EUROPEAN PHARMACEUTICAL MARKET RESEARCH ASSOCIATION (EphMRA)

RESPONSE TO

IMPLEMENTING MEASURES IN ORDER TO HARMONISE THE PERFORMANCE OF THE PHARMACOVIGILANCE ACTIVITIES PROVIDED FOR IN DIRECTIVE 2001/83/EC AND REGULATION (EC) NO 726/2004

THE CONCEPT PAPER SUBMITTED FOR PUBLIC CONSULTATION

PCIM/11/01 - Public Consultation on implementing measures for pharmacovigilance

Introduction

The European Pharmaceutical Market Research Association (EphMRA) is an industry association representing those engaged in multi-country healthcare market research in Europe.

EphMRA is a well established organisation – 50 years old this year, widely known and respected in its field.

Member companies are made up of:

- Pharmaceutical manufacturers (38 members - the majority of whom are actively involved in research and development) who regularly conduct multinational market research and operate an international market-research function.
- Market research suppliers/agencies most of whom specialise in the healthcare field (154 members).

The purpose of EphMRA is to develop and improve standards and techniques in Europe for market research in the field of health and healthcare, and to strengthen the role of the Association in the relevant decision-making processes in order to support its members in their international activities and to create transparency to the general benefit. EphMRA's Code of Conduct, developed in conjunction with EFPIA is designed to safeguard the rights of respondents and protect data integrity. It provides comprehensive ethical and legal guidance for those involved in healthcare market research.

EphMRA also recognises that market research can perform a useful role when it comes to pharmacovigilance. EphMRA's Code of Conduct states:

> "*EphMRA is in complete support of the need to ensure that patients taking a pharmaceutical product are safeguarded from any short or long term adverse effects that could compromise their well-being. EphMRA supports the pharmaceutical companies need to comply with the policies set out by the authorities to try to ensure that any adverse events are reported to the appropriate manufacturer.*"

Consequently EphMRA considers itself a stakeholder association with regard to the consultation process.

3 November 2011

EphMRA
European Pharmaceutical Market Research Association

Background on market research

> *Market research is the systematic gathering and interpretation of information about individuals or organisations using the statistical and analytical methods and techniques of the applied social sciences to gain insight or support decision making. The identity of respondents will not be revealed to the user of the information without explicit consent and no sales approach will be made to them as a direct result of their having provided information.*
>
> *ICC/ESOMAR International Code 2007*

Typically market research projects are commissioned by pharmaceutical companies to be conducted by independent market research agencies. There are two different types of market research:

1. Ad hoc market research is designed and paid for by just one client company or marketing authorisation holder, the study is exclusive and unique to the commissioning company, who own the resulting data.

2. Syndicated market research is shared – both the findings and the costs - by a number of clients, however the data is owned by the market research agency.

   Syndicated data may or may not include longitudinal data i.e. repeated observations of the same items collected over a period of time, the population remains constant, the sample may or may not be the same.

Within the different types of market research one of two broad approaches can be taken:

- ☐ Qualitative – market research relying on open questions to explore the opinions and value judgements of individuals and from which collective general conclusions can be drawn.
- ☐ Quantitative – measurable data is gathered via closed questions from a representative sample. A profile of the population can be extrapolated from this data.

Each of these two approaches can be carried out using a variety of different mediums – face to face, on the telephone, online, through social media and via observation. Sometimes an interviewer is involved in the process and sometimes the market research is a self-completion exercise carried out independently.

General comments and questions

The issues and questions raised below are specific to the forwarding of adverse reactions from market research studies and reflect current concerns and confusion. EphMRA very much welcomes the opportunity the consultation process offers to clarify the role of market research in the forwarding of adverse reactions.

The role of market research

There is no specific mention of market research as a source of adverse reactions. Does the new legislation require adverse reaction reporting from market research? If so, does market research fall under the heading a "spontaneous" source from "non-clinical data" or not?

There seem to be very different views with regard to the role of market research within the collection of adverse reactions. This ranges from those who believe that:

- market research conducted by sub-contractors should be excluded, judging it sufficient that market research interviewers advise physicians to report potential adverse reaction to the marketing authorisation holder and patients be advised to report them to their physician

to those who believe that:

- all forms of market research should be included and that patient identifiers are unnecessary.

What is the most appropriate (and proportionate) role for market research to play?

EphMRA is anxious to have clear guidance that takes into account the valuable role that impartial and comprehensive market research can make to drug development.

Limitations of adverse reactions generated from market research sources

Feedback from some drug safety and pharmacovigilance departments to their in-house market research colleagues suggests that adverse reactions reported from market research sources are not good quality and can cloud the true picture so they do not serve the patients' best interests. Two reasons account for this:

1. The available information is vague and poor quality:
   - Market research respondents will not always allow their contact details to be passed back to the marketing authorisation holder for follow up even after repeated requests. EU data protection legislation prohibits the transfer of personal identifiable information without the fully informed consent of the individual concerned. Consequently there may be a conflict between pharmacovigilence and data protection legislation.
   - Some market research is conducted independently (e.g. online self-completion exercises) and the data processed automatically, so there is no opportunity within the process to collect data upon a potential adverse reaction, in these cases follow up is always required.
2. They may be duplicate reports, physicians sometimes report that they have already advised the appropriate party/body.

