European Medicines Agency
Post-authorisation Evaluation of Medicines for Human Use

London, 18 December 2007
Doc. Ref. EMEA/601107/2007

EXECUTIVE SUMMARY REPORT
ON
EMEA MEETING WITH INTERESTED PARTIES AND RESEARCH CENTRES ON ENCePP
(EUROPEAN NETWORK OF CENTRES FOR PHARMACOEPIDEMIOLOGY AND PHARMACOVIGILANCE)

28 JUNE 2007, EMEA

Chairperson: Thomas Lönngren

1. AGENDA AND PRESENTATIONS

9:30 to 11:30

- Welcome (Thomas Lönngren)
- Introduction of Participants (Veronika Jekerle)
- Presentations:
  - ENCePP in the context of the EU Risk Management Strategy (Noël Wathion)
  - Scenarios for Post-Authorisation Safety Studies (PASS) (Panos Tsintis)
  - ENCePP – Conduct of “independent” PASS (Henry Fitt)
  - Introduction for Working Group discussions (Ingemar Persson)

11:50 to 17:15

- Working Groups (WG 1-5):
  1. Roles and organisation of Centres in ENCePP
  2. Principles and Code of Conduct for ENCePP
  3. Functional organisation of the network I: Health Care Databases and Registries
  4. Functional organisation of the network II: Therapeutic Areas
  5. Quality Assessment and Assurance within and by ENCePP
- Presentation of the outcomes of WG 1-5
- Discussion and conclusions

2. BACKGROUND AND SCOPE OF ENCePP

The EMEA and the European Commission are jointly working to facilitate the availability of innovative medicines to patients. Thus, new legal tools have been introduced to reduce the time-to-authorisation of certain medicines by enabling their approval with a more limited dataset (i.e. Conditional Approval) and allow for faster evaluation timelines (i.e. Accelerated Assessment). However, in order to ensure a positive benefit-risk balance, it is also essential to have a thorough post-marketing surveillance system of medicinal products.

In the past, pharmacovigilance has tended to be a reactive process mainly concentrating on spontaneous reporting. This is limited by under-reporting, as well as by data quality, which is often insufficient to allow a meaningful assessment. However, there has recently been an important shift to a much more proactive approach, involving a broader evidence base and a widening of expertise, resources and methodologies.

This is partly due to the increasing need to address certain emerging issues in the field of the safety of medicines, such as the importance of large scale studies to capture very rare and potentially life-threatening events (e.g. for vaccines) or new advanced therapies that may be associated with serious, unpredictable, long-term and occasionally life-threatening effects. In the light of these new challenges, additional legislation has been implemented in 2005 to strengthen the EU pharmacovigilance requirements and promote a proactive conduct of pharmacovigilance based on risk management.

Although numerous high quality research centres to study the safety of medicines already exist in the EU, the combined Pharmacoepidemiology (Ph'Epi) & Pharmacovigilance (Ph'V) studies needed to provide answers to the above issues have hitherto proven difficult to realise. This is mainly due to the inherent fragmentation of research and knowledge in the EU, where relevant research centres have access to smaller patient numbers and stand-alone databases with more limited sample sizes. Therefore, an appropriate infrastructure resulting from the networking of the various research activities and data sources available to several centres in a particular therapeutic field would generate sufficient sample sizes and be in a position to collect the necessary high-quality data.

In line with the EMEA Road Map and the European Risk Management Strategy, (which is a joint initiative of the EMEA, the European Commission and the Heads of Medicines Agencies (HMAs) of the Member States), the EMEA is working on the establishment of the European Network of Centres for Pharmacoepidemiology & Pharmacovigilance or ENCePP, a network of Ph'Epi Centres, Medical Care Centres, automated Health Care Databases and electronic Registries, which will significantly contribute to identify, characterise and assess risks relating to medicinal products marketed in Europe, thus enabling a more proactive conduct of pharmacovigilance. In an initial phase more than 60 European Ph'V and Ph'Epi centres have been identified and included in an inventory held by the EMEA.

3. EXECUTIVE SUMMARY

The meeting was organised by the EMEA in order to inform interested parties of the current status of the project, to discuss a possible Working Model for ENCePP and, importantly, to receive feed-back on the proposed concept. Thus, it was intended to achieve general agreement on the network concept and further refine the next phases of the project. The meeting was chaired by Thomas Lönngren, the Executive Director of the EMEA.

More than 50 centres currently in the EMEA inventory, including clinical research centres and Health Care databases and already existing EU networks for rare diseases were represented at the meeting, as well as representatives of the EMEA, the Agency's Committee for Human Medicinal Products (CHMP), the EMEA Scientific Committees Working Party with Patients' and Consumers' Organisations, the EMEA CHMP Working Group with Healthcare Professionals' Organisations, the European Centre of Disease Prevention and Control (ECDC), the International Society of Pharmacovigilance (ISoP), the European Association for Clinical Pharmacology and Therapeutics (EACPT) and the European Federation of Pharmaceutical Industries (EFPIA).

