Introduction

Pharmaceutical legislation provides a legal framework, to ensure the availability of acceptably safe, effective enhancement and high-quality medicines to patients. Within this framework marketing authorization holders (MAHs) are requested to establish and maintain pharmacovigilance (PV) systems. These systems should be capable of detecting, assessing, understanding, and preventing adverse effects or any other possible drug-related problem [1].

In our setting, we merged four different PV systems in a new Headquarter (HQ)-Affiliate model in the European Union (EU) context. This occurred through a deep and comprehensive due diligence, with subsequent harmonization and enhancement of procedures and tools in order to comply efficiently with the legal framework.

This integration aimed to establish of a clear, transparent, and centralized organizational structure with peripheral dependencies at the country level. A functional reporting and management system has been developed in order to ensure efficient data collection and processing, as well as the detection, assessment, understanding, mitigation and communication of medicinal product risks, in accordance to EU regulations and international requirements.

The PV systems integration offered the opportunity to enhance quality and compliance of processes and to centralize Companies' relationships with regulators and commercial partners.
The principal aim was the rationalization and strengthening of the PV system, with a centralized HQ overview supported by local Affiliates.

Discussion

1. Qualified Person for Pharmacovigilance

As part of the pharmacovigilance system in the EU, any MAH shall have permanently and continuously at its disposal an appropriately qualified person responsible for pharmacovigilance (QPPV) [2].

In our starting scenario, each of the four Companies had a different QPPV appointed. After systems integration in an HQ-Affiliates model, a unique QPPV, responsible for the whole system, MAHs, and products, has been designated at HQ level.

The nominated person, in accordance to current legislation, has sufficient authority to influence the performance of the quality system and the pharmacovigilance activities, as well as authority over the PV system. The QPPV submitted its name and contact details to the Competent Authorities (CA) in the EU Member States and the European Medicines Agency (EMA) [3]. Upon verifying the information, an EMA officer validated the information and approved the role [4].

Once officially approved, the appointed QPPV also nominated Local Responsible Persons for each Affiliate with country-specific responsibilities. These locally nominated representatives are expected to be knowledgeable in the specifics of the national PV system, speak the national language and facilitate communication with the National Regulatory Authorities at the local level.

Both QPPV and Local Responsible Persons identified a trusted Deputy to ensure business continuity and back-up procedures.

Under respective responsibilities, HQ and local PV teams have been implemented, with the definition of hierarchical relationships and assignment of roles. Any delegation was documented in writing.

The choice of QPPV and PV staff appointments took into account qualifications, theoretical and practical expertise for the performance of pharmacovigilance activities.

The QPPV oversees the whole PV system and periodically hosts meetings with HQ PV staff and Local Responsible Persons to adequately control the performance of the quality system and the pharmacovigilance activities and to promote, maintain and improve compliance with the legal requirements.

2. Pharmacovigilance System Master File

Certainly, in the integration of pharmacovigilance systems, one of the most challenging and delicate tasks was related to the merging of different Pharmacovigilance System Master Files (PSMFs).

Indeed, the structure of the PSMF changed drastically in our HQ-Affiliate model to reflect, in a clear and complete way, the new organization of the PV system.

PV legal framework provides the general requirements of the PSMF detailing the contents of each section (including Annexes). The very first thing to remember is that according to EU requirements, upon a change in the QPPV or location of the PSMF information, the Article 57 database shall be updated by the MAH immediately and no later than 30 calendar days [5].

An important impact was on the size of the Annexes and the PSMF itself. Information from previous Companies has been collected under one unique document. PSMF's Annex B (summarizing the commercial partners) and Annex H (reflecting the company portfolio) were carefully reviewed in order to avoid loss of information; in this sense, a close collaboration respectively with the business and regulatory departments (both at HQ and local level) became necessary.

