

Prescrire's contribution
to the European Commission Targeted Stakeholder Consultation on the
Amendments to Commission Implementing Regulation (EU) 520/2012
on Pharmacovigilance Activities (TSC/2021/24)¹

Paris, 14 October 2021

Responding organisation: Prescrire

About Prescrire:

Prescrire is a non-profit continuing education organisation that works to improve the quality of patient care. Prescrire publishes evidence-based information about treatments and treatment strategies, in total independence, as a basis for truly informed decision-making. Prescrire is funded exclusively by its subscribers. It receives no other financial support whatsoever and carries no advertising. It has no shareholders or sponsors. More info: www.prescrire.org

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From the outset, *Prescrire* has attached great importance to the European pharmacovigilance system. *Prescrire* has analysed the proposed amendments of the Regulation (EU) 520/2012 very carefully as, in association with the International Society of Drug Bulletins (ISDB), we had contested several aspects of the implementing Regulation when it was designed in 2010². **We appreciate that the European Commission learns from the experience gained by the EMA and the Pharmacovigilance Risk Assessment Committee**, reflected in the proposed amendments. Our analysis aimed to see whether the provisions envisaged indeed contribute to the improvement of patient's safety, in particular by correcting some of the flaws we already identified ten years earlier.

Chapter I - Pharmacovigilance system master file

This amendment addresses the need for effective oversight of pharmacovigilance activities by the marketing authorisation holders (MAH) themselves and not by a subcontractor.

¹ Targeted stakeholder consultation on the amendments to Commission Implementing Regulation (EU) 520/2012 on pharmacovigilance activities https://ec.europa.eu/health/human-use/consultations/amendments-regulation520-2012_en

² International Society of Drug Bulletins (ISDB) "Answer to the consultation on the "Concept paper on pharmacovigilance implementing measures": Signal detection left to pharmaceutical companies: danger!" 2 November 2011.

<https://english.prescrire.org/en/79/549/49234/3689/3477/SubReportDetails.aspx>

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Experience showed that subcontracting pharmacovigilance activities reduces the MAH oversight effectiveness. Indeed, beyond the appearance of specialisation, the externalisation of activities weakens the essential oversight of the effective safety of medicines from both the marketing authorisation holders and the effective control by the agencies' inspectors.

However, we consider that it is not enough to “*allow inspectors to check in the contracts between marketing authorisation holders and third parties that risk-based controls are planned for and that they will be actually conducted by the marketing authorisation holder*”.

This amendment should go further by **also introducing a control of the pharmacovigilance subcontractors by the regulators, and not by the MAH**. As already stressed in our response in 2011, we call on to increase the number of inspectors in order to let them effectively examine the 'pharmacovigilance system master files' during an inspection (1). Developing and expanding joint inspections, including even with the FDA, would contribute to strengthen this monitoring capacity by regulators. The proposed amendment is a step in the right direction, introducing transparency on what is done and who is in charge of each pharmacovigilance task.

However, **it will be necessary to establish:**

- a precise framework and clear apportionment of roles and responsibilities,
- a strong public control done by inspectors with clear specifications, enforcement and injunctions or sanctions in case of non-compliance by the marketing authorisation holders and subcontractors¹.

Chapter III - Minimum requirements for the monitoring of data in the Eudravigilance database

We welcome the European Commission statement that companies should not be involved in the validation of pharmacovigilance signals, a task to be left to health authorities and agencies. A late but welcome correction.

Indeed, in 2011 we were surprised and disagreed that this central role was imprudently granted to marketing authorisation holders, and pointed out that pharmacovigilance tasks and processes should mainly be covered by independent competent Authorities, not by the marketing authorisation holders. Numerous and persistent examples show that pharmaceutical companies often withhold data or delay their disclosure, so as to delay decisions that would adversely affect sales³. This intrinsic conflict of interest was illustrated with the cases of *rofecoxib* (Voixx°), *olanzapine* (Zyprexa°) and *paroxetine* (Deroxat°/Seroxat°), or shown in 2012 by the concealment by Roche of more than 80,000 cases of suspected adverse reactions, including more than 15,000 in deceased patients⁴; or in France by the Mediator° criminal trial⁵.

