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Agreed by the PhVWP and the CHMP through written procedure following their meetings of May 2006

**Proposals from the CHMP Pharmacovigilance Working Party (PhVWP)
and the Committee for Medicinal Products for Human Use (CHMP)**

for the Strengthening of the EU Pharmacovigilance System

**in the framework of the European Commission's Public Consultation on their
Assessment of the Community System of Pharmacovigilance**

I. INTRODUCTION

The Pharmacovigilance Working Party (PhVWP) and the Committee for Medicinal Products for Human Use (CHMP) welcomes the European Commission's (EC) initiative in favour of strengthening the system of pharmacovigilance in the European Community. This is the PhVWP's response to the EC's consultation calling for comments on the current functioning of the system and how it might be further developed, in the interest of public health. It provides a general perspective on the challenges facing pharmacovigilance, describes outputs of some broad-ranging discussion groups held by the PhVWP, and indicates priorities for the way forward. It was presented to the CHMP and supplemented by the CHMP's comments. Overall, the PhVWP and CHMP are strongly supportive of better integration of vigilance in the product life cycle, which in turn means effective interfaces between the CHMP and its Working Parties and optimising the use of vigilance expertise at all stages. Importantly, the move to proactive pharmacovigilance will without doubt require increased resources.

II. APPROACH TO EC CONSULTATION

The discussion of the way forward focussed on the core recommendations of the independent study conducted by the Fraunhofer Institute which address six key areas:

- Data sources and detection of safety concerns;
- Use of legal framework and new legal tools;
- Decision-making in pharmacovigilance;
- Impacts of communication and actions;
- Compliance of marketing authorisation holders with their legal obligations; and
- General principles of quality management and continuous quality improvement.

In doing so, the major stakeholders in pharmacovigilance, namely healthcare professionals, patients, marketing authorisation holders and the public, were kept in mind. Their engagement is vital to effective pharmacovigilance and their needs for timely action and up to date information on safe use of medicines are paramount.

III. ROLE OF THE PhVWP

The PhVWP's mission is to provide advice on the safety of medicinal products authorised in the European Union (EU) and the investigation of adverse reactions to enable effective identification, assessment and management of risk at any phase in the product life cycle. On the basis of such advice, the PhVWP will provide, where applicable, recommendations for regulatory action to its stakeholders, the CHMP and EMEA, and the national Competent Authorities. This should enable effective management and subsequent communication of risk. At all times, the PhVWP considers best use of pharmacovigilance resources available in the EU when trying to achieve its objectives.

Since its creation in 1995 the PhVWP has worked continuously to improve its practices, both to deal with the ever increasing workload and to contribute harmonised and co-ordinated regulatory action at the national level. The Working Party's discussion paper 'Pharmacovigilance in Europe: the way forward' (see Annex) recognises the great potential for improvement of pharmacovigilance to the benefit of public health. Members of the Working Party have also contributed to the Heads of Agencies' European Risk Management Strategy which encompasses a rolling programme of work to strengthen pharmacovigilance.

Recognising the need to reinforce the expertise within the PhVWP, eight additional expert members have been co-opted from March 2006, bringing expertise in pharmacoepidemiology and biostatistics, risk management, risk communication, biotechnology, and paediatrics. The aim is to optimise integration of this additional expertise with demonstrable impact on the quality of PhVWP's deliverables to its stakeholders.

IV. ENVIRONMENT AND CHALLENGES

IV.1 Changing access to medicines

In debating the way forward, the PhVWP was conscious of the changing environment of medicines use: the growing range of prescribers, expanding self medication options, multiple suppliers for medicines, including via the internet and complementary therapies. These changes in the pharmaceutical marketplace heighten concern about the capability to obtain complete and valid information about exposure to medicines (at a particular point in time and over time), particularly in patients with multiple morbidity and long-term use of medicines. The science of pharmacovigilance depends on good links with real-life use of medicinal products.