The structure of the newly born PV organization has been represented in a clear way, reflecting the relationships with other Affiliates, which have been now included among the sources of safety data (Annex C). In this sense, it is recommended to list Affiliate offices and providing a contact point (address, telephone, and e-mail) for each site [5].

When a rearrangement takes place is anyway important to identify in the PSMF the main site of PV activities, and MAH should have an appropriate rationale for the location decision. In our set up the location of PSMF resides on the QPPV office identified at the HQ. Local Responsible Persons have been requested to provide their input on some PSMF sections like e.g. the local service provider, screened local journal for safety purposes, status of any local study/programme which may have an impact on pharmacovigilance activities. For this purpose, an internal PSMF procedure has been designed requiring it to be read and understood by all PV staff, including personnel acting within the Affiliates.

3. Safety Database

A critical topic to deal with in PV systems merge is the safety database. In our scenario safety data was stored in four different databases, computer systems, or storage types, one per each of the Companies. As a consequence, these data were collected, processed, and stored in different ways. This represents a challenge to deal with when data migrations are planned. Due to these aspects, safety data migration should be accurately defined, planned, performed, and tracked.

At first, per each data migration, we performed an impact assessment, to evaluate data types, characteristics, and volumes in order to plan the migration and choose the best strategy. The planning defined quality con-

trol to be performed before and after data transfer and assigned roles, responsibilities, and main deliverables, taking into account technical requirements and potential risks.

As a prerequisite, all the source data was appropriately cleansed and purged before migration. In our setting, source data owners (Affiliates) and target data owner (HQ) collaborated in the quality control of data, defining migration rules, information to be exchanged, and activities to be conducted.

In our scenario, the three main types of data migration strategies have been performed. The identified HQ has been defined as the target system, and this means that its structured database has been configured to accept and correctly map all the incoming information; Part of the source data was originally managed by Affiliates on paper and on an electronic register of cases and events. In order to migrate this data type, a manual data migration strategy has been planned and conducted. This type of migration was based on the full manual processing of pharmacovigilance cases into the target system. Each case was then individually entered and controlled by the HQ PV team.

Another partition of data from the former Companies was originally managed on a pharmacovigilance structured database, and due to its characteristics an E2B data migration has been planned and conducted. This type of migration is based on .xml files transfer from the source system into the target system.

These files contain single case information structured in compliance with E2B data elements, as defined by ICH [6].

This data migration strategy was conducted with standard validated functionalities of the source (export of .xml files) and target system (import of .xml files). This process implied manual data entry of some non-E2B parameters in accordance also to target safety database configurations. Each case was individually imported and controlled by the HQ PV team.

The high amount of remaining data was managed in a structured database, which characteristics permitted the execution of an ETL (extract/transform/load) data migration strategy. This type of migration is managed through a process which uses scripts and tools for data extraction, transformation, and loading from the source system to the target system. The process implied data mapping, development, and validation of scripts and consisted of the whole data transfer directly from the source database to the target database.

Per each migration a final report has been issued, describing background, materials and methods, results and overall discussion of the data migration. Actions and deviations that occurred were here tracked and discussed.

4. Process Integration

a. Individual case safety report management:

As known, a PV system should take appropriate measures to collect, collate and evaluate all reports of suspected adverse reactions from unsolicited or solicited sources [7].

In our setting, different PV systems have been merged in an HQ-Affiliate model where Individual Case Safety Report Management (ICSR) management is under the responsibility of HQ. This implied the transition from separate processes to a unique system that has been developed to guarantee the acquisition of information and to ensure that the collected reports are authentic, legible, accurate, consistent, verifiable, and as complete as possible for their clinical assessment.
To do so, internal procedures have been harmonized, and a new flow of safety information has been set in order to ensure both the centralized receipt at HQ level and the local management of incoming reports.

