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Dear Dr. Arlett,

PUBLIC CONSULTATION ON LEGISLATIVE PROPOSALS FOR PHARMACOVIGILANCE

I am responding to the legislative proposals from the Commission, dated 5 December 2007. These are my personal views based on my experience as a former regulator and as an academic with interests in the field. It is a personal view and is not necessarily the view of The London School of Hygiene and Tropical Medicine, nor the view of the Pharmacovigilance Working Party of CHMP, of which I am a co-opted independent member.

In general I warmly welcome the proposals and think that some major steps have been taken, in the right direction. I will not go into detail on the proposals that I support. Nor will I make detailed comments on the wording changes in section 4 of the Consultation.

a) The evidence related to the burden of adverse drug reactions relates largely to well-known effects in well-established drugs. These clearly have benefits as well as harms, but the Commission needs to make proposals, at least for research, to reduce the harms and improve the drug usage to avoid harms. The current emphasis on the blunt instruments of SPCs is insufficient.

b) There does need to be a strengthening of Pharmacovigilance at the CHMP level. There is an inevitable human tendency to justify our past decisions. This can lead to reluctance by committees such as the CHMP to change their mind on the safety of a recently authorised product. This same tendency has occurred in the US and leads to inertia in decision-making. There needs to be higher hurdles set by CHMP for products that are not first in their class to justify their introduction to the market. At the same time there needs to be more careful active monitoring of products that are first in their class, following their marketing. This applies particularly

when medicines are licensed on the basis of surrogate outcomes and evidence on true clinical benefit is lacking. A balance of powers then needs to be achieved between the decision makers assessing the harms and those who concentrate on benefits.

c) The Committee structure at present is almost entirely based on those employed in competent authorities. It should have less national basis and include more independent clinical members.

d) I agree with reducing some of the regulatory burden on industry for pharmacovigilance, where this is based on process measures that are not demonstrably improving public health. Industry will approve of this, but it is important that their objections to the powers required by regulators to insist on better post-marketing monitoring do not result in a weakening of the Commission proposals. Th e "Risk Management" activities need to be evaluated and the quality of what is done needs to be improved. The sanctions against MA holders who fail to meet their obligations need to have an impact such that reasonable obligations are met. This should include the ability to remove the indication for putting new patients on a medicine, if the knowledge of safety has not increased. Safety is always provisional, and when a medicine is marketed there is an implicit assumption that it will only continue on the market if the knowledge of safety improves. In the past we have been content with an absence of evidence on harms, but we need to move to a position where we have evidence of absence of harm. Failure to obtain that evidence requires penalties to be exacted.

e) There have been instances where clinical trials for a new indication have been done, but no new application is made but safety issues arising in such trials are not communicated to regulators. It is vital that this problem is dealt with explicitly in the legislation.

f) Post-authorisation studies are a vital part of what I have suggested and they must be done to high standards. Any observational study should be done using all the patients receiving a medicine. It may be reasonable to report separately on those that are using the medicine under the terms of the marketing authorisation, but ALL patients must be reported on.

g) The "Intensive monitoring scheme" is reasonable, but whether it should be similar to the UK "Black Triangle" scheme is questionable. The internal extra vigilance at the MHRA can be useful as is the marking of some product information to warn prescribers that safety knowledge is limited. The reporting of non-serious suspected

reactions is not the key feature that will benefit public health. What will help is some incentive for health professionals to report serious reactions. It is also important for patients to be aware that a drug is new, and they may be more vigilant in reporting themselves. Patient reporting is likely to be useful, and fears that it will be overwhelming seem to be unfounded based on those European countries which have introduced it. However the key aspect is that simply relying on spontaneous reporting is insufficient for true intensive monitoring. There have to be active plans for surveillance. In terms of communicating the issues to patients, I would like to see a three-level labelling. 1) New medicine, provisional safety 2) Existing medicine, some knowledge on safety 3) Well-established medicine with confirmed absence of harm – known safety. It would be assumed that all medicines in categories 1 and 2 are prescription-only. Some in category 3 may be prescription-only.

Yours sincerely

Stephen JW Evans