance Risk Assessment Committee

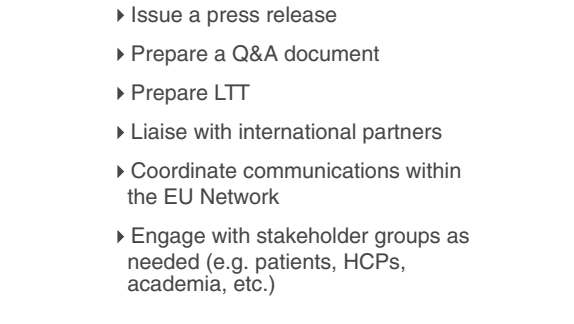

FIGURE 3 Communication and stakeholder engagement measures toolbox. LTTs, lines-to-take, Q&A, question and answer, HCP, healthcare professionals

scientific committees and which provides administrative and scientific support.

A schematic representation of the interface of the main EU-IMP phases is provided in Figure 4.[7]

None of the incidents that have occurred in the 10 year period covered by this descriptive analysis have led to escalation while even complex issues (see the example of sartans in section 7) could be dealt with through routine measures.

In order to test the suitability of the EU-IMP to handle a potential crisis, a dry run was conducted in 2017 with members of the IRN, the EU-ETF, EC, EMA, and MSs. This was based on a fictitious scenario involving the suspension of a CAP (containing the same substance as several NAPs) in a MS after receipt of several reports of suspected adverse drug reactions with a fatal outcome.[7] The exercise confirmed the capability of the EU-IMP to handle crisis situations. Additionally, the experience gained over these years has provided opportunities for improvement in several areas including process streamlining, communication, interactions, composition, success factors, and technical considerations. These have been translated into subsequent system enhancements with for example the inclusion in the IRN of a larger expertise (risk management, communication, quality), the increased duration of the IRN mandate, technical upgrades to allow recording of the IRN meetings and storing of audio material, and clarification of practicalities concerning the preliminary risk analysis (who drafts it, expected timelines, etc.), in case an incident risks escalating into a crisis.

5 | METHODS FOR A DESCRIPTIVE ANALYSIS OF 10-YEARS' EXPERIENCE

All EU-IMPs are tracked in EPITT and receive an identifier when the first IRN teleconference is held for the issue. Records were retrieved from EPITT for the period spanning from August 20, 2009-August 19, 2019.

In parallel, a more granular tracking system is maintained to keep detailed records of each individual IRN teleconference, as well as the final outcome of the issue. This provides key information such as date of first notification; source; geographical origin; channel of communication; product concerned; authorization route of the product; description of the issue; category of the issue (safety, quality, Good Clinical Practice [GCP] non-compliance, and so on); type of issue; date of IRN; IRN recommendation and outcome of the issue. Whenever an EU-IMP results in a referral