The value of the adverse reaction data from market research sources does seem to be disproportionately low.

Definition of an adverse reaction

In 2010 the UK Association of the British Pharmaceutical Industry (ABPI) recommended the inclusion of 'expected' lack of efficacy (as well as 'unexpected' lack of efficacy) within the definition of a reportable event. Is this appropriate?

There has been concern expressed amongst marketing authorisation holders that this has led to the reporting of 'noise'. This occurs particularly in therapeutic areas where there are a relatively high proportion of cases of expected ineffective treatments that do not present a safety concern but are unfortunately only a reflection upon the limitations of currently available treatments. In addition the forwarding of cases where tolerance to the medication develops – again expected is being inappropriately captured due to the extension of the definition. Similarly these cases create unnecessary and misleading noise.

Is this definition appropriate?

Definition of a patient

Again in the UK, revised ABPI Guidelines now require the forwarding of adverse reactions that are cited in the context of *any actual patient* or *patients w*hether or not a specific identifier is present. As a result adverse reactions cited in groups of patients and aggregated patient data now also need to be forwarded. Again, there is concern that this is resulting in inappropriate forwarding of adverse events and potentially dilution of signal detection.

Is this definition appropriate?

The inclusion of adverse reactions from syndicated market research data

Syndicated studies generally collate large volumes of quantitative data. There is currently no legal responsibility for the supplier (the market research agency) to forward adverse reactions, as the supplier is not the legal agent of the marketing authorisation holder at the time of data collection. The legal responsibility to collect adverse reactions currently lies with the pharmaceutical company that purchases the syndicated data.

However there is concern that including syndicated data sources increases the volume of poor quality adverse reaction reports such that this dilutes rather than enhances signal detection and is contrary to patients' interests.

Responses to specific consultation items:
(Only those items where EphMRA has comments to offer are referenced.)

Consultation item no. 3: Is it necessary to be more precise on potential delegation, e.g. in the case of co-marketing of products? Please comment.

A. Pharmacovigilance system master file
6. Delegation
The marketing authorisation holder may delegate certain tasks of the pharmacovigilance system to third parties. He nevertheless retains full responsibility for the completeness and accuracy of the pharmacovigilance system master file.

In those cases the pharmacovigilance system master file shall contain a description of the delegated activities and/or service provisions relating to the fulfilment of pharmacovigilance obligation, indicating the parties involved, roles undertaken and concerned product(s) and territory(ies). Copies of the signed agreements shall be included in the master file.

Is it correct to assume that the delegation referred to above is outsourcing or sub-contracting of PV tasks and would not refer to the use of a sub-contractor to carry out market research on behalf of the marketing authorisation holder i.e. a market research agency.

Consultation item no. 7: Do you agree with the requirements for marketing authorisation holders? Please comment.

B. Quality systems for the performance of pharmacovigilance activities – Common obligations
9. Scope
Marketing authorisation holders, the national competent authorities and EMA must establish and follow a quality system adequate and effective for the purpose of performing their pharmacovigilance activities.

10. Audit
Audits of the quality system shall be performed at regular intervals, and not less than every two years, to assure that the quality system is in compliance with the established quality system requirements and to determine its effectiveness.

Does this suggest that marketing authorisation holders will have to audit the adverse reaction reporting processes that their market research agencies have in place?

Consultation item no. 7: Do you agree with the requirements for marketing authorisation holders? Please comment.

C. Quality systems for the performance of pharmacovigilance activities by marketing authorisation holders

13. Resource management

A sufficient number of competent and appropriately qualified and trained personnel shall be available in the operation of pharmacovigilance activities. In that context, it shall be ensured that the qualified person for pharmacovigilance has acquired adequate theoretical and practical knowledge for the performance of pharmacovigilance activities. If the qualified person is not medically qualified, access to a medically qualified person should be available.

The duties of the managerial and supervisory staff, including the qualified person for pharmacovigilance shall be defined in job descriptions. Their hierarchical relationships shall be defined in an organisation chart. In that context, it shall be ensured that the qualified person for pharmacovigilance has sufficient authority to influence the performance of the quality system and the pharmacovigilance activities of the marketing authorisation holder.

All personal involved in the performance of pharmacovigilance activities shall receive initial and continued training. Training plans and records for documenting and maintaining and developing the competences of personal shall be kept and made available for audit or inspection.

Is adverse event report training deemed compulsory for all persons that might be in a position to identify and forward a potential adverse event during the course of a market research study? If so, what are the training requirements? Would centralised and consistent EphMRA sponsored training be sufficient?

Consultation item no. 7: Do you agree with the requirements for marketing authorisation holders? Please comment.