Tracking systems have been therefore revised as well as reconciliation processes and compliance monitoring activities. Within this quality topic, data collection, transfer, management, and coding, and case validation, evaluation, follow-up, submission, and archiving, have been structured and addressed in internal procedures and tools. Upon receipt of such safety, information, HQ has the responsibility to further process ICSRs. Each report is individually triaged, tracked, entered in the centralized safety database, controlled for quality, and medically reviewed. The developed system has been also structured in a way that allows for reports of suspected adverse reactions to be validated in a timely manner and exchanged, in accordance to data protection laws, between CAs and MAHs within the legal submission time frame.

In this integrated PV system, electronic data storage allows traceability of all data entered or modified, including dates and sources of received data, and dates and destinations of transmitted data.

Overall, the integrated PV system harmonized data collection, coding, and evaluation, ensuring higher standards than was before in separated and fragmented systems. This brought consistency and value to data quality and system performance.

b. Safety evaluation and risk Management:

Continuous monitoring of product risk-benefit profiles, result of evaluation, decision-making processes, and risk minimization measures are primary requirements in pharmacovigilance. This include:
• Signal generation, detection and evaluation [8];
• Periodic safety update reports (PSUR) scheduling, production and submission [9];
• Risk management and monitoring of the outcome of risk minimization measures [10].

In our scenario, each Company managed such activities based on internal procedures, and the challenge to face during PV systems integration was to plan a quality-based safety evaluation and risk management harmonization.

With product portfolio integration, and overall product mapping was conducted to review marketing authorization status and evaluate safety profiles, requirements, and commitments with CAs. The identified HQ summarized signal management procedures and findings of all Companies assessing strengths, weaknesses, and overall impact on pharmacovigilance activities to be managed by the HQ PV team, establishing a risk-appropriate approach to signals [11].

Each active substance safety profile has been individually reviewed and reassessed.

The whole process led to the definition of roles and responsibilities, the development of new global structured signal detection and evaluation methodologies, properly reflected in internal procedures, new signal management, tools, and schedule, in order to plan, conduct, and track any action of the signal management processes.

The identified HQ collected and analyzed also periodic and ad hoc safety reports prepared by all concerned Companies. Based on such review, new strategic and tactical plans for PSUR submission were issued at

HQ level, considering the standard submission schedule, the European Union reference dates (EURD) list, and local CAs regulations for what concern extra-EU authorizations.
In the integrated PV system, new roles and responsibilities were identified, with a clear definition of interactions between HQ and Affiliates and other Companies' departments for a well-controlled and managed centralized scheduling, production, and submission of periodic safety update reports. This added value not only for harmonization purposes and reduction of administrative burden, but also to facilitate true global periodic benefit–risk assessment for the medicinal products.

Upon collection of ongoing and approved Risk Management Plan (RMPs) from all Companies, HQ evaluated the opportunity to prepare new RMPs and to harmonize different RMPs for same active substances in a core document.

A re-evaluation of products' lists of safety concerns, significant changes in the existing additional pharmacovigilance or additional risk minimization activities was conducted. RMPs and related provisions were summarized and tracked along with the results of this evaluation. The overall process led to gather knowledge and understanding on the product's safety profile, to its critical review, to assess gaps and to plan safety evaluation and risk management activities.

c. Quality assurance and compliance

Another critical process during the integration of PV systems was to ensure a quality and consistent system through the whole newly created organization.

We know that MAH, for performing its pharmacovigilance activities, shall establish and use quality systems that are adequate and effective for this performance. In this regard, general principles of the ISO 9000 Standards on good quality management practices were applied.

We performed an adequate impact analysis resulting in a change management process, which supported and coordinated this significant transformation within the organization.

Close collaboration between the PV and quality departments was needed to move towards a single system.

A new set of procedures has been developed; such procedures assigned the respective roles of HQ and Affiliates in order to manage the new system in a harmonized way.

The integration of PV systems between Companies from different Countries required specific indicators to monitor the compliance over the activities of each newly identified Affiliate.

These local performance indicators were necessary to prove once again that QPPV had an adequate oversight and that appropriate corrective actions can be put in place where there is non-compliance.

