Brussels, 2 November 2011

Signal detection left to pharmaceutical companies: danger!

Answer to the consultation on the "Concept paper on pharmacovigilance implementing measures"[1]

Summary

- The "Concept paper on pharmacovigilance implementing measures" released for consultation is a technical document aimed at implementing the pharmacovigilance legislation adopted on 15 December 2010 (Directive 2010/84/EC and the Regulation (EC) 1235/2010).

- It reveals the consequences of the implementation of the new pharmacovigilance legislation. In practice, the first and critical step in pharmacovigilance, namely the detection of safety signals, is left to pharmaceutical companies, despite their conflict of interest.

- In addition, the proposition to rely on sophisticated technologies to detect signals and monitor data shows a deep misunderstanding on how pharmacovigilance works in practice.
For example:
- the proposed use of internationally agreed terminology can strip the spontaneous reports from all clinical meaning;
- the use of statistics and a quantitative approach to detect and assess pharmacovigilance signals is often useless if not counterproductive. Few significant clinical cases very often suffice to make a relevant signal if they are reported to experienced and independent teams.

- As independent scientists and representatives of civil society, we take the opportunity of this consultation to urge the European Agency and National Competent Authorities not to rely too much on technical illusions such as "data mining" and "statistically significant signal detection". Caution is especially required since pharmaceutical companies are expected to monitor to a large extent their own products.

- Transparency of decision making, including in the early "validation" stage of a suspected adverse drug reaction, is key to avoid missing safety assessment opportunities.

[1]- European Commission Health and Consumers Directorate General "Implementing measures in order to harmonise the performance of the pharmacovigilance activities provided for in Directive 2001/83/EC and Regulation (EC) N° 726/2004" Brussels, Concept paper submitted for public consultation 08/09/2011
(Deadline for Public Consultation: 7 November 2011; sanco-pharmaceuticals@ec.europa.eu ; PCIM/11/01 - Public Consultation on Implementing measures for pharmacovigilance)

- Concrete proposals for improvements include:

- full transparency of the ongoing work on pharmacovigilance among National Competent Authorities and the European Medicines Agency (minutes of ad hoc working groups and of pharmacovigilance committees made available online);
- public access to the full content of the Eudravigilance database in order to allow independent teams to work on the data;
- public access to the periodic safety update reports (PSURs) and to the assessment reports of the PSURs prepared by the Competent Authorities;
- continuous monitoring of the pharmaceutical companies' pharmacovigilance system, through inspections by health authorities, and not only "audits" by colleagues from the same pharmaceutical company even if they work in another department;
- requirement for an annual report of the pharmaceutical company on their pharmacovigilance activities, to be made publicly available on the Competent authorities' website;
- dissuasive penalties in case of non-compliance, withholding of data, or minimisation/misinterpretation of safety data.

- Political willingness to make the doubts benefit the public in the first place will be a decisive factor if pharmacovigilance is to be reinforced in Europe.

Detailed answer to the consultation

We thank the European Medicines Agency for the opportunity to comment on the measures for implementing the new pharmacovigilance legislation.

The "Concept paper on pharmacovigilance implementing measures" released for consultation is a technical document aimed at implementing the Directive 2010/84/EC and the Regulation (EC) 1235/2010. Our answer therefore follows the proposed consultation items. In some cases, we also comment on other critical parts of the document.

One remark is about terminology: we advise replacing "benefit-risk profile" by "benefit-harm profile", which scientific publications and medical journals now prefer.

A. Pharmacovigilance system master file

Consultation item no. 1: Should additional processes and pharmacovigilance tasks be covered?

Processes and pharmacovigilance tasks should mainly be covered by independent Competent Authorities, not by the marketing authorisation holder (read our general comment on point E. "Signal detection and risk identification").

In addition to regular periodic safety update reports (PSURs), the pharmacovigilance master file should include:

- in point (6) *"(f) (New) A description of the process for communicating without delay safety concerns to competent authorities in case of a death or of an hospitalisation suspected to be linked to the use of their product*".
  Such an early process for signalling serious adverse drug reactions is needed in order to avoid important new safety information is delayed by waiting for the next PSUR.
- in point (7) "*(f) (New) An annual report on the pharmacovigilance activities carried out by the pharmaceutical company notably including:*
  -- for each product: number of reports received for each type of adverse drug reactions, among them the number of reports further investigated and the number of reports not further investigated with the reason for not having investigated them, the actions taken and their rationale;

-- significant changes/modifications to the master file;

-- the number and dates of the audits performed, and a summary of their results;

-- the results of the performance indicators used to continuously monitor the good performance of pharmacovigilance activities.

This annual report is transmitted to Competent Authorities and made publicly available on the Competent Authorities' website" (read below).

Without prejudice to the production of PSURs, such a yearly report would not only ensure that the staff is dedicated to pharmacovigilance activities, but also that this staff has adequate means to carry out its tasks.