C. Quality systems for the performance of pharmacovigilance activities by marketing authorisation holders

14. Compliance management

. . . . . pharmacovigilance data . . . . referred to in Article 101(1) of Directive 2001/83/EC . . . . . The marketing authorisation holder must follow-up such information independent of its source, including information spontaneously reported by patients or healthcare professionals

Is EphMRA correct in believing that when market research is carried out by a market research agency on behalf of the marketing authorisation holder, the agency to whom the market research has been sub-contracted is obliged to inform the marketing authorisation holder of any potential adverse reactions mentioned or recorded during the course of the market research rather than advising the reporter to forward/report the adverse reaction?

Consultation item no. 7: Do you agree with the requirements for marketing authorisation holders? Please comment.

C. Quality systems for the performance of pharmacovigilance activities by marketing authorisation holders

15. Record management

. . . . . marketing authorisation holders shall establish mechanisms enabling traceability and follow-up of adverse reaction reports while complying with data protection legislation.

Consultation item no. 8: Do you agree with the quality system requirements? Please comment, if appropriate separately as regards requirements for marketing authorisation holders, national authorities and EMA

D. Quality systems for the performance of pharmacovigilance activities by national competent authorities and EMA

18. Compliance management

Specific quality system procedures and processes shall be in place in the national competent authorities and in EMA in order to:

(a) evaluate the quality; including completeness, of pharmacovigilance data submitted

Please could EphMRA have details of what information would constitute a complete adverse event report? It should be noted that adverse reactions when mentioned during a market research exercise do not always allow for collection of additional data, e.g. when the respondent completes a questionnaire made up of multiple choice questions alone online, so follow up would be required.

Consultation item no. 8: Do you agree with the quality system requirements? Please comment, if appropriate separately as regards requirements for marketing authorisation holders, national authorities and EMA

D. Quality systems for the performance of pharmacovigilance activities by national competent authorities and EMA

19. Record management

Pharmacovigilance system-related documents shall be retained as long as the system as described in the pharmacovigilance master file exists and for a further 10 years after it has ceased to exist. Product-related documents shall be retained as long as the marketing authorisation exists and for further at least 30 years after the marketing authorisation has ceased to exist.

It is assumed that the documents referred to above are pharmacovigilance records, is this correct?

Consultation item no. 10: In the Commission's view the aim of this part is to establish common triggers for signal detection; to clarify the respective monitoring roles of marketing authorisation holders, national competent authorities and EMA; and to identify how signals are picked up? Are the proposed provision sufficiently clear and transparent or should they be more detailed? If so, which aspects require additional considerations and what should be required? Please comment

E. Signal detection and risk identification

24. Work sharing of signal management

EMA shall make public a list of active substances and of the lead Member State appointed for their monitoring in Eudravigilance.

25. Signal detection support
EMA shall support the monitoring of the Eudravigilance database by providing access to:
– customised grouping and stratification of data enabling the identification of patient groups with a higher risk of occurrence of adverse reactions or with a risk of a more severe adverse reaction;

Should EphMRA's guidelines to members on signal detection vary from those for forwarding adverse reactions? The British Healthcare Business Intelligence Association (BHBIA) have recently extended the definition of patient from an identifiable patient to any patient or patients on the grounds that this is required for signal detection, is this now the case?

This has resulted in both an increase in adverse reactions forwarded and what appears to be a corresponding increase in unnecessary 'noise'.

Consultation item no. 14: Do you agree with the proposed format and content? Please comment.

Annex I – Electronic submissions of suspected adverse reactions
3. Content of electronic transmission of suspected adverse reactions
4. For the purpose of electronic reporting of suspected adverse reactions, Member States and marketing authorisation holders shall provide all available information on each individual case, in particular:
The information below has been summarised.

(a) Administrative information
(b) Literature reference
(c) Study type, name, sponsor study number or study registration number
(d) Primary source(s), which refers to the person(s) who reports the facts
(e) Patient identifiable information
(f) Relevant medical history, concurrent conditions, relevant past history.
(g) Suspect/interacting medicinal product(s).
(h) For biological medicinal product(s), the batch number(s)
(i) Concomitant medicinal products and past-medical drug therapy for patient
(j) Suspected adverse reaction(s): start date and end date and/or duration, seriousness, outcome of the suspected adverse reaction(s) at the time of last observation, time intervals between suspect medicinal product administration and start of adverse reaction and the original reporter's words and/or short phrases used to describe the reaction(s).
(k) Results of tests and procedures relevant to the investigation of patient.
(l) Date and reported cause of death
(m) A case narrative where a serious adverse reaction(s) is/are reported by marketing authorisation holders.
(n) Reason for nullification or amendment for nullification and amendment reports.

Market research exercises do not allow for the collection of the kind of information and detail described above as all interviews (irrespective of type) are booked for specific and limited periods of time and many are completed independently by the respondent (e.g.

online) i.e. there is no one present to collect this information. Collection of the type of content proposed would require follow up after the market research study which as mentioned previously is dependent upon the respondent giving permission for their contact details to be passed on to the marketing authorisation holder.

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