

European Commission's public consultation on the EU pharmacovigilance system



Grant Castle

The European Commission has launched a consultation on proposed amendments to strengthen and rationalise the European Community (EC) pharmacovigilance rules and systems established by Directive 2001/83/EC and Regulation (EC) No 726/2004. Comments were sought from stakeholders by 1 February 2008. Grant Castle and Robin Blaney summarise the key proposals and discuss some of the issues that they raise.



Robin Blaney

Generally, the Commission's proposals should be welcomed. They focus on improving patient safety and increasing the transparency of the pharmacovigilance system, while at the same time increasing efficiency and easing the administrative burden on marketing authorisation holders (MAHs). The proposals also give a legal

basis to issues that to date have been dealt with only in guidance. This offers all concerned in the pharmacovigilance system greater legal certainty and should make it easier for the relevant authorities to enforce the provisions where necessary.

However, some of the proposed changes, especially those concerning Community-level pharmacovigilance procedures require clarification. Further, some proposals will require consequential amendments to the Annex of Directive 2001/83/EC and thus we will only be able to assess fully the impact of those proposals once the necessary consequential amendments to the Annex have also been proposed.

...administrative structure

The Commission is proposing to establish a Committee on Pharmacovigilance within the European Medicines Agency (EMA) to co-ordinate pharmacovigilance and make recommendations on the safety of medicines to the existing Committee on Human Medicinal Products (CHMP). This new committee would replace the existing Pharmacovigilance Working Party.

...Community assessment and binding decisions

The proposal contains significant amendments to referral procedures. Currently, under Articles 31 or 36 of Directive 2001/83/EC, the CHMP may be asked to adopt an opinion on safety or other "Community interest" issues that form the basis for a binding Commission decision. These referral procedures, including the MAH's rights to make representations, are well defined. The amendments propose a new Article 101k referral procedure with an expanded list of grounds for the initiation of the procedure, including: when a Member State considers that a new contraindication, a reduction in the recommended dose or a restriction to the indications is necessary; and when a Member State has conducted a pharmacovigilance inspection and found serious deficiencies. Following an Article 101k referral, the Committee on Pharmacovigilance will, in most circumstances, hold a public hearing at which MAHs and the public may participate. The Committee on Pharmacovigilance will make a recommendation

to the CHMP, which will adopt an opinion on what steps should be taken. Ultimately, the Commission will adopt a final binding decision.

There are, however, a number of procedural issues that require clarification. Firstly, the initiation of the procedure and details of the proposed public hearing will be announced by the EMA via a web portal, with no requirement for either the EMA or the referring Member State to notify the MAH by any other means. There seems no reason why either the referring Member State or the EMA could not be required to engage the relevant MAH(s) proactively.

Secondly, although in most circumstances there will be a public hearing at which MAHs may participate, the level of MAH participation remains unclear. Further, it seems that the Committee on Pharmacovigilance will not be required to reach any decision at the public hearing, so the ultimate decision and the reasoning behind that decision is likely to occur behind closed doors.

Despite the potential significance of the decisions reached by the Committee and then the CHMP, the MAH has no clear right to make written or oral submissions and will have no opportunity to appeal, as it would under Articles 31 or 36. Furthermore, the proposal lacks clarity on the relationship between the Committee on Pharmacovigilance and other entities that are legally responsible for assessing the safety of products, including the Reference Member State for products approved via the decentralised and mutual recognition procedures, and the Rapporteur or Co-Rapporteur for products approved centrally.

...adverse reaction reporting

The proposal significantly amends what adverse reactions need to be reported and to whom they should be reported. Currently, serious adverse reactions must be reported within fifteen days. All other adverse reactions are covered by the periodic safety update reports (PSURs). This will continue to be the case for serious adverse reactions occurring outside the European Community, but the new Article 101e(2) would require MAHs to report within fifteen days all adverse reactions, whether or not serious, that occur in the European Community.

Currently, a complex set of rules governs to which authorities MAHs must report adverse reactions. Depending on where the adverse reaction occurred and the mechanism by which the product had been approved, MAHs may have to submit reports to every Member State and the EMA. The proposal is that whenever a reporting requirement is triggered, the MAH will submit a single report to the EMA only via the Eudravigilance database.

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At present, MAHs are required to monitor the worldwide scientific literature and report any adverse reactions involving their products. This can result in a significant duplication of reports to authorities. For example, if a single journal article described an adverse reaction involving aspirin, hundreds of companies would be required to submit the same adverse reaction report to the authorities. The proposal is that in future the EMEA will be responsible for monitoring the worldwide literature, and MAHs will not be required to submit adverse reaction reports based on literature alone.