IV.2 Key challenges facing pharmacovigilance

The PhVWP identified the following particular challenges in order to strengthen the EU pharmacovigilance system. These are:

- A need to develop new and better methodologies;
- Improvement of consistency of regulatory actions;
- Involving and engaging health professionals, patients and the general public in the process;
- A need to monitor public health outcomes; and in order to achieve all this
- Strengthening of resources in terms of staff, expertise, funding and education.

V. KEY AREAS FOR STRENGTHENING THE EU PHARMACOVIGILANCE SYSTEM

V.1 Data sources and detection of safety concerns

The input of any pharmacovigilance activity is signalling a potential safety concern, using data from single case safety reports, the literature, clinical trials, epidemiological studies and other data sources. **Single Case Safety Reports** will continue to be the backbone of the input step of pharmacovigilance. The spontaneous reporting systems in the EU should remain embedded in the national healthcare/regulatory systems in order to have a 'local face' (as particularly underlined by the newer Member States), to maintain short links and feedback to the reporters (e.g. physicians and other healthcare professionals), to ensure the quality of the reports and to provide for electronic submission as well as education and training of reporters. Some Member States ask for improvements with respect to privacy law, legislation promoting blame culture and other legal hurdles for reporters ("The doctor should be protected").

With respect to **additional data sources** for signalling of potential safety concerns, the following are important: hospital medical records, patient and consumer reports of adverse reactions, registries, (large simple) clinical trials, prescription databases, record linkage databases. The WHO centre at Uppsala maintains a worldwide database which is an important resource for signal detection and there is a need to foster collaboration. In relation to vaccine vigilance, collaboration with the European Centre for Disease Control is essential to minimise duplication of efforts and maximise the utility of studies carried out in particular Member States.

It is strongly recommended to further invest into **signal detection** with regard to valid statistical methodologies (beyond counting reports and quantifying the signal/noise ratio), harmonisation of reporting methods and standardisation of quality assurance (challenge for EudraVigilance). The meaningful use of Periodic Safety Update Reports (PSURs) should be further investigated. In general there needs to be less focus on the administration of data collection, and greater use of resources in analysing the data collected.

Recommendations:

- 1. Spontaneous adverse reaction reporting needs to be embedded in local healthcare systems, sharing best practice between Member States.**
- 2. Access to additional data sources e.g. disease registries, record linkage databases, should be optimised both for improved signal detection and strengthening signals.**
- 3. Development of signal detection and other methodologies requires further investment and systematic use of Eudravigilance needs to be implemented.**

V.2 Use of legal framework and new legal tools

A new legal framework and new legal tools were introduced by Directives 2004/24/EC, 2004/27/EC and 2004/28/EC as well as Regulation (EC) No 726/2004. In principle, the implementing guideline for **Risk Management Plans** in the EU will improve the pharmacovigilance activities by (1) specifying identified safety concerns and patient groups at risk or lack of information (2) proposing specific activities to provide the missing information (pharmacovigilance plan) and specific activities to reduce the identified risks to a minimum (Risk Minimisation Plan). This new tool will guide stakeholders to undertake proactive pharmacovigilance.

Moreover, under the new legislation improved transparency will be implemented in regulatory procedures and improved communication tools will be used for dissemination of information to healthcare professionals and patients. Ultimately, the new system will have tools to follow-up the impact of activities taken to reduce risks. Altogether, this will probably provide considerable improvements compared to the system in place before the new legal framework.

There are a number of issues which need further consideration in relation to the implementation of the new legislation and of the new legal tools, to ensure these work effectively and are demonstrably effective. Guidelines will need clarification or improvement with experience of use of the new tools, and roles (in particular the Qualified Person Responsible for Pharmacovigilance) will need better definition.

Some areas of the legal framework may require revision to operate optimally. This could include allowing for harmonisation of submission schedules for PSURs and renewals, and revision of the current legal requirement for marketing authorisation holders to inform the competent authorities of important safety information prior to or simultaneously with a public announcement (prior to is preferable).

