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Using Resources for Scientific-Driven Pharmacovigilance

From Many Product Safety Documents to One Product Safety Master File

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Abstract

Current regulations require a description of the overall safety profile or the specific risks of a drug in multiple documents such as the Periodic and Development Safety Update Reports, Risk Management Plans (RMPs) and Signal Detection Reports. In a resource-constrained world, the need for preparing multiple documents reporting the same information results in shifting the focus from a thorough scientific and medical evaluation of the available data to maintaining compliance with regulatory timelines. Since the aim of drug safety is to understand and characterize product issues to take adequate risk minimization measures rather than to comply with bureaucratic requirements, there is the need to avoid redundancy.

In order to identify core drug safety activities that need to be undertaken to protect patient safety and reduce the number of documents reporting the results of these activities, the author has reviewed the main topics included in the drug safety guidelines and templates.

The topics and sources that need to be taken into account in the main regulatory documents have been found to greatly overlap and, in the future, as a result of the new Periodic Safety Update Report structure and requirements, in the author's opinion this overlap is likely to further increase. Many of the identified inter-document differences seemed to be substantially formal. The Development Safety Update Report, for example, requires separate presentation of the safety issues emerging from different sources followed by an overall evaluation of each safety issue. The RMP, instead, requires a detailed description of the safety issues without separate presentation of the evidence derived from each source. To some extent, however, the individual documents require an in-depth analysis of different aspects; the RMP, for example, requires an epidemiological description of the indication for which the drug is used and its risks. At the time of writing this article, this is not specifically required by other documents.

The author has identified signal detection (intended not only as adverse event disproportionate reporting, but including non-clinical, laboratory, clinical analysis data and literature screening) and characterization as the basis for the preparation of all drug safety documents, which can be viewed as different ways of presenting the results of this activity. Therefore, the author proposes to merge all the aggregate reports required by current regulations

into a single document – the Drug Safety Master File. This report should contain all the available information, from any source, regarding the potential and identified risks of a drug. It should be a living document updated and submitted to regulatory authorities on an ongoing basis.

The newly issued EU legislation[1,2] ensures Marketing Authorization Holders (MAHs) have a robust system for collecting safety information from all available sources, critically analysing its scientific meaning and reporting it to regulatory authorities in due time. The final goal is to identify the drug risks and to evaluate all the available information regarding these risks, taking into account any uncertainties, therefore taking appropriate measures to minimize their impact on patient's safety and provide patients with drugs that have the best possible benefit-risk balance.

In the current environment, in which profit margins of pharmaceutical companies are shrinking and resources are limited, any bureaucratic burden or duplication of information that needs to be provided to regulatory authorities can possibly hinder a thorough scientific evaluation of a drug's safety profile as people working in drug safety departments might devote their efforts to maintaining regulatory compliance. It is easy to imagine that in a busy department, employees are likely to produce similar documents in an uncritical manner as if they were working on an assembly line[3] rather than focusing on the scientific meaning of what they do. Regulators have acknowledged the need to simplify pharmacovigilance regulations, and significant steps have been undertaken to reduce bureaucratic requirements,[1,2] especially those regarding the reporting of adverse reactions and the evaluation of Periodic Safety Update Reports (PSURs).

Unfortunately, the possibility of reducing the number of drug safety documents in order to focus on the actual science underpinning drug safety, rather then devolving resources to produce overlapping documents, does not seem to have attracted sufficient attention. Urushihara and Kawakami[4] have proposed merging the PSUR with the Development Safety Update Report (DSUR) and the International Conference on Harmonisation (ICH) E2C[5] business plan recognizes the overlap between the PSUR,[6] the DSUR[7] and the safety specification section of the risk management plan (RMP),[8] but states ''the issue will be re-evaluated once more experience on these documents is gained''. In addition, the overlap between these three documents, the signal detection report,[9] the answer to regulatory authorities' request for information that companies need to provide in the context of a referral, and the benefit-risk assessment report seems to have not been considered.

The subsequent risk is to shift the available resources from the real scope of drug safety to the production of documents.

1. Review of the Contents of Drug Safety Documents

The main topics required by drug safety guidelines to be discussed in drug safety documents and the relevant templates have been reviewed. The aim is to point out in what areas they differ so as to identify the core drug safety items that need to be considered and the activities that need to be undertaken for documenting and describing the risks of a drug in one single document.