³ Prescrire Editorial Staff "Adverse effect reporting: pharmaceutical companies can't be trusted" *Prescrire International* 2015 ; **24** (165) : 256.

<https://english.prescrire.org/en/81/168/51423/0/NewsDetails.aspx>

⁴ Prescrire Editorial Staff "Malfeasance on an industrial scale" *Prescrire International* 2013 ; **22** (135) : 32.

⁵ Casassus B "Drug company Servier is found guilty of manslaughter and aggravated deceit over Mediator diabetes drug" *BMJ* 2021;372:n873 doi: <https://doi.org/10.1136/bmj.n873> + "Mediator° - the



It is therefore welcome that the European Commission takes away the drug companies' control over the handling of the pharmacovigilance data and gives back to the EMA a greater capacity to control their use.

Even if we consider the intention to precisely integrate bibliographic references, **the meaning and implications in the proposed amendment relating to article 18.2 are not clear.** What is meant by the monitoring of data available in the Eudravigilance database by the marketing authorisation holders *"in a manner proportionate to the risk, together with other available data sources"*: to which medicines will the companies have access to? Only their own? What is covered by the notion of *"proportionality to the risk"*?

It is also a matter of protecting these procedures from the influence of industry. What are the human resources for counter-assessing PSURs and other reports requested from companies (cumulative data in the evaluation of signals, for example)? **Sufficient funding needs to be allocated to European and national agencies to monitor and assess the data.**

Chapter IV - Use of terminology, formats and standards

It is of good practice to use only the latest updated terminologies, formats and standards as they are the condition for consistency in the processing of pharmacovigilance data. It would be better to affirm this principle in a general way in the EC Implementing Regulation, rather than having to amend it according to the various updates of this reference system.

We appreciate the inclusion of the EDQM terminology, which is particularly important for the approach to practical conditions of use of medicines, and thus the analysis of the circumstances of medication errors. **It would also be very welcome and helpful to respect the systematic use of INNs as soon as they are assigned by the WHO INN Programme.** This has not been the case, for example, with Covid-19 mRNA vaccines. With regard to medication errors, we would like to stress **the efforts that still need to be made to clarify the terminology used by MedDRA** and encourage the European Medicines Agency to take a more active part in its development by the ICH. Indeed, having only access to an aggregated interface, which is rudimentary, the Prescrire team encounters many problems, with splintered undesirable effects that are not easily found, as they are diluted in several organs; vocabulary words that are missing or badly translated; etc.⁶

Chapter V - Transmission of suspected adverse reactions

The deletion of *"expedited"* is welcome as **all cases must be filled in as soon as possible**; and the use of the DOI of bibliographic references makes the pharmacovigilance data more relevant and operational.

criminal trial - A special section from Prescrire International"

<https://english.prescrire.org/en/221/1931/PositionsList.aspx>

⁶ Prescrire Editorial Staff "MedDRA and pharmacovigilance: a complex and little-evaluated tool" *Prescrire International* 2016 ; **25** (175) : 247-250.

<https://english.prescrire.org/en/81/168/52206/0/NewsDetails.aspx>

However, organisations like *Prescrire* need a wider access to EudraVigilance to allow them to strengthen and to contribute to the knowledge on and the prevention of adverse effects and medication errors.