Furthermore, the legal base could be enhanced in areas which are key to delivery of proactive pharmacovigilance. Worksharing by Member States currently has an informal status for PSUR assessment only. The worksharing principle could be extended to other areas of pharmacovigilance work if the legal framework supported this. Completion of the studies agreed as part of pharmacovigilance plans cannot currently be enforced. And better resources for independent pharmacoepidemiological studies, possibly through fees from industry and public co-funding, will be critical. The Innovative Medicines initiative, under the EC's VIIth Framework, may be vitally important in achieving a way forward.

Recommendations

- 4. Risk Management Plans are key to proactive pharmacovigilance and should be supported by improved guidance, use of the scientific advice procedure and peer review of protocols, and there should be a clear legal requirement for completion within an agreed timeframe.**
- 5. Further work is needed to fully implement transparency provisions in regulatory procedures.**
- 6. The legal framework should support worksharing of PSURs to reduce reduplication of work and this principle should be extended to other pharmacovigilance activities.**

V.3 Decision-making in pharmacovigilance

Decision-making in pharmacovigilance takes place against a background of diversity in medicines supply, clinical practice and prescribing behaviour, which can even differ regionally within Member States. Pharmacovigilance issues and safety concerns are usually of a complex nature and Competent Authorities take decisions at the population or patient group level, not at an individual patient level. Moreover, Competent Authorities serve a range of stakeholders with differing interests – consumers/patients healthcare professionals and pharmaceutical companies/marketing authorisation holders. And frequently there is a tension between the need for timely, sometimes urgent decision-making and a scientifically robust position.

There is need to streamline decision-making processes from signal detection to regulatory action in the EU resulting in formal harmonised decisions binding in all Member States, and their harmonised communication to the public, because patients should receive similar safety information across the EU. In this regard there needs to be a better system for harmonising safety information in SPCs for products containing the same active.

While recommendations from PhVWP in relation to nationally authorised products currently remain non-binding, there is need for a process to guarantee their timely, consistent implementation in all member states. Formalising interactions with the Co-ordination Group (CMD(h)) may assist this process; otherwise new legal powers will be required, possibly a “light touch” referral. The urgent safety restriction procedure has worked well, though some practical aspects need improvement.

In view of the public health importance of safety referral procedures, these need to be as expeditious as feasible. A change in legislation should be considered in to support an immediately binding CHMP Opinion in cases of urgency instead of requiring EC action.

The PhVWP was cautious about a proposal for expanding the conditional approval principle, bearing in mind the existing procedures to licence medicinal products of high importance to special patient groups. On balance it was considered that in cases of premature applications pharmacovigilance instruments like Risk Management Plans cannot serve as vehicles for early authorisation.

Recommendations

- 7. Decision-making procedures need to be streamlined from signal detection to regulatory action and referrals kept as short as feasible.**
- 8. Legal provisions supporting harmonised decisions in all member states should be reviewed, with consideration of a “light touch” referral.**
- 9. A single system for communicating common regulatory decisions as well as principles and guidance developed at the EU level should be established.**

V.4 Impact of regulatory action and public communication - Engagement of healthcare professionals, patients and public

The **effectiveness** of regulatory decisions is a key element for the ability of pharmacovigilance systems to protect public health. Measures taken to improve the safe use of a medicinal product need to be rapidly assessed and corrected as necessary. National Competent Authorities and the EMEA as well as marketing authorisation holders should establish systems to collect and evaluate data allowing assessment of the effectiveness of communication to healthcare professionals and to patients (and to identify barriers to it), to evaluate the level of compliance of prescribers and patients with the recommendations, to assess the impact of regulatory decisions on morbidity/mortality, to identify implementation failures at an early stage and to decide additional actions as necessary. This system should also be designed as an on-going learning process on how to deal effectively with drug safety hazards, e.g. how to improve communication strategies. The knowledge gained through a critical examination of previous experience should normally be translated into a change of practice and procedures.

