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From:
VAD (German association of importers of medicinal products)

To:
peter.arlett@cec.eu.int
European Commission
Directorate General Enterprise and Industry
B–1049 Brussels

Subject: European Commission consultation on pharmacovigilance
Strategy to better protect public health by strengthening and rationalizing EU pharmacovigilance
Public consultation on legislative proposals

Dear Mr Arlett,

The *Verband der Arzneimittelimporteure Deutschlands e.V.* (*VAD* — German association of importers of medicinal products) would like to comment on the EU Commission's legislative proposal on a "Strategy to better protect public health by strengthening and rationalising EU pharmacovigilance" (hereinafter "proposal") of 05.12.2007 as follows:

I. Considerations in principle

1. Distinction between authorisation holders and parallel importers

Section 2 of the proposal (page 2) rightly mentions importers explicitly as a part of the pharmacovigilance system. However, they are not in the same position as the original manufacturers to make an effective contribution to strengthening the pharmacovigilance system. The role of the parallel trade and its responsibilities in this system therefore need to be clarified for the purposes of section 3.2.2 (page 4). We take the view that the concept of the authorisation holder needs to be differentiated when an obligation to take measures is imposed. The legislative system so far is neither comprehensive nor clear.

It should be emphasised that the information about a medicinal product available to original manufacturers and parallel importers is entirely different. All the information up to authorisation, particularly from studies, is in the possession of the original manufacturers. Parallel importers are not in a position to carry out any comprehensive risk-benefit assessment for the medicinal product which would enable the authorities to draw comprehensive conclusions about the reference authorisation since, for example, they have no access to the authorisation file submitted. Nor can they contribute any international findings on undesirable effects because they only market the medicines nationally. For the sake of completeness, we would point out that this does not result in any disadvantage for the pharmacovigilance information system, as all the information required is in the hands of the original manufacturers. The circumstances are similar to those in the Centrapharm ruling (ECJ judgment of 20 May 1976), that reports were requested from parallel importers unnecessarily for which they had no competence, since they were not in possession of the necessary documentation and could not obtain it. The

requirements for the proposed instruments for parallel importers must also allow for these constraints in keeping with the principle of proportionality.

We would underline the importance of the pharmacovigilance system master file, whose requirements are supposed to cater for the special circumstances of the parallel trade (cf. section 3.2.3, page 5) and should be taken into account when the details are being worked out. The same applies to the requirements for risk management plans (cf. section 3.2.4, page 5).

A distinction should be made between different "marketing authorisation holders" or the concept of a “parallel distributor” should be added with parallel requirements, since, in practical terms, we believe that it is more important to clarify the role of the parallel importer with regard to the original manufacturer and the authorities because of original manufacturers' and importers' partly conflicting interests in re-importing or parallel importing activities.

Parallel importers must, of course, play their part in the process of safeguarding the markets by, for example, collecting data on, observing and reporting risks and implementing information and recall measures, but only in keeping with the principle of proportionality and safeguarding free movement of goods. Otherwise, however, they cannot take part in any further cooperative measures..

The German legislator has already made partial provision for this and has exempted parallel importers from preparing a PSUR in § 63b(5), sentence 8, of the *Arzneimittelgesetz* (Medicinal Products Act). This exemption should be introduced for all importers at European level too.

2. Changing the contents of the PSUR

The contents of the PSUR are to be changed (section 3.2.7, page 8). Since it is currently the instrument for reporting minor adverse reactions to the authorities, changes to the components also have an impact on parallel importers. According to the proposal for Article 101f(1) (page 24) of Directive 2001/83/EC, case reports are no longer to be listed in the PSUR.

Instead, Article 101e (page 23) requires all the reports from authorisation holders — on all events in the Community and all serious adverse reactions outside the Community — to be reported to the authorities via the EudraVigilance System within 15 days. In the case of parallel importers this would fall short of the measure's wider aims, since national marketing generates only reports from the national marketing territory and no further findings from other countries.

Consideration should therefore be given to requiring parallel importers to report only to the respective original manufacturers in their marketing territory within a given period of time. Practical experience has shown that fewer adverse reactions tend to be reported to importers, most of them being communicated to original manufacturers. Reports from importers could therefore complete the picture at original manufacturer level. If necessary, importers could forward an additional report on any serious adverse reactions to the authorities (as is already the case today).