Chapter VIII - Post-authorisation safety studies

Prescrire fully supports the proposal to request MAHs to register all imposed post-authorisation studies in the EU PAS register and to include study protocols as well as study results. The Covid-19 pandemic again illustrated that fast public access to study protocols and results is beneficial for public health, researchers, healthcare professionals and patients. It is regrettable that during the Covid-19 pandemic, as studies were still on-going, essential safety information has been concealed by the companies with the consent of the EMA, as was recently the case with *tozinameran* (Corminaty[®]). To make informed decisions, both efficacy and adverse events data are needed. **Efficacy data should always be published together with adverse events data** for both completed and ongoing trials. Withholding/redacting information is not the way forward, on the contrary it fuels mistrust and disregards public health interest. The introduction of reporting requirements for post-marketing safety studies are even more important due to the implicit deregulation by accelerated marketing authorisations delegating the collection of more solid evidence to post-authorisation studies. **Public access to deadlines, nature of the data to be collected, study protocols appear to be a strict minimum of information to be published.** The proposed amendment hopefully might contribute to raise the transparency on these important clinical evaluations⁷.

Currently, we noticed that the publication of PRAC meeting minutes takes more than 6 months. Also, the data provided in **the PRAC meeting minutes is very scarce regarding post-authorisation safety studies, signals evaluated or whether decisions has been taken.**

We would like to have full access to these studies (currently not granted). The PRAC reports should be systematically made available online. Indeed, they are much more informative and according to our experience with those we have requested and received, little adaptation of the form would be required to make them releasable (example: the report on the evaluation of the death signal with the *selexipag*). Beyond this basic transparency, national agencies should be allowed to publish their reports on their own websites.

⁷ Prescrire Editorial Staff "Post-market follow-up studies: many studies requested but where are the results?"

Prescrire International 2008 ; **17** (95) : 125.

Prescrire Editorial Staff "Conditional Marketing Authorisation: based on very little data" *Prescrire International* 2018 ; **27** (190) : 54.

Prescrire Editorial Staff "Proper evaluation, for patients' sake" *Prescrire International* 2020 ; **29** (217) : 171. <https://english.prescrire.org/en/81/168/58778/0/NewsDetails.aspx>

Additional remarks: fulfilling better access to qualitative and quantitative pharmacovigilance data

The application of the Implementation Regulation urgently needs to be improved by fulfilling better access to qualitative and quantitative pharmacovigilance data. In the EU, health professionals and patients, who are major contributors to the EudraVigilance database through the spontaneous reports, are paradoxically those who are the most confronted with lack of access and secrecy.

Unfortunately, since 2012, the public interface Adrreports (www.adrreports.eu) has provided access to only a limited number of quantitative information, e.g. the number of individual cases associated with a given substance, with a limited access to a listing of case summaries ("Line listing Reports").⁸

Together with the Cochrane Adverse Effects Methods Group (AEMG), Health Action International (HAI) Europe, the International Society of Drug Bulletins (ISDB) and Medicines in Europe Forum (MiEF), *Prescrire* responded to a public consultation of the European Medicines Agency organised on the revision of its 2011 policy on the access to the European pharmacovigilance database EudraVigilance.⁹ Our demand to have public access to useful qualitative data such as anonymised summaries of cases has not been satisfied by the EMA.

We therefore reiterate our request for better access to more detailed data through more accurate queries and especially to the detailed reports of the PRAC. This is essential for independent organisations such as *Prescrire* to fulfil their mission of informing healthcare professionals and patients about and preventing adverse events and medication errors.

In summary, most of the proposed amendments seem to go in the direction of greater independence from the drug companies and **better quality control and disclosure** of pharmacovigilance data. It is the European Commission's duty to improve the public access to these data and to facilitate the dissemination of knowledge on the risks of adverse drug reactions and medication errors.

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⁸ Prescrire Editorial Staff "Obstacles to transparency over pharmacovigilance data within the EMA" *Prescrire International* 2015 ; **24** (165) : 278-279.

⁹ Joint response to the EMA consultation by the Cochrane AEMG, HAI Europe, ISDB and MiEF "EMA's policy on pharmacovigilance: access to qualitative data is needed, pharmacovigilance data are not "trade secrets" 15 September 2014.

<https://english.prescrire.org/en/79/549/49234/3928/3477/SubReportDetails.aspx>