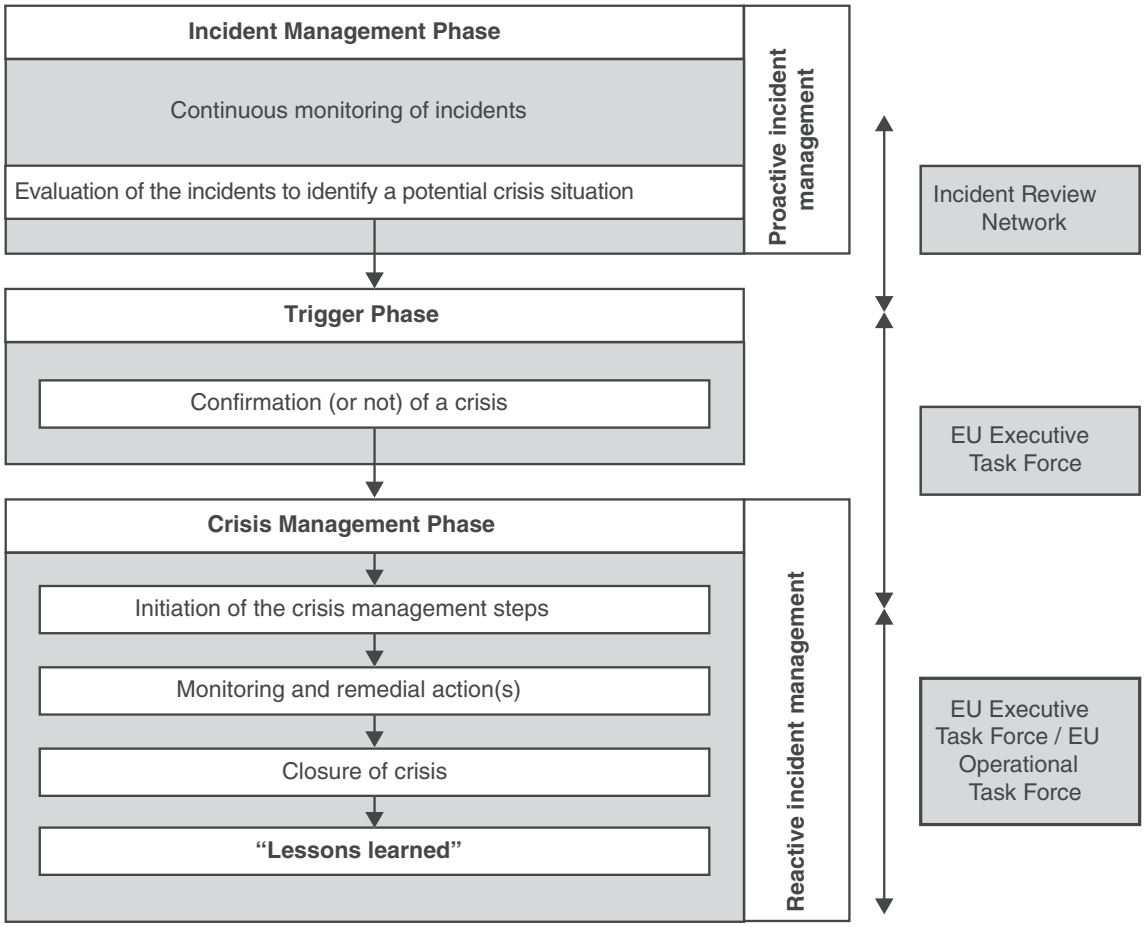

FIGURE 4 Schematic representation of the EU-IMP phases. Figure taken from "The European Union regulatory network incident management plan for medicines for human use EMA/351583/2012"

procedure, the article from the legislation underpinning its triggering is also tracked.

The information from EPITT and from the complementary tracking system was used to derive the results presented in the next section.

6 | RESULTS

During the first 10 years of operation of the EU-IMP, a total of 78 incidents were reviewed by the IRN. A teleconference was organized by the EMA to discuss each new incident and, if applicable, follow-up information on a known issue. While for the majority of incidents a single IRN teleconference was sufficient, 13 of them (8 safety and 5 quality), due to their complexity, as well as the need to gather further evidence, needed more than one iteration. This led to a total of 106 teleconferences organized for the 78 incidents.

Examples of complex issues include the identification of shortcomings in the quality management system (in relation to the aseptic filling process) of Ben Venue Laboratories (manufacturer of a large number of CAPs and NAPs[16]), or the identification of impurities in products containing sartans with a tetrazole ring (see section 7), for which a total of 5 and 7 follow-up teleconferences, respectively, were needed over the months.

The initial notification to the EMA came from a variety of sources: mainly EU NCAs (55, 70.4%); followed by MAHs (13, 16.7%); the FDA (5, 6.4%); the Press (2, 2.6%), the European Centre for Disease Prevention and Control, US Academia or a whistle-blower (1 each, ~1% each) (Figure 5).