Currently, MAHs must submit PSURs to the authorities in every Member State where the product is authorised, and also to the EMEA for centrally approved products. The proposal is for a single PSUR to be submitted to the EMEA. The default position on frequency remains similar to the current situation, but the new Committee on Pharmacovigilance will have the ability to specify a different frequency of reporting. The consultation paper suggests that for well-established products the submission of PSURs may not be required at all.

...biological medicinal products

The proposed Article 101a of Directive 2001/83/EC will include the following paragraph: "Through the method of collecting information and where necessary through the follow-up of adverse reaction reports, the Member States shall ensure that any biological medicinal product prescribed and dispensed in their territory which is the subject of an adverse reaction report is identifiable."

This appears to be an attempt to address concerns relating to the recent approval of similar, or follow-on, biological medicinal products with the same international non-proprietary name (INN) as the reference medicinal product, despite clear structural differences and in contravention of the WHO's Guidelines on the Use of International Non-Proprietary Names for Pharmaceutical Substances. The products in question, erythropoietins, were approved in late August 2007 with the INN of Janssen-Cilag's epoetin alfa product, EPREX/ERYPO, despite clear differences in the glycosylation patterns between the follow-on products and EPREX/ERYPO. Since differences in glycosylation pattern and the manner in which biological products are manufactured and formulated are likely to result in differences in safety profiles, the WHO requires the use of different Greek letter suffixes to designate erythropoietins with different glycosylation patterns.

To comply with this new provision, Member States may need to require adverse reaction reports for biological medicinal products to distinguish between products by reference to the brand name and/or the manufacturer, rather than merely to use the INN. The problem is that, without a substantial change in prescribing and dispensing practices, plus restrictions on existing generic substitution practices, doctors may not know which biological product is ultimately dispensed, and it is difficult to see how effective such measures would be.

...pharmacovigilance system

At present, every MAH must submit a detailed description of its pharmacovigilance system. Thus, if the MAH subsequently amends its pharmacovigilance system, it should submit a variation to this effect. For large pharmaceutical companies holding multiple marketing authorisations, a single change to their pharmacovigilance system therefore triggers a requirement to submit a large number of variations.

The Commission has recognised this disproportionate administrative burden and proposes that in future only a summary of the pharmacovigilance system should be submitted with marketing authorisation applications. The MAH shall maintain a detailed pharmacovigilance system master file for each product, which must be kept up to date and accessible to the relevant authorities on request.

...risk management system

At present, Article 8(3)(ia) of Directive 2001/83/EC requires marketing authorisation applicants to submit a detailed description of the risk management system "where appropriate." The proposed amendments delete the qualification. Thus, in future every marketing authorisation applicant will be required to submit a detailed description of the risk management system, which should "be proportionate to the identified and potential risks."

This obligation is inconsistent with the description of the proposal in section 3 of the consultation document, where it is stated that: "The effect of the clarified legal provisions will be that written management plans are only submitted when they are needed but that they are fully complied with." Therefore, rather than clarify the existing situation, the proposal has the potential for additional confusion. It may be that the requirement that the risk management system is "proportionate to the identified and potential risks" suffices because there may be no need to submit significant documentation where products have established safety profiles.

...post-authorisation safety study (PASS)

The definition of post-authorisation safety study (Directive 2001/83/EC Article 1(15)) will be amended to broaden its scope. The original definition was: "a pharmaco-epidemiological study or a clinical trial carried out in accordance with the terms of the marketing authorisation conducted with the aim of identifying or quantifying a safety hazard relating to an authorised medicinal product." The proposed definition is: "a pharmaco-epidemiological study or a clinical trial with an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard or confirming the safety profile of the medicinal product."

The definition now covers not only on-label, but also off-label studies, meaning that regulatory authorities can require a PASS to be conducted outside the scope of the marketing authorisation. It also means that the requirement that MAHs seek the approval of PASS protocols and submit periodic and final study reports is expanded to off-label studies.

The proposed Article 101h of Directive 2001/83/EC sets out the rules that will apply to any PASS falling outside the scope of Directive 2001/20/EC. These new rules will apply to most non-interventional studies, because any study assessing the safety profile of the product in general, rather than targeting a specific safety concern, would now fall within the definition of a PASS. It would be rare for any study investigating the efficacy of a product to evade assessing the safety of a product as well.

...post-authorisation commitments

Currently, Article 22 of Directive 2001/83/EC permits marketing authorisations to be granted subject to requirements for the applicant to meet certain post-authorisation conditions. The competent authorities are entitled to impose these requirements "in exceptional circumstances and following consultation with the applicant". Under

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the proposals, any marketing authorisation could be granted subject to a requirement to conduct post-authorisation safety studies or to certain other conditions.