2. Results

As shown in table I, (where the DSUR, PSUR and RMP – the most structured documents for which detailed templates are available – are considered) the topics and sources that need to be taken into account in the main regulatory documents greatly overlap. Many of the inter-document differences are substantially formal; for example, the DSUR and, to a lesser degree, the PSUR, require to separately present the safety issues emerging from different sources and then to perform an overall evaluation of each safety issue. The RMP,

Table I. Development Safety Update Report, Periodic Safety Update Report and Risk Management Plan content comparison

Topic	DSUR	PSUR	RMP[a]
Pre-clinical safety concerns	Yes	Yes	Yes
Marketing authorization status	Yes	Yes	No
Patient exposure	Yes	Yes	Yes
Limitations of human exposure database	No	No	Yes
Reference safety information changes	Yes	Yes	X
Regulatory actions taken for safety reasons	Yes	Yes	Yes
Presentation of risks emerging from analysis of pre- and postmarketing adverse events	Yes	Yes	Yes
List of ongoing or completed company-sponsored studies	Yes	Yes	X
Safety issues originating from studies	Yes	Yes	Yes
Risk characteristics	X	X	Yes
Epidemiology of drug indication and of risks	X	X	Yes
Literature review	Yes	Yes	X
Drug interactions	Yes	Yes	Yes
Pharmacological class effects	Yes	X	Yes
Benefit-risk considerations	Yes	Yes	X

a Safety specification only.

DSUR = Development Safety Update Report; **No** = not required; **PSUR** = Periodic Safety Update Report; **RMP** = Risk Management Plan; **X** = not specifically mentioned but required for completing one or more template sections; **Yes** = specifically required by the regulatory template.

instead, requires a detailed description of the main safety issues, without separately presenting the evidence derived from each source. Only to a limited extent do the safety documents require an in-depth analysis of different components; only the RMP, for example, specifically requires a description of the epidemiology of the indication for which the drug is used and its risks. Furthermore, the RMP is the only document requiring discussion on the limitations of the human safety database, while the presentation of the worldwide marketing authorization status is not requested and the list of studies is limited to those included in the pharmacovigilance plan.

The comparison between drug safety documents has been performed using the current template, but it cannot be ignored that at the time of writing this article the European Commission had released for public consultation a concept paper[10] including the proposal of a new PSUR and RMP format. Only the titles of main sections are available, but if the structure of the RMP does not seem to differ too much from the present structure, for the PSUR significant changes are proposed. The newly proposed PSUR structure seems to be very similar to that of the DSUR, with an additional section presenting an overview of ongoing and close signals, and one for signal and risk evaluation. Therefore, the new PSUR will probably overlap with both the DSUR and the signal detection report to an even greater extent than at present.

For signal detection, there is no template or guideline specifying the contents of the report that needs to be prepared for this activity, but both the EudraVigilance Expert Working Group Guideline on the use of statistical signal detection methods[11] and the report of CIOMS Working Group VIII[9] specify how to perform this activity; adverse drug reaction terms are analysed, looking for new signals that are subsequently evaluated and taking into account information from multiple sources. Therefore, signal detection is a prerequisite for preparing other drug safety documents such as the DSUR, PSUR and RMP safety specification section.

Also, for benefit-risk reports no *ad hoc* template is available, but the Committee for Medicinal Products for Human Use (CHMP) specifies the RMP can be used as a basis for this report

since it considers the important potential and identified risks.[12]

Finally, for referrals, the authorities issue a list of questions that MAHs need to answer by providing all the required information they have. These questions are targeted to gather information on specific aspects of one or more drug risks that could negatively affect patients' safety. The aim of these questions is to therefore obtain the information that is needed to confirm, disprove or better characterize a risk and subsequently make an informed decision on the actions that need to be taken to protect patients.

3. Discussion

3.1 The Document Describing the Safety Profile of a Drug

It is clear that the DSUR, PSUR, RMP, signal detection reports and benefit-risk reports greatly overlap, but none of them are the reference document containing all information on the drug risks. Even if they differ one from the other to some extent, the degree of divergence between the documents is limited and can easily be overcome. Therefore, in the author's opinion it is time to switch from the preparation of multiple documents addressing the current knowledge of drug risks to one single document. The EU legislation has introduced the concept of the Pharmacovigilance System Master File, a collection of documents describing the system used by the MAH to fulfil their pharmacovigilance responsibilities. These documents need to be kept available for inspection and are provided to the authorities within 7 days from request. Upon submitting a marketing authorization application, pharmaceutical companies will only need to present a very brief summary of the main elements of their pharmacovigilance system,[1,2] thereby avoiding the need to repeat information already contained in other controlled documents and to submit variations due to changes in the Detailed Description of Pharmacovigilance System document.[13]

In analogy with the Pharmacovigilance System Master File, companies should prepare a product safety master file for each drug. This document should describe all the drug potential and identified risks, and should be a living document updated with the available information on an ongoing basis.