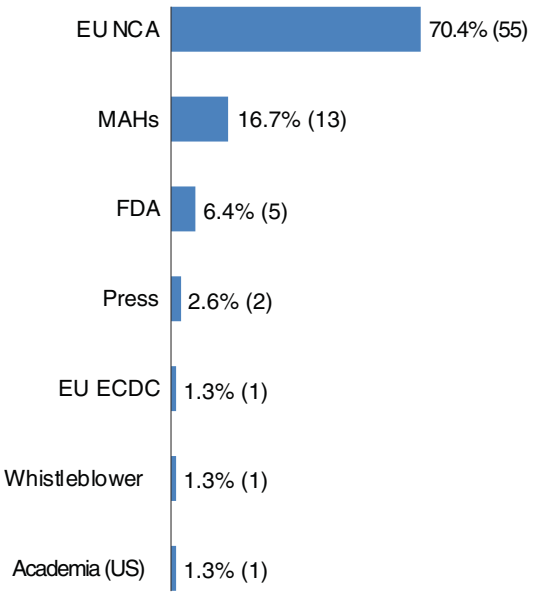

FIGURE 5 Sources of initial incident notification to the EMA. ECDC, European Centre for Disease Prevention and Control; EU, European Union; FDA, Food and Drug Administration; MAH, Marketing Authorization Holder; NCA, National Competent Authority; US, United States [Colour figure can be viewed at wileyonlinelibrary.com]

These sources notified incidents mainly via direct communication (email or phone call), rapid alerts through the Rapid Alert Network (in case of quality issues), EPITT Rapid Alerts or Non Urgent Information (for safety issues).

Mechanisms are in place to ensure continuous collaboration and multilateral exchange of information among international regulators from the initial notification and throughout all the stages of the assessment of the issue, until its resolution. For instance, whenever an issue discussed at IRN is deemed to be of relevance internationally, the outcomes of the discussion, together with relevant documents are promptly shared with international regulators with whom confidentiality agreements are in place. For issues of major public health impact new ad-hoc confidentiality agreements and collaborations may be set-up, as has happened for example, in response to the nitrosamine contamination. Additionally, strategic partnerships across the regions, usually referred to as "clusters," have been established, with experts from the EMA and other RAs who meet periodically via teleconference.[17] For instance, the pharmacovigilance cluster offers the opportunity to promptly share information on drug safety issues, including product-related risk assessment (especially if emerging safety concern) and to provide advance notice on anticipated regulatory actions, public information, and communication prior to decision making and publication.[18]

An IRN teleconference was organized on the same or the day after the initial notification in 42% of the cases. For the remaining 58% of the cases, more information was needed prior to organizing an IRN teleconference. IRN recommendations have always been implemented within the shortest possible delay. For instance, when the IRN recommended that the issue should be addressed via a signal procedure, this was commenced at the following planned PRAC meeting, which happened within 1 month from the concerned IRN. When the IRN recommended to issue a stand-alone press release, this was published within 1 week of the date of the IRN, but most commonly within 2 days.

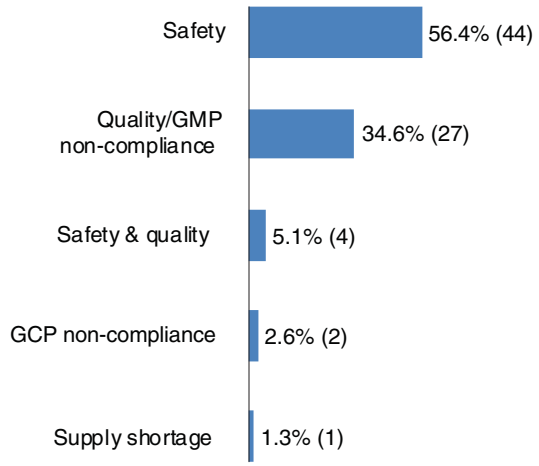

FIGURE 6 Categorization of issues. GCP, Good Clinical Practice; GMP, Good Manufacturing Practice [Colour figure can be viewed at wileyonlinelibrary.com]

During the observation period (see Figure 6), most of the issues dealt with related to safety (44, 56%), quality (27, 35%), or a combination thereof (4, 5%).