Following an overview on the current European Risk Management Strategy and real life examples of safety issues that are presently difficult to address, the general concept of ENCePP was introduced to the participants. The attendees were then introduced to and divided into 5 Working Groups in order to discuss important aspects of the proposed network, as shown in the above agenda. The outcome of the various WPs was then discussed at the plenary session leading to the following conclusions:

There was overwhelming support for the ENCePP concept. Regarding the *organisation of the Network*, it was pointed out that the wide and miscellaneous group of centres and institutions with very different research interests and expertise involved in the network, and the diverse nature of the research questions to be addressed by ENCePP, present a serious organisational challenge. The majority of centres raised the concern that a rigid structure with predefined, disease-oriented, so-called "therapeutic" subnetworks, plus a database subnetwork, each overseen by a Coordinating Centre, would not be appropriate. Instead, a flexible approach was preferred, whereby ENCePP centres would be well characterised in a detailed and frequently updated inventory available for public consultation. Thus, when a research question is put to ENCePP, ad-hoc groups of collaborating centres can be formed and submit research proposals to address the issue in question. A possible option that was discussed would be to have a suitably competent and transparent panel to select the most appropriate research proposal. However, such a procedure would take time and might thus only apply to less urgent requests where public money is involved and where there is no established selection panel. It was agreed that a different procedure should be followed in the case of an urgent safety issue, which needs to be promptly investigated. In such a case, it should be possible to identify without delay an organised group of centres able to promptly begin a study in a specific therapeutic domain. It would therefore be important to identify such groups of centres organised by therapeutic area or clinical domain and with a strong methodological background.

The existing list of ENCePP centres and any established groups or networks of centres has to be updated in order to generate a comprehensive, transparent and searchable inventory, electronically and publicly available, thus facilitating collaborations between the centres. Centres included in the inventory should be free to carry out research within or outside the ENCePP rules and scope. However, if a centre (or group of centres) undertakes research under ENCePP, it must follow the established rules of procedure. It was agreed that "a centre" can comprise a range of resources, from a single expert to a large research organisation with many staff and other resources e.g. databases.

It was unanimously agreed that the *quality and independence of* any *research,* undertaken by ENCePP, defined on the basis of best standard scientific methods and transparency, is of paramount importance. As regards the quality of the research, the centres concurred that there is a need to agree and implement common quality standards within ENCePP, applicable to the centres, the methodologies, the data and the conduct of the studies. It was suggested that rather than initially establishing a strict "accreditation system" for centres to be included within ENCePP, a process of self-assessment on the basis of detailed criteria followed by a suitable peer-review would be preferable. Moreover, at this early stage of the project and in view of the diverse nature of the centres included, participation of the centres in ENCePP should not be restricted whilst the quality criteria and standards are being developed and agreed. Consequently, it was suggested to establish a Working Group to look into existing standards (e.g. ISPE's Guidance on Good Ph'Epi Practice, ICH Guideline on Good Clinical Practice, CONSORT statement, etc) and how a quality system can be established for ENCePP. Moreover, in view of the range of resources and expertise evident across the wide spectrum of the centres, there is great potential for *training* and further development of participating centres, particularly in the fields of Ph'Epi and research methodologies.

In order to ensure maximum independence, there needs to be a *set of rules and principles* addressing all relevant steps in the research process, including identifying and refining the research question, carrying out the research, presenting the results, an adequate peer-review and disseminating the results. In addition, a *standard funding/business contract* should be applied with a clear set of rules for the involvement of the study sponsor; this is especially relevant for research funded by commercial sponsors. Further suggestions to enhance scientific independence included the online-publication of the final study protocol and the establishment of a public register of initiated and concluded Ph'V studies.

A major objective of ENCePP should be to identify existing data within the Member States using available data sources in clinical or administrative, automated databases, and to coordinate these data in a comprehensive registry. Such a registry should also include existing databases and networks for rare diseases. The idea of having a common coding system for the diverse data sources in order to facilitate the combination of different datasets was abandoned and replaced by a more pragmatic solution including the application of a common protocol. It was further suggested to design a questionnaire in order to obtain details on the datasets. In this context, the concern was raised that the release of patient-related data from one country to another could have legal implications. Similarly, ENCePP should be charged with the development, promotion and dissemination of high quality research methodologies.

In order to set up the network and oversee its subsequent development and maintenance, the centres agreed that there is a pressing need to establish a *governance body* or *steering group*. Notably, there was a strong desire for the EMEA to lead and run ENCePP.

As regards the financial aspects of the Network, there was a strong request for the EMEA to guarantee some level of funding. Should this prove possible, standard EU procedures would be followed, as with any Community funds. In addition, the centres welcomed the role of the EMEA in facilitating the interaction with other funding bodies, namely the European Commission's (EC) 7th Framework Programme and the Innovative Medicines Initiative. In this respect, the EMEA has put forward suggestions to the EC on specific research topics in the field of drug safety to be publicly funded and has organised joint Workshops on how to apply for such funding.

4. CONCLUSION

Further to this open, interactive and fruitful meeting, the following conclusions can be drawn on the ENCePP project:

- Unanimous support from all invited parties, including industry.
- Clear call for the EMEA to lead and run ENCePP.
- The EMEA should explore and facilitate funding options (public, private, and/or public-private partnerships).
- Independence of any research undertaken by ENCePP is of paramount importance and should be achieved through ensuring best-standard science and transparency.
- Quality standards and training need to be developed, agreed and implemented across ENCePP.
- For ENCePP to be a success, it should be flexible, dynamic and not unnecessarily bureaucratic.
- Regarding the structure of the Network, it should comprise a group of centres with very diverse research interests, activities, and methodologies. It is therefore difficult to populate an organisational structure defined according to individual therapeutic areas led by an established Coordinating Centre. A more flexible consortium-type approach, with ad-hoc collaborations is preferred, in order to better address the particular research questions.
- There is a need for a Steering Group to oversee the Network and ensure scientific quality assurance. It would be advisable to already provide for interim arrangements to help the EMEA further develop quality criteria and standards.
- The ENCePP Inventory should be further developed to include detailed information on the scientific profile of the centres and made available to all centres at the time of the Project launch, in the first half of 2008.