3. Change in the definition of adverse reaction

The definitions in Article 1(11), 1(13) and 1(16) of Directive 2001/83/EC are to be changed, which involves redefining an adverse reaction and constitutes a key change. In essence the restrictions with regard to correct use, which are important in Germany, are to be dropped and, as a result, unexpected adverse reactions and misuse are to be dispensed with. This would greatly extend the definition. An adverse reaction would then be "a response to a medicinal product which is noxious and unintended". If the definitions of correct use and misuse were dispensed with, it would make classification and causal link analysis more complicated and more work-intensive. In September 2007 the *Verband Forschender Arzneimittelhersteller* (Association of researching manufacturers of medicinal products) estimated that 30 to 50% of adverse reactions could, in principle, be avoided if medicinal products were actually used as intended.

Irrespective of whether this proposal is a useful means of increasing the efficiency of the pharmacovigilance system, this change is expected to have a not inconsiderable influence on the liability system under medicinal product law, at least in Germany, since, according to § 84(1), sentence 2, No 1, of the German *Arzneimittelgesetz* (*AMG* — Medicinal Products Act), liability hinges largely on a product being noxious when used correctly. The adverse reactions mentioned in the packaging leaflet do not as a rule provide a basis for claims for compensation. This will probably have to be dispensed with or a definition of an adverse reaction for the purposes of liability law would have to be laid down in addition to the pharmacovigilance system's new definition. The full ramifications of the crucial impact on the liability regime ought to be considered here.

II. Effect of individual proposals in practice

1. We are critical of the proposal to supplement packaging leaflets with forms for patients to report adverse effects (section 3.2.6, page 7). Some packaging leaflets are already so bulky that they are attracting universal criticism. An alternative would be for dispensing chemists to have forms available or to have them available on the Internet in the health authorities' download area.

2. Extending the key safety information in the leaflet by inserting a box with special graphics specifically addressed to the authorisation holder could give rise to further problems [cf. in Annex 1 the proposal regarding a Directive 2001/83/EC, Article 59(1)(ba), page 19]. The aim of this proposal is to put certain new medicinal products on a monitoring list in accordance with Article 101j (page 29) and Article 22(2) (page 15) of Directive 2001/83/EC and to subject them to monitoring for five years. In this transitional period, reports on adverse reactions are to be collected intensively. The aim is welcome but would lead to more work for parallel importers without any significant benefit for pharmacovigilance. It would make more sense to be allowed to specify the original manufacturer directly as the addressee and not the parallel importer when the product is repackaged or newly labelled by the parallel importers. The cost-benefit assessment can only be made in full by the original manufacturer. The same is true of the proposal on Article 11(3b) (page 13) of Directive 2001/83/EC on product characteristics.

3. In the same context as presented under 3, labelling should also include such key safety information under Article 54(o) (page 18) of Directive 2001/83/EC. This would lead to a further constraint in view of the limited space available to parallel importers in particular, for the additional information required under trademark law

when products are newly labelled. It would be preferable to have symbols to be used throughout Europe — similar to the British black triangle mark. If the current text variant were to stand, the addressee should be the holder of the authorisation for the original preparation.

4. According to Article 101e (page 23), authorisation holders are to be obliged to make all their reports via the electronic EudraVigilance System only, i.e. reports on all events at Community level and all serious adverse reactions outside the Community. Apart from the fundamental change it introduces in the system for reporting in I.2 above, this requirement also has a technical impact. This comprehensive obligation requires a substantial investment to be made in setting up such an operating system which will scarcely be used to capacity. The exemption system in the comparable national provisions in Germany should be applied here. Paragraph 3(1) of the Order on the electronic reporting of adverse reactions to medicinal products enables reports to be made in writing in keeping with the principle of proportionality ("Obligations to report to the competent senior Federal authority may, by way of exception from paragraph 2, be met by a single report on paper if electronic reporting would be unduly onerous for the person obliged to submit the report. In justified exceptional cases, the authority may order a report on paper to be made. If the person who has to make the report has additional information which cannot be transmitted electronically for the reasons given in paragraph 2, an additional report on paper must be submitted to the competent senior Federal authority"). For many small and medium-sized enterprises this exception is a necessity.

5. Finally, we would like to emphasise as a precautionary measure that post-authorisation safety studies should not be imposed on all authorisation holders but only those for the original product (section 3.2.5, page 6).

The VAD is willing to cooperate constructively on the legislative proposal.

Yours sincerely,

Thilo Bauroth
Director