The vast majority of safety issues were triggered by signals from post-marketing experience and studies, while most of the quality and GMP non-compliance issues originated from notifications of contamination and data integrity compromise. The identification of major flaws in bioequivalence studies[19] or of systematic data manipulation in clinical trials[20] triggered GCP non-compliance issues. The only issue of supply shortage handled through the IRN was caused by fishing restrictions in Japan following a natural calamity in 2011, with consequent impaired sourcing of raw material for protamine sulphate.[21]

Due to the intrinsic nature and unpredictability of incidents, the number of initial notifications varied significantly across the different years of observation, with a peak of 15 in 2011 and a low of 1 in 2019 (for which only 8 months fall in the reporting period). Figure 7 displays the number of initial notifications that were received per year.

The average number of initial notification per year was 11 for the period 2009 to 2012 and 5 for the period 2013 to 2019. Considering that the decrease in notifications concerning safety issues was the major contributor to the drop in the overall number of initial notifications after 2012, it may be argued that the implementation of the revised pharmacovigilance legislation in 2012 introduced clear roles and responsibilities and offered robust regulatory tools to manage most of the incidents without recourse to the IRN mechanism.

Incidents occurred with NAPs and CAPs at comparable frequencies: 30 (38%) with NAPs; 26 (34%) with CAPs; and 22 (28%) with a combination of both.

The IRN recommended to trigger a referral in almost half of the total number of incidents, that is, in 37 (47%) cases, while other assessment pathways (see Figure 2) were advised in 41 (53%) cases. The legal bases underpinning the triggering of the referral procedures were different articles of the EU legislation, depending on the type of underlying issue, mainly Articles 31 (10, 13%) and 107/107i (10, 13%) of Directive 2001/83/EC and Articles 20 (7, 9%) and 5(3) (4, 5%) of Regulation (EC) 726/2004, or various combinations thereof. Article 31 or 20 is invoked in case of safety, quality, or efficacy issues, when the concerned products include at least a NAP or exclusively CAPs, respectively. An article 107/107i procedure is triggered in case an urgent regulatory action is necessary due to a safety concern with an authorized medicinal product, while article 5(3) is invoked when an opinion on a scientific matter related to the evaluation of medicines for human use is sought from the CHMP.

A communication strategy was recommended for the vast majority of incidents, at the time of the initial and/or follow-up teleconference, as applicable. When the total number of IRN teleconferences is taken into consideration, that is, 106 teleconferences for 78 incidents, one or multiple communication approaches were considered necessary in 80 cases (75%), while only in 36 instances (25%), no immediate communication was warranted. Depending on public health needs, one or more options were implemented, with the most frequent being LTTs and press releases (see Figure 8). LTTs and public communication materials were shared within the network prior to publication through the so-called "Early Notification System," a system set up to coordinate communication actions on critical issues across the EU and to support consistency of the message to the public.

The final outcomes of the incidents managed through the EU-IMP differed significantly, depending on the nature of the issue and the robustness of the evidence. They ranged from maintenance of the unaltered marketing authorization (22% of cases) to its variation (46% of cases), through to its suspension (10% of cases) or revocation (9% of cases) (see Figure 9). One more recent issue is still ongoing at the time of this analysis.