3.2 General Principles and Periodicity

As for PSURs and DSURs, the periodicity with which a new version of the product master file is prepared and submitted to regulatory authorities should depend upon whether the drug has already been marketed and the time elapsed since its launch. Additionally, upon regulatory authority request, such as on the occasion of a referral regarding one or more specific safety concern(s), the section(s) regarding these concerns should be added or expanded and the Drug Safety Master File relevant parts should be submitted.

Any new important safety information, such as that originating from study results, should also trigger an update of the document. If the new information on a safety concern is sufficiently convincing and the severity of the risk might alter the drug benefit-risk balance, the section regarding this concern should be submitted to the regulatory authorities.

Furthermore, upon routine preparation and submission of the document, emphasis should be placed on new risks or on those not yet fully characterized, for which a decision on whether an action is needed has not yet been taken or on those for which the adequacy of the already taken actions needs to be assessed. Well known risks for which adequate actions have already been taken, as well as refuted signals, should only be succinctly described, maybe in table format. The benefit of this approach is evident as the overall picture and history of all the drug risks is in one single document and further details on resolved safety concerns can be retrieved in previous versions.

Since the main aim of drug safety is to identify and characterize signals, assess their importance and minimize their impact on patients, the preparation of the document should start with signal detection that should not only regard adverse event disproportionate reporting, but should also include interim and/or final study results and lit-

erature review. Therefore, all possible sources of new signals would be taken into account, the overall view of the evidence confirming or disproving the signal would be provided, and a better evaluation on the importance of the risk and actions required could be performed.

3.3 Main Structure and Contents

Since the scope is a single document focusing on a critical description and evaluation of the risks of a drug, the author proposes to divide the Pharmacovigilance Master File into sections, each of which should address a specific drug risk (e.g. hepatic failure, Steven's-Johnson syndrome); this should be the most important part of the Drug Safety Master File. Therefore, a significant part of the resources and skills available in a drug safety department should be devoted to the preparation of this part of the document.

Each section should describe how the risk was identified (e.g. adverse event disproportional reporting, literature review, the outcome of a study) and by whom (company or regulatory authority) and should contain multiple sub-sections, one for each source contributing to the risk body of evidence (i.e. spontaneous reports, investigational and non-investigational studies sponsored or supported by the company and literature). Therefore, for example, for hepatic failure risk there should be one sub-section describing information derived from interventional studies, one for information derived from spontaneous reports, etc. This section should not only include adverse events information and analysis but should also include laboratory and clinical test results along with pre-clinical data.

The section dedicated to a specific risk should also contain sub-sections on biological plausibility, risk factors and patients' sub-populations at increased risk of experiencing the adverse reaction and on the evaluation of the importance of the risk – its severity, seriousness, frequency and likelihood that it will affect the decision of the healthcare provider to prescribe the drug or the decision of a patient to take it.

For important risks that might contribute to change, the drug benefit-risk balance, a sub-section describing the incidence of the risk in the background population and the increased risk associated with the drug of interest could be added, therefore putting the risk into context. Finally, any actions taken by the company or regulator as a consequence of the risk should be discussed.

3.4 Other Points to Consider

As required by other drug safety documents, the risks to be considered should include potential risks originating from non-clinical concerns whose significance to humans has not yet been confirmed or disproved by clinical data, interactions, pharmacological class effects, medication errors, abuse and misuse, risks related to use in pregnancy and lactation, and to special populations etc.

Furthermore, there should be specific sections for product worldwide authorization status and inventory of clinical ongoing and completed studies during the reference period, changes to the reference safety information and regulatory actions taken during the reference period and patient exposure (including specific relevant populations for which exposure is missing). The Drug Safety Master File proposed table of contents is shown in table II.

Line listings of adverse reactions pertaining to the presented risks could be added in order to facilitate review and retrieval of the relevant cases. Their scope should not be the submission of all the received cases to the regulatory authority (as it currently is for the PSUR) since, with the EU new legislation, this role is already fulfilled by the submission of all serious and non-serious cases to EudraVigilance.