Some of the measurable and reproducible indicators that were implemented include:
• Timely exchange of ICSRs from Affiliate to HQ as well as consistent reconciliation processes;
• Timely submission of safety variations to local CA;
• A check that all risk activities/commitments locally required are duly followed

Such locally identified performance indicators will necessarily have an impact on the indicators that are mandatory requested for the PSMF (Annex F).

Inadequate oversight at an affiliate level can result in unidentified risks or issues, which, left unmanaged, can develop into major findings or quality deficiencies, with a potential consequence of poor regulatory compliance. HQ Audit planning has been reviewed in this sense in order to include the Affiliates sites.

Training topic is deeply discussed in EU regulations, and such provisions should be taken into account to ensure high-quality standards of PV processes and guarantee the availability of a sufficient number of appropriately qualified and trained personnel. In our setting, this applied to both personnel acting at HQ and to local contact points acting within Affiliates for whom an ad-hoc training plan must be available. The EMA recently produced a summary document where are detailed skills and requirements of the person acting at the local level for pharmacovigilance: the ability to communicate in a local language or scientific background is some of the requests of the local CAs [12].

d. Pharmacovigilance agreements governance

Of course, the integration of PV systems had a big impact on the governance of Pharmacovigilance agreements and contracts. According to measures drawn up in the EU, there should be mechanisms to ensure that the QPPV can access all relevant safety information, including those coming from MAH's business partners. These agreements must be adhere throughout the duration of the commercial contract, and the MAH is highly recommended to perform regular risk-based audits of the other organization.

Any information about third parties (license partners or local distribution/marketing arrangements) should be included in the applicable sections of the PSMF (Annex B).

In our HQ-Affiliate model, we ensured that no information about each MAH's commercial partners was lost, but rather that they were easily and quickly accessed by the identified QPPV and the regulatory authorities (through the PSMF).

For this reason, contract governance was established in the newly created organization, which took over the overall responsibilities on PV contracts. To ease this, HQ created guidelines for the drafting of contracts and made available standard templates in order to facilitate consultation and ensure the required oversight of the QPPV. In order to ensure global consistency, English language or bilingual contracts became mandatory. In addition to business partner's contracts, we detailed roles, responsibilities, and relationships between each single affiliate and HQ in writing.

This led to distinguish the activities that remained within the Affiliates (like e.g. the local literature, local periodic safety reports, and interaction with local CAs) and other that were centralized (e.g., the global literature screening, the CA submission, the management of ICSR). An enhanced tracking file was created as a sole repository, which would help retrieving our data for Annex B of PSMF but also to have a quick access to main responsibilities as defined in PV contracts.

Conclusions

The integration of different pharmacovigilance systems cannot disregard an in-depth early analysis of all the critical processes that will be affected. Merging should be conducted firstly by taking into consideration the regulatory framework. Adequate resources must be allocated, and close inter-and intra-company collaboration are needed.
Transfer of PV responsibilities has to be done carefully, evaluating which activities necessitate to be centralized (in our setting, the HQ

took over the whole responsibility on risk-assessment and case management activities) and which can be appointed at the local level while always ensuring adequate oversight of the new designated QPPV.

All these changes should be reflected in the structure of the new PSMF. Integration also represented an opportunity to improve certain processes to streamline and make more efficient some processes (in our setting, that was particularly true for signal detection activities and management of contracts). That became necessary also as a result of the increased workload.

A key point was certainly the collection of adverse events in a single safety database. A challenge, not only because of migration from different databases (different s olutions w ere a dopted d epending o n the starting situation) but also because of a higher amount of cases to be managed by guaranteeing both quality and compliance.
For PV systems integration, it should be kept in mind that changes will not only have an impact on processes but also on all involved staff, which is going to deal with a deep renovation and has to be stimulated to adapt to this new way of working. Overall, a highly rate of turnover was observed from our experience.

Conflict of Interest

No conflict of interest has been declared by the authors.

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