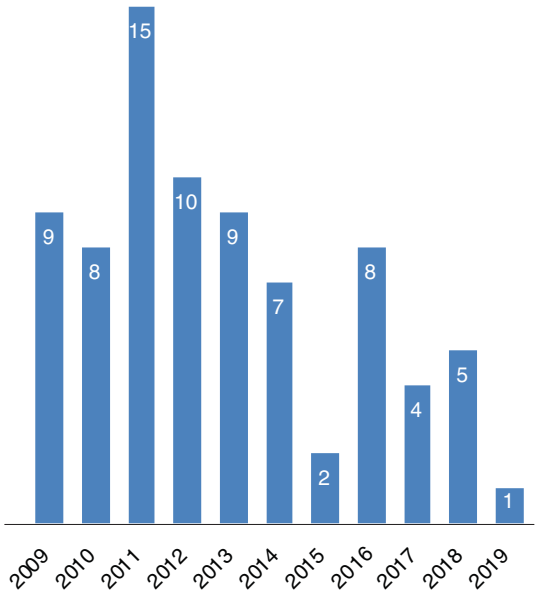

FIGURE 7 Number of initial notifications per year [Colour figure can be viewed at wileyonlinelibrary.com]

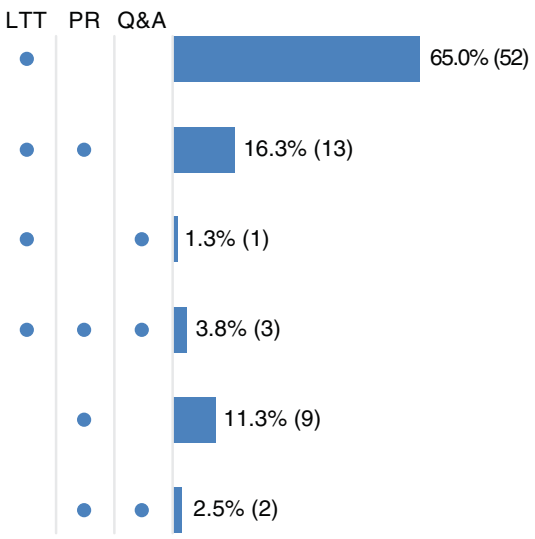

FIGURE 8 Main types of communication approaches recommended at the IRN teleconference. LTT, lines-to-take; PR, Press Release; Q&A, question and answer [Colour figure can be viewed at wileyonlinelibrary.com]

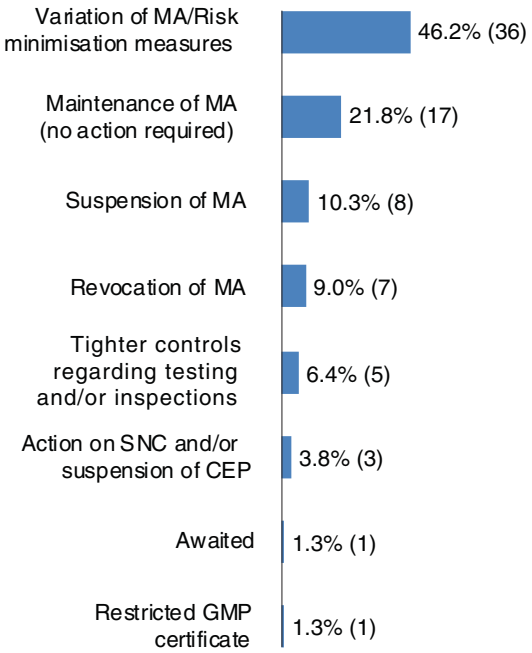

FIGURE 9 Final outcome of EU-IMPs. GMP, Good Manufacturing Practice; MA, Marketing Authorization; CEP, Certificate of Suitability to the monographs of the European Pharmacopoeia; SNC, statement of non-Compliance with Good Manufacturing Practice [Colour figure can be viewed at wileyonlinelibrary.com]

7 | EXAMPLES OF ISSUES MANAGED THROUGH THE EU-IMP

The IRN has supported the network while dealing with several important incidents. A number of examples in some more detail are provided to illustrate the proactive work of the EU-IMP and its interface with the existent regulatory framework.