3.5 Possible Obstacles, Disadvantages and Challenges

An obstacle for having a single safety document instead of the current multiple documents could be that different departments are frequently in charge of drug safety according to the stage of the drug life-cycle. The separation of responsibilities not only applies to pharmaceutical companies but also to regulatory agencies where the departments monitoring a drug's pre- and postmarketing safety might be different ones. It could be felt that one

Table II. Drug safety master file sections

1. Introduction
2. Worldwide market authorization status
3. Inventory of ongoing/completed safety studies[a]
4. Changes to Reference Safety Information[a]
5. Regulatory actions taken for safety reasons[b]
6.1 Patient exposure[b]
6.2 Limitations of human safety database
7. Drug risks currently under evaluation
7.1 General introduction (describe how the risk was identified and by whom)
7.2 Sources of evidence
7.2.1 Spontaneous reports
7.2.2 Company sponsored/supported interventional studies
7.2.3 Company sponsored/supported non-interventional studies
7.2.4 Literature
7.2.5.Other sources
7.3 Risk characterization and evaluation
7.3.1 Risk factors and sub-populations at risk
7.3.2 Risk severity/seriousness and frequency
7.3.3 Biological plausibility
7.3.4 Clinical plausibility (evidence strength and consistency)
7.3.5 Risk impact on compliance and benefit-risk balance
7.3.6 Actions taken and further actions that could be taken
8. Summary of resolved drug risks

a During the reference period.

b Cumulative and during the reference period.

single drug safety document with both pre- and postmarketing safety information could contain unnecessary information for one of the two departments. However, the fact that the safety profile of a drug is more complete only when information from all possible sources is evaluated together cannot be ignored. In fact, for this reason, the DSUR has a paragraph on postmarketing safety information (in case the drug is marketed) and the PSUR has a paragraph on premarketing safety information. Therefore, having one single drug safety document would help regulators and companies to better assess the safety profile of the drug.

A further solution could be to merge pre- and postmarketing safety departments into one single unit. In the author's opinion this would permit better assessment of the evolving safety profile of a drug and avoid duplication of work by different people or departments who are having to work on the same information.

The main challenge for the preparation of the Drug Safety Master File will probably be in ensuring multiple pharmaceutical professionals with different skills and knowledge cooperate, communicate and share knowledge to integrate information derived from multiple sources and of a different nature into one single document. This challenge is not new to drug safety since this discipline is at the crossroad of multiple sciences and is faced when preparing or reviewing comprehensive documents such as the RMP. However, this challenge might be further enhanced when all the safety information on a drug is summarized into one single document.

Generic companies could be disadvantaged by the implementation of the Drug Safety Master File since, with the new legislation, they will not be required to prepare PSURs unless there are any ongoing safety concerns that need to be better assessed, characterized or understood. To overcome this potential new burden, the author proposes that generic companies could be required to prepare the Product Safety Master File only when the same conditions requiring the preparation of a PSUR are met. Furthermore, generic companies could be required to prepare a simplified version of this document (e.g. without the paragraphs on interventional and non-interventional studies as proposed by the Drug Safety Master File sections presented in table II).

3.6 Proposed Roadmap for Implementing the Product Safety Master File

Having one single document addressing the safety profile of a drug would represent a significant workload reduction only if all regulatory authorities worldwide would implement this proposal. Having regulatory authorities of one region accept one single product safety document while authorities of other regions of the world still require multiple drug safety documents would be of little benefit and would represent an increased workload. In this scenario, for multinational companies operating worldwide, the Product Safety

Master File would only be an additional document to prepare.

To obtain worldwide consensus the author proposes that the Drug Safety Master File should become a topic to be addressed by a CIOMS working group. Once the CIOMS working group reaches consensus and edits its final report, the topic could be addressed at ICH level and, finally, could be implemented in all regulations and guidelines worldwide.

4. Conclusions

The main drug safety documents consider signal detection, characterization and evaluation. It therefore seems reasonable to have one single document presenting the results of signal detection and discussing the risks of a drug rather than multiple documents, which might lead to work duplication and risk of inconsistencies, and which might represent an obstacle to a thorough scientific assessment because of resource limitation. It is therefore proposed to merge the PSUR, DSUR, RMP safety specification and the signal detection report into one single document that could also be used for answering regulators' questions within the context of a referral and as a basis for identifying the risks to be included in a formal benefit-risk assessment report. Having one document would favour the scientific assessment of the drug risks since the safety profile of a drug is the result of the aggregate evaluation of both pre- and postmarketing data.

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