With regard to **communication to healthcare professionals**, a range of activities should be initiated. Regular contacts between regulators and healthcare professionals are essential, i.e. through workshops, meetings, seminars, at national as well as at EU level. National Competent Authorities and the EMEA must understand the needs and demands of the healthcare professionals to be able to provide information that has the intended impact. A working group and an expert network of healthcare professionals at EU level could be created. The working group should give advice on risk communication in general and the network should give advice as appropriate.

Outcomes of regulatory actions should be assessed, when possible systematically. Drug utilisation data should be collected regularly in Member States in order to be able to evaluate the effect of actions and public communication. Available methods of describing actual medicinal practice should be compiled and evaluated through a pilot study if they allow measuring the impact of communication within the EU.

Since a major problem seems to be the lack of knowledge amongst prescribers of the status of Direct Healthcare Professional Communication (“Dear Doctor-Letters”) and also the Summary of Product Characteristics, **education** about these tools is necessary. Training is suggested at pre- and post-graduate level. Short bulletins should be issued regularly by the Competent Authorities or other public health organisations with information on important aspects of the risk-benefit balance of medicinal products.

Administrative and technical support should be given to healthcare professionals, for instance subscription of newsletters/press releases/phone text messages, in order to quickly reach healthcare professionals with regard to important safety news. Such systems make it possible to reach healthcare professionals in a situation of urgent safety information.

National Competent Authorities could introduce in their Member State a specific colour of the envelope or a sign on the envelope of a Direct Healthcare Professional Communication that identifies the letter as safety information provided in cooperation with the Authorities, distinguishing it from promotional material. A guideline on Direct Healthcare Professional Communications has been adopted by the CHMP. There is also a need for regulatory guidance on public statements/press releases.

With regard to **communication to the public**, regular meetings and seminars with representatives from the media, aiming at better understanding of how to interpret safety information is proposed. National Competent Authorities and the EMEA can provide information on their websites specifically for the media and call for a meeting with media representatives, if necessary, when press releases are issued in order to provide the opportunity for clarification. When individual case safety data are released to the public, general explanatory information on the value and limitations of that data in understandable language should be provided by the national Competent Authorities and the EMEA. It is proposed to set up a working group on how to take care of consumer reports on adverse reactions

and how to integrate the data in the evaluation of safety. Knowledge from Member States with experience in the field should be considered.

Recommendations

- 10. A range of activities should be undertaken to engage, involve and educate health professionals; an expert healthcare professional network at EU level should be set up to advise on risk communication.**
- 11. Data on the effectiveness of communication with healthcare professionals on medicines safety issues should be collected and evaluated.**
- 12. The contribution of consumer adverse reaction reports to pharmacovigilance should be evaluated, and communication materials on pharmacovigilance developed for the public.**
- 13. There should be proactive engagement with the media to promote better understanding of safety issues and risk-benefit profile.**

V.5 Monitoring of compliance with pharmacovigilance requirements - Need for quality management systems

Quality management is clearly perceived as a tool that should ensure excellence from the scientific as well as from a procedural point of view. It is acknowledged that many steps have already been taken to improve the system, particularly by means of the new legislation and guidelines which facilitate work at EU level with a somewhat lesser impact at national level, which is however equally important.

Further changes are needed, and the provision of the appropriate **resources** by the Competent Authorities for pharmacovigilance, in particular of qualified staff, is thought to be a main issue to bring this forward. Such resources need to be adequately allocated for routine pharmacovigilance activities as well as pharmacovigilance activities tackling both marketing authorisation holders' compliance and compliance of the Competent Authorities. Staff working in pharmacovigilance need to be trained and a continuous educational programme should be in place, ensuring that pharmacovigilance staff have the required standard for their activities and that they are offered the opportunities to maintain a high level of scientific and regulatory knowledge.