Among the many significant safety examples, one was the notification from the Paul-Ehrlich-Institut of cases of possible immune-related encephalitis in association with daclizumab, a medicine used to treat adult patients with relapsing forms of multiple sclerosis. An IRN meeting was promptly convened and after consideration of the evidence available at that point in time, it was concluded that the issue could be handled through an Article 20 referral procedure triggered by the EC and that product withdrawal should be urgently considered within that procedure (routine measure). As a provisional measure, the marketing authorization of daclizumab was suspended within 2 weeks of the initial notification, in line with the legal mandate of the PRAC, while a formal review via a referral procedure was ongoing and a press release was issued to inform the public.[22] This temporary measure was taken after weighing the evidence available at that point in time against the seriousness of the potential issue. It was also agreed to prepare LTTs, to ask the Clinical Trial Facilitation Group (CTFG) whether other relevant cases were observed in clinical trials, and to inform international partners. As a result of the high level of cooperation and information sharing among all the concerned stakeholders, and after carefully assessing all the available evidence, the PRAC was in a position to finally conclude within three-months that the risk with the product outweighed the benefit.[23] Meanwhile, the MAH had taken the decision to voluntarily withdraw the marketing authorization for this product.

A second safety example concerns the notification of the MAH's intention to terminate several ongoing clinical trials with idelalisib, a cancer medicine used to treat adult patients with chronic lymphocytic leukemia (CLL) or follicular lymphoma, due to increased risk of serious respiratory infections and associated deaths observed in three studies. Two IRN teleconferences were held in the days following the initial notification to agree that the issue could be handled via routine measures, specifically the prompt initiation (by the EC) of an Article 20 referral procedure. Through the IRN, the information gaps were identified, the available evidence was shared with international RAs, the relevance of the issue (observed in off-label use) to the on-label use was discussed, and engagement with the MAH on interim measures and proposed actions was initiated. The IRN agreed that the CTFG was to be consulted on the draft DHPC, LTTs had to be drafted and a press release[24] issued. After giving due to consideration to the seriousness of the potential issue, as well as the incomplete evidence available, the PRAC resolved to adopt (within 1 week of the initial notification) a temporary measure (restriction of the indication in previously untreated patients with CLL and a certain genotype) and a DHPC.[25] Four months later, after reviewing the complete dataset, consulting the relevant expertise within the referral procedure, and taking into consideration the absence of alternative suitable treatments, the PRAC recommended that the temporary restriction should be lifted. However, in order to better protect patients, risk minimization measures were strengthened. Warnings were added to the product information to request that treatment is not started in cases where there are ongoing systemic infections, and that effective monitoring of these and adequate prophylaxis specifically for *Pneumocystis jirovecii* pneumonia (during treatment and up to 6 months after interruption) is in place.[26]

The IRN has also dealt with numerous important quality issues. Shortly after the initial notification of potential genotoxic impurities (N-nitrosamines) in valsartan containing products (used to treat hypertension), an IRN teleconference was convened. Considering that the impurity was due to the route of synthesis and cross-contamination, the IRN discussed that the issue could also be relevant for products containing other sartans (provided they had a tetrazole ring). Therefore, the issue was judged to significantly impact public health (there were about 13 000 sartan containing medicines on the EEA market) and likely to attract media interest. Due to its complexity, as well as the limited information initially available, several IRN teleconferences were needed to discuss the most appropriate routine measures to handle the issue. These included recommendations for harmonized market actions (batch quarantines and recalls), initiation of an Article 31 referral procedure,[27] development of harmonized LTTs and issuing of press releases.[28] Other actions included sampling and testing proposals for the EDQM and the OMCL network, and working with international partners toward an harmonized approach to the assessment, inspections, and communication. The evaluation resulted in a