These requirements will no longer be limited to products approved under exceptional circumstances, and authorities need not consult with the applicant in imposing these conditions. Where necessary, the marketing authorisation will also include deadlines for the fulfilment of these post-authorisation conditions.

Any product subject to such post-authorisation conditions shall be included in a list of intensively monitored products. The product's summary of product characteristics and package leaflet will be required to contain a statement that the product is on this list. The proposal also contains a mechanism whereby the competent authority that granted the marketing authorisation may at a later date require the MAH to conduct a PASS if there are serious concerns about the product's risk-benefit balance.

However, there is a potential problem with the drafting. Article 22 of Directive 2001/83/EC must be read in conjunction with Section 6 of Part 2 of the Annex. Together they provide a legal basis for granting marketing authorisations when the applicant is unable to provide comprehensive data on the efficacy and safety of the product under normal conditions of use, e.g. because of the small patient population, or because it would be unethical to do so.

The Annex will need to be amended to take into account the proposed amendments to Article 22. It is possible that these consequential amendments to the Annex, taken together with the amendments to Article 22, would remove the legal basis for accepting marketing authorisation applications without comprehensive safety and efficacy data. If that is the effect, this would be a real issue for many orphan

medicines, for which it is often impossible to obtain the full package of clinical data.

...package leaflet

Article 59 of Directive 2001/83/EC will be amended to require each product's package leaflet to include key safety information about the product and how to minimise risks. This information will be presented in a box surrounded by a black border.

Drawing the patient's attention to the key safety information ought to improve patient safety, but if there is a black box in every package leaflet, it may be difficult for patients to identify easily which products present a significant concern. It might be preferable to require a black box around safety information only when there is a particular concern, e.g. if the product is on the list of intensively monitored products. This would be similar to the FDA's black box warning system.

...EU portal and Eudravigilance database

Under the proposal, the EMEA will be required to maintain a European medicines safety website, containing important information for the public, such as information about how to report suspected adverse reactions, agreed PASS protocols and a list of the qualified persons for pharmacovigilance for each MAH. Finally, individual adverse reaction reports held on the Eudravigilance database will be made available on request to the general public unless this would compromise the anonymity of the subjects of the reports. *

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Ukraine marches forward towards tighter control over pharmaceutical advertising

The Ukrainian ministry of health has put forward a proposal to introduce tighter controls over the drugs, medical devices and other healthcare products advertising in the Ukrainian media. In an amendment to the country's Act on Advertising, health minister Vasyl Knyazevich has proposed that before a drug advertisement is made public it should be first authorised by the national healthcare authorities.

Currently, the rules of medicinal products advertising directed at general public are governed by Article 21 of the Act. In accordance with the Article, it is prohibited to advertise prescription medicines or to promote medicinal products using the image of a healthcare professional. The Article also stipulates the type of information that must be included in the advertisement, e.g. the name of the advertised product, the name of the manufacturer, etc.

...advertisers go unpunished

Potential penalties imposed on advertisers that infringe the advertising law are also included in the Act. In advance of these measures, the health ministry points out, the provisions of Article 21 are breached by advertisers on a regular basis because the monitoring in the area of drug advertising – which is currently outside the administrative powers of the country's healthcare authorities – is not sufficient. All this leads to an uncontrollable and irrational use of medicines, which may have a negative impact on public health, Mr Knyazevich argues.

...prior approval necessary

The idea behind the ministerial proposal is therefore to make the drug advertising legislation more effective. The amendment – if indeed implemented – would create the legislative grounds for the healthcare ministry to impose control over drug advertising and would enable it to monitor this sector of the advertising market. It would mean that that drug advertisers would be obliged to have the content of the advertising material approved by the country's healthcare authorities, operating under the ministry of health – such as the State Service for Drugs and Medical Devices – in accordance with a procedure yet to be established by the ministry.

The ministry believes that amending the current legislation would help to create a control mechanism over the advertising market, similar to those existing in the "majority of civilised countries". "For example, in EU Member States, it is strictly forbidden to use in an advertisement the image of a healthcare professional – or to direct it at children. In the Ukraine, everything is upside down. On the television, all day long, we watch people in white uniforms promoting numerous products that are supposed to cure practically every condition – including alcoholism and drug addiction – with an immediate effect," said Mr Knyazevich. Enforcing the control of the healthcare authorities over the drug advertising market may therefore be an answer and solve the current problems related to advertising in this area, he concluded. *