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Dr. P. Arlett,  
Enterprise and Industry,  
European Commission,  
Brussels,  
Belgium.  
by e-mail to: [peter.arlett@ec.europa.eu](mailto:peter.arlett@ec.europa.eu)

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Dear Dr. Arlett,

**PUBLIC CONSULTATION ON LEGISLATIVE PROPOSALS FOR  
PHARMACOVIGILANCE**

I am responding to the legislative proposals placed on the Commission's website dated 5 December 2007. These are my personal views based on 20 years experience in the field as a regulator and in academia.

First, I would like to congratulate the Commission for bringing forward innovative proposals which would markedly improve the legislation in this field. These changes have the potential to facilitate the development and use of safer medicines, and therefore to have a significant positive influence on public health.

Although the regulatory burden on industry for pharmacovigilance has increased considerably in the past 15 years, the system has not necessarily become more effective or efficient. As I have argued in the medical literature [1], regulators need stronger post-authorisation powers but this does not mean that the requirements placed on industry need to be increased further. Instead there is a need to reduce the current burden on industry and to more clearly focus their activities on gathering data which will enhance safety knowledge about their products. Finally, greater public awareness of and confidence in the system is needed, and the proposed major increase in transparency is to be welcomed.

In that context, I would like to strongly support implementation of each of the following proposals into EU legislation:

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### **Measures to strengthen regulation**

- Development of a Good Vigilance Practice standard
- An increased focus on risk management
- An obligation on companies to submit to the authorities all clinical trial data promptly once a product is authorised
- Regulatory oversight of post-authorisation studies backed by legal powers
- Scope for better communication outputs
- Powers to limit supply to existing users of a drug (i.e. to forbid use in previously unexposed individuals)

### **Measures to increase efficiency in industry**

- Requirements for pharmacovigilance system documentation simplified through introduction of a master file
- Simplified ADR reporting requirements
- PSUR requirements to be reduced and ultimately dropped for older products
- Primary responsibility for literature monitoring to be transferred to the regulators

### **Measures to increase transparency**

- Introduction of a web portal for pharmacovigilance information
- Information about Risk Management systems to be in the public domain
- Referral procedures to be more open with public hearings

There is little in the Commission proposals that I would strongly oppose but I have various comments and suggestions on some specific points, as follows:

### **Clinical trials**

Data from clinical trials have become increasingly important in pharmacovigilance. It should be made clear in Article 23 that the legislative requirement applies to any clinical trial of which the company is aware, including those conducted in patients who do not have the authorised indication(s). This is because the occurrence of a safety issue is rarely specific to an indication. Current legislation appears to allow industry leeway to

regard clinical trials conducted to develop new indications, and potentially producing important safety data, as not being relevant to the safety of the marketed product.

### **Post-authorisation studies**

The proposal to redefine a post-authorisation study (Article 1(15)) is appropriate and it particularly important that the words “in accordance with the terms of marketing authorisation” are removed since these studies should represent the “real world” and no patient should be excluded from observational research because the drug was not used in accordance with the authorisation.

The legal power for the authorities to oblige a company to conduct a study and within a reasonable timeframe is particularly important. It should be recognised that post-authorisation are not only required when there are “serious safety concerns” (as stated in Article 101g) – they are also essential to extend safety knowledge about drugs which might appear to have no serious safety concerns and to define the safety of medicines in ordinary practice.

### **Product information**

With regard to improving communication tools, I would support highlighting of essential safety information in authorised product information as a step forward. However, there is a need to recognise SPCs are widely not considered useful as a prescribing aide by clinicians. To address this it would be appropriate for the legislation to provide for the possible development of specific new tools for clinicians which would also be subject to regulatory approval.

### **Powers to limit supply**

The ability to prohibit use of a drug in new patients is potentially very important, because levels of risk are often lower in patients established on a treatment than in new users. Also, this power might potentially be used punitively against a company which failed to meet its safety obligations whereas the power to suspend or revoke an authorisation would rarely, if ever, be appropriate in such circumstances, primarily because of the resultant disadvantage to existing users.