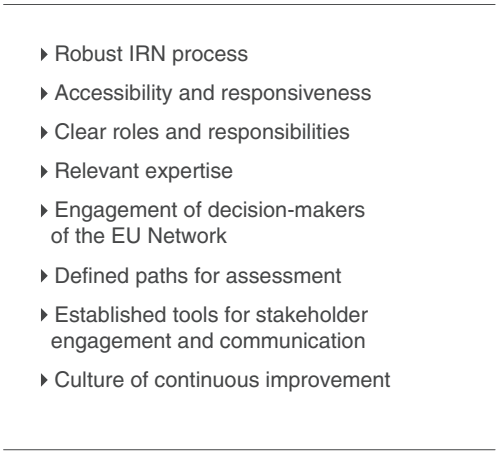

FIGURE 10 Core factors of the EU-IMP

recommendation for MAHs to review their manufacturing processes, introduce rigorous testing regimens, and ensure that sartan medicines currently on the EU market would only contain levels of those impurities below agreed safe thresholds, and that by 2021 no quantifiable levels of those impurities should be present in sartan products.

8 | MAIN LIMITATIONS AND PERSPECTIVE FOR FUTURE RESEARCH

As this analysis is descriptive in nature, with the main objective to summarize the experience in the first 10 years of operation of the EU-IMP, there was no comparator arm, nor any attempt to measure the effectiveness of the individual regulatory interventions[29] that followed the review of incidents by the IRN.

A comparison of the EU-IMP with the processes followed by other regulators to manage incidents, together with the measurement of the impact of risk minimization activities, in line with the PRAC Impact strategy[30] are considered the priorities for future research. Such research should inform on the consequences of regulatory interventions, and offer a benchmark with other regulatory systems, which will drive the strengthening of the EU system.

9 | CONCLUSIONS

Over its first 10 years of operation, the EU-IMP has proved capable of managing a wide scope of incidents with important public health impact through routine measures, without the need for escalation to a crisis. This has been made possible through a series of core factors, as highlighted in Figure 10.

The EU regulatory framework has provided the necessary tools to deal with the full spectrum of patient safety and public health issues concerning all types of medicinal products authorized in the EU.

The implementation of the revised pharmacovigilance legislation in 2012 has offered robust regulatory instruments and has established clear roles and responsibilities to directly manage most safety issues without the need to go through the IRN mechanism. In so doing, it has reduced the number of ad-hoc IRN meetings needed, thus making use of the already existing regulatory options and increasing the overall efficiency of the Network.

Through the cooperation of NCAs, the EC and the EMA, the EU-IMP supports the Network in fulfilling its mission to protect public health by ensuring that medicines on the EU market are safe, effective, of high quality and by advising on the necessary actions, when issues arise that might have a serious impact on public health. While recognizing the prerogative of MSs to take the actions they deem appropriate in their territory, the EU-IMP offers a platform to coordinate actions and communication at EU-level, to rapidly pool expertise, as well as to minimize duplications.

During the first 10 years of operation, the EU-IMP has been progressively strengthened with the introduction of enhancements needed to ensure that it can continue fulfilling its mission, while coping with ever complex and new health challenges.

This descriptive analysis aims to document the foundations of the EU-IMP. In so doing, it should support further research aimed at specifically appraising the performance of the system and benchmarking it against the approach followed in different jurisdictions to drive future enhancements.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge Georgy Genov and Morgane De Verdiere for their critical review and Radoslav Zhelev and Loris Piccolo for their contribution to the graphics.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DISCLAIMER

The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on the behalf of or reflecting the position of the European Medicines Agency, one of its committees or working parties, or any regulatory agency or organization with which the authors are affiliated.

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How to cite this article: Santoro A, Caplanusi I, Sweeney F, et al. Navigating stormy waters: 10 years of operation of the European Union Regulatory Network Incident Management Plan for Medicines for Human Use. *Pharmacoepidemiol Drug Saf*. 2020;29:1343–1352. https://doi.org/10.1002/pds.5133