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Comments of The Office for Registration of Medicinal Products, Medical Devices and Biocidal Products of Poland on the document „Strategy to Better Protect Public Health by Strengthening and Rationalizing EU Pharmacovigilance: Public consultation on legislative proposals”.

We welcome the Commission proposal on the change of the legal framework for the EU pharmacovigilance system, which should ultimately result in better protection of public health and more rational allocation of resources in the NCAs and the industry. We strongly support the proposed instruments to strengthen the pharmacovigilance systems of MAHs, including the introduction of the Pharmacovigilance System Master File and the Good Pharmacovigilance Practice. The proposal is extensive and encompasses a number of issues, some of which we would like to address below, at the same time looking forward to in-depth discussion during further steps of the legislation drafting.

1. Proposed modification of the definition of „adverse reaction”, defined as “ a response to medicinal product which is noxious and unintended” raises doubts, particularly because there is no proposal of a definition of „medication error” and the definition of „abuse” is proposed to be deleted. In this situation all reactions, regardless of whether they are the effect of normal dose, overdose, off-label use, misuse etc., are put into one broad category resulting in an increase of number of reports and making more difficult and resource-consuming identification and assessment of new safety information (signals), which may actually influence the risk-benefit balance of a medicinal product, which in turn may lead to untimely or erroneous action to protect public health.

If the new definition is to be accepted, some differentiation of reporting of reactions should be considered to allow for the efficient search in the databases for the important new information, which may influence the risk-benefit balance.

In view of the proposed definition it is not clear, why in the text of Article 101a of the Directive the wording: “unexpected adverse reactions” is proposed.

It should be also noted that the WHO data base on adverse reactions has been based on the current definition of an adverse reaction, introduced in 1972 and the introduction of a new definition will result in inconsistencies of the data, particularly for the older products.

2. Proposed consequential change in Art. 11 of the Directive (SmPC, point 3b) seems too general and unclear using the wording: “key safety information and how to minimize risks” . The question arises whether the key safety information relates to use in accordance with the SmPC or to other uses, e.g. overdose, off-label use, misuse.

The timelines for the implementation of “key safety information” in the SmPC and consequently in the package leaflet should be precisely defined, since many products will have already renewals for indefinite period of time and it is not clear what is meant by „major variations”.

3. In the proposed absence of the PSURs for products other than authorized under Art. 8 of the Directive it is not sufficient to obtain the information on safety profile in a document which will address „any other new information, which might influence the evaluation of the benefits and risks”. The term “any other new information” is very general and may cause different interpretations of the term by MAHs. It might be understood in a subjective way, when and what type of information need to be provided to the competent authorities. If the new concept in relation to PSURs is implemented, effective pharmacovigilance activities will be possible, if MAH develops specific procedures for medical and epidemiological evaluation to analyze, if the information carries „any changes in the benefits and risks” and such analysis is presented to the competent authority. As a consequence, these procedures should be incorporated into Pharmacovigilance System Summary, accepted by the competent authority.

4. As regards the aforementioned concept of eliminating the PSURs for certain categories of medicinal products we have doubts, if this should be done in the case of generic products. The generic products constitute majority of the medicinal use of an active substance and the PSURs for originators would present an analysis of exposure only to a fraction of an active substance, which will result in the incomplete picture of the risk of use. Although all individual adverse reaction reports will be available, in practice the processing and analysis of the data will be highly resource-consuming and this may result in a delayed identification of signals on the safety of use and in consequence - a delayed action to protect public health. Another problem would be the lack of PSURs for the originators, which are no longer marketed, then there would be no PSURs for an active substance at all.

5. The aim of adding a new criterion to the definition on non-interventional post-authorization trial is not clear („confirming the safety profile of the medicinal product”) because the criteria given in the first part of the definition seem to be sufficient. The study to confirm the safety profile may have a promotional character.

6. In art. 101e, point b should end with the word: “unknown”, because the proposed wording would narrow reporting and lead to exclusion of reports of adverse reactions, in which temporal relationship is not very suggestive.

7. The status of the Committee’s on Pharmacovigilance recommendation, as described in the art 101k, point 9 and 10, is not clear in a sense that it is unknown, if this recommendation is binding for the CHMP or subject to further discussion and/or rejection.

8. As a subject separate from the pharmacovigilance issues we would like to address the proposed change in Art. 26, that is deletion of current point b, stating the grounds for refusal of a marketing authorization when the therapeutic efficacy of the product is insufficiently substantiated by the applicant. This change is not related to pharmacovigilance and concerns a system of the assessment of a medicinal product prior to its authorization, which is based on quality, safety and efficacy. Proposed deletion seems to undermine this system, since it would prohibit refusal of authorization due to lack of efficacy, which is a sine qua non condition of the use of a medicinal product. Guideline on the definition of a potential serious risk to public

health in the context of Article 29(1) and (2) of Directive 2001/83/EC — March 2006 provides that, “a potential serious risk to public health in relation to a particular medicinal product can mainly be considered to exist under the following circumstances:

— Efficacy: the data submitted to support therapeutic efficacy in the proposed indication(s), target population(s), and proposed dosing regimen (as defined by the proposed labelling), do not provide sound scientific justification for the claims for efficacy; adequate proof for bioequivalence demonstrated by generic medicinal products to the reference medicinal product is lacking”.

The risk-benefit balance in the Guideline constitutes a separate ground for a consideration of a potential serious risk to public health and assessment of the efficacy of a given product precedes further assessment of its risk-benefit ratio, which is made upon establishing the product efficacy. Therefore leaving in the text the risk – benefit balance and deleting the efficacy as the ground for refusal is difficult to accept, particularly that the grounds for the proposed change have not been presented in Section 1. We would appreciate, if such justification could be made available for further discussion.

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