### **Intensive monitoring scheme**

Broadly, the underlying purposes of this scheme should be to increase awareness amongst users that there is limited safety information about a drug, and to provide an incentive to industry to actively gain safety information before the drug can be removed from the list. It will be necessary to develop clear criteria for inclusion in and removal from such a list. Whilst I would support the scheme as a step in the right direction, it would be desirable in the longer-term to develop a better categorisation system for the safety of medicines. Consideration might therefore be given to providing a broader power for the safety of medicines to be explicitly categorised by the regulators.

## **The Pharmacovigilance Committee**

It is proposed that the new Pharmacovigilance Committee would report through the CHMP. This is not sufficiently different from the current arrangement. As has been pointed out in medical literature, a much stronger arrangement would be for this new Committee to have the power to form an opinion to be directly transmitted to the Commission [2]. Some overlap in membership of the two committees would be desirable but this should be limited.

## **ADR reporting**

The proposal to broaden the definition of an adverse reaction seems appropriate but I am unconvinced that the wording of Article 101e (1) - relating to what should be recorded and reported - is entirely appropriate. The second sentence appears to place too much of the onus on the MA holder to decide on causality and indent (b) seems too broad and reliant on temporal relationship. In this instance, existing criteria for reporting seem preferable, broadly this is any adverse event which the reporter considers at least possibly related to the drug plus any event which the MA holder considers at least possibly related to the drug (in cases where the reporter does not or has not indicated so).

Article 101e (2) would introduce a new requirement that non-serious reports occurring within the EU be submitted to Eudravigilance within 15 days (i.e. as “expedited” reports) when currently they are included in PSURs. There would seem to be no public health gain from such an approach. Losing the additional “expectedness” reporting criterion for reports arising outside the EU would, however, simplify reporting. My view is therefore that, regardless of where they arise from, serious suspected ADR reports require submission to regulators within 15 days and non-serious reports are best covered in PSURs or submitted at the specific request of authorities.

## **PSURs**

I fully support the principles behind Article 101f paragraph 3 removing the requirement for PSURs for generic products and certain other products. It could, however, be questioned whether it is necessary for the original product to continue to be subject to PSUR requirements in these circumstances. I also note that paragraph 2 of this article gives the authorities leeway to specify when they require submission of PSURs. In order that the authorities can focus their assessment resources on the most important products (those which are new, widely used and for which there are important safety concerns), it would be useful to create an interim situation (between routine submission of PSURs for new drugs and no PSURs for old ones) during which MA holders prepare PSURs but they are only viewed by authorities when they consider it necessary or as part of the inspection process.

## **Community assessment**

The general situation that there “appears to be a need to re-evaluate the risk-benefit balance of a medicine” does not seem to be embodied in the proposals for the referral

procedure. In order that the system will be able to cope and meet the 90 day deadline, it is important to word these so that only relatively important issues can be referred.

It would be useful to explicitly allow for an urgent safety restriction to be incorporated into the beginning of a referral procedure, if necessary.

### **Proposed legislation on funding**

In article 101(c), the heading “independence” looks odd and the scope of the text is unclear, for example, as to whether such funding might be used for post-authorisation studies conducted entirely independently of MA holders.

### **Enforcement powers**

The proposed legislation does not specify what enforcement powers are appropriate (Article 101o). Whilst accepting that this is ultimately for the member states to enact, there ought to be some expansion of the principles here. An important one which is missing here is that the penalties should not, as far as possible, be potentially detrimental to public health or disadvantageous to users of the relevant medicine.

Yours sincerely,

*by e-mail*

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### **References**

[1] Patrick C Waller, Stephen J W Evans, and Keith Beard. Drug safety and regulation BMJ, 2005; 331: 4 – 5.

[2] Silvio Garattini and Vittorio Bertele. How can we regulate medicines better? BMJ, 2007; 335: 803 – 805.

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