In order to facilitate compliance with pharmacovigilance requirements, **quality management systems** specifically dedicated to pharmacovigilance activities should be implemented by the Competent Authorities, or, if these do not (yet) exist, the pharmacovigilance units need to interact with quality management functions at their Authorities (where a quality management system specifically dedicated to pharmacovigilance exists, the pharmacovigilance units should also interact with the quality management functions of their Authorities). In the absence of a quality management system at the Competent Authority, or while developing them, interaction with existing quality management systems, particularly those within the EMEA, could be used as a support.

Standard operating procedures facilitating harmonised working practices across the Competent Authorities within the EU with a specific effort at reducing duplication of work should be developed and implemented. Standard operating procedures should specifically aim at ensuring high quality of the data in the national adverse reaction databases and EudraVigilance. Internal audits should be

conducted at the Competent Authorities, and maximum value gained from the rollout of the EU bench-marking exercise, whose first cycle will be evaluated towards the end of 2006.

In collaboration with the inspector services, a system should be developed that will ensure the important activity of monitoring marketing authorisation holders' compliance. Such a system should be designed to avoid duplication of work across the EU.

Recommendations

14. Quality management systems dedicated to pharmacovigilance activities should be implemented by the Competent Authorities.

15. Appropriate resources should be targeted to check and support compliance by marketing authorisation holders with pharmacovigilance obligations

VI. PRIORITIES FOR ACTION

From this broad-ranging discussion, a large number of recommendations has emerged. In recognising that the EC consultation provides a unique opportunity for change, the PhVWP and the CHMP wished to focus on high-level priorities for action. This is by no means simple given the range of valid and worthwhile initiatives. The proposed "top ten" can be grouped under 3 headings, the criteria for selection being the potential to support and reinforce the shift from reactive to proactive pharmacovigilance, improve timeliness and consistency of regulatory action, and enhancement of the impact of safety communications, so that there is measurable effectiveness of the system. While much can be done on an informal level, CHMP was clear that in some areas changes will only be achieved by new legal provisions clarifying accountability.

1. Evidence sources and methodologies

- A systematic approach to signal detection should be implemented, maximising the utility of the Eudravigilance database.
- Efforts should be made to gain more robust forms of evidence than single case safety reports, supported by appropriate allocation of resources to the utilisation of a range of data sources.
- Appropriate scientific and pharmacoepidemiological expertise should be allocated to pharmacovigilance planning as a priority for successful implementation of the new legal tools.

2. Rapid timely decision-making

- Streamlined procedures should be introduced to reduce, as far as feasible, time from signal to regulatory action, and relevant performance measures should be agreed
- Implementation of risk management plans and completion of agreed safety studies should be supported by new legal powers.
- Worksharing principles should be extended from the current PSUR pilot to other pharmacovigilance activities and supported by appropriate legislative provisions.
- Resources for pharmacovigilance at Member State level should be reviewed by Competent Authorities in the light of requirements for "best practice" operating procedures.

3. **Engagement with healthcare professionals and the public**

- A multi-stranded initiative should be established to support the active engagement of healthcare professionals with pharmacovigilance inputs, outputs and processes, based in the first instance on inclusion in education and training. This should include improvement of measures evaluating the impact of regulatory actions.
- Pharmacovigilance systems should be better geared to involvement of patients and the public, and the contribution of patient adverse reaction reporting should be evaluated where this has been introduced.
- Access to information underpinning regulatory decisions should be provided with levels of detail appropriate to all stakeholders needs.

VII. CONCLUSION

The experience of the 11 years since the PhVWP's inception has supported the evolution of pharmacovigilance systems and introduction of new approaches. In putting forward these proposals for strengthening the EU system for pharmacovigilance in response to the European Commission's consultation, the CHMP and the PhVWP recognise that further analysis and discussion of these ideas with other stakeholders will be essential, and wish to contribute to the post-consultation process as it goes forward, to support the best possible outcome for public health and EU citizens.

ANNEX:

PhVWP's discussion paper 'Pharmacovigilance in Europe: the way forward'