Consultation item no. 2: The aim of the pharmacovigilance master file is two-fold: to concentrate information in one global document and to facilitate maintenance by uncoupling it from the marketing authorisation. Therefore changes to the content of the master file will be no longer subject to variation obligations. Would it be nevertheless appropriate to require the marketing authorisation holder to notify significant changes/modifications to the master file to the competent authorities in order to facilitate supervision tasks?

Yes, to facilitate supervision it is indispensable to require marketing authorisation holders to notify significant changes/modifications in the master file to the competent authorities.

If so, how should this be done?

Such changes/modifications should be included, together with the rationale for these changes/modifications, in an annual report on the pharmacovigilance activities of pharmaceutical companies (see our answer to item no.1 above).

Variations are made publicly available in the form of steps taken on the European Medicines Agency's website, which is very useful to track evolutions and their rationales. We therefore require the annual report on the pharmacovigilance activities of pharmaceutical companies to be made publicly available as well. The wish to make the maintenance of pharmacovigilance master files easier should not result in less transparency of pharmacovigilance activities.

Should the master file contain a date when it was last reviewed?

The master file should of course contain the date when it was last reviewed: this is a basic practice in quality management.

Moreover, "*any deviation from pharmacovigilance procedures, together with their impact and management, should be noted*" and retained in the master file even if the issue is resolved.

The results and achievements of the staff charged with pharmacovigilance will then be transparent.

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.

Delegations are difficult to monitor. A precise framework and clear apportionment of roles and responsibilities are required.

Consultation item no. 4: Should a copy of the audit report be retained in the master file? Would it be appropriate to require documentation of audit schedules?

A copy of the audit report should of course be retained in the master file to document the outcomes and progress made. It is also appropriate to require documentation of audit schedules in order to monitor their proper implementation.

Moreover, audit results should be included in the annual report on pharmacovigilance activities transmitted to Competent Authorities in order to detect repeated failures that should prompt an inspection (for more details on this proposal for an annual report on pharmacovigilance activities, read our answer to item no. 1).

Consultation item no. 5: Overall, do you agree with the requirements as regards the content and maintenance of the pharmacovigilance master file? Please comment.

We do not agree. The pharmacovigilance master file is based on declarations made by pharmaceutical companies on their functioning. The arrangement whereby a "*summary of the applicant's pharmacovigilance system"* is submitted in support of a marketing authorisation application, rather than a "*detailed description"* of how their pharmacovigilance is organised, has been proposed in order

to reduce the workload of pharmaceutical companies, but to the detriment of patients' interests. Although 'pharmacovigilance system master files' could be examined during an inspection, many of them won't be inspected routinely because many Member States are short of inspectors.
Given the obvious conflict of interest of pharmaceutical companies when it comes to pharmacoviglance, the pharmacovigilance master file should be complemented by annual reports on pharmacoviglance activities (for more details on this proposal for an annual report on pharmacovigilance activities, see our answer to item no. 1) and by inspections and dissuasive sanctions in case of non-compliance.

Additional remark on performance indicators:
Systematic monitoring of pharmacovigilance activities is crucial. Performance indicators to be designed by the European Medicines Agency should be subject to a public consultation, we therefore propose to change the wording as follows: "EMA ***shall*** ~~may~~ publish a list of performance indicators after the consultation of the Pharmacovigilance Risk Assessment Committee ***and of the public***".

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

Consultation item no. 6: Is there a need for additional quality procedures, e.g. in relation to study reporting in accordance with Article 107p of the Directive, in relation to communication on pharmacovigilance between the marketing authorisation holder and patients/health professionals; in relation to processes for taking corrective and improvement actions or in relation to the detection of duplicates of suspected adverse reaction reports in the Eudravigilance database?
There is a need for the following additional quality procedures:
- in point (a), add "*including the monitoring of all literature sources on their products which are not on the list of publications monitored by the Agency or the national Competent Authorities*";
- in point (c), add "*on corrective and improvement actions*";
- add as a point (f): "*produce a final study report in accordance with Article 107p of Directive within 12 months of the end of data collection and submit the study results to the national Competent Authority or the Pharmacovigilance Risk Assessment Committee*;
- add as a point (g): "*submit communication on pharmacovigilance targeting patients/health professionals for prior approval to the national competent authority or the Pharmacovigilance Risk Assessment Committee*" in order to comply with article 106 a of the Directive[2] and article 88 of Directive 2001/83/EC (prohibition of direct-to-consumer advertising).

There is no need to detect the very few duplicates of suspected adverse reaction reports that could be registered in the Eudravigilance database [only if a health professional reports a suspected adverse reaction to the health authorities and to the marketing authorisation holder] because suspected adverse reactions are very much under-reported[3].

Consultation item no. 7: Do you agree with the requirements for marketing authorisation holders? Please comment.
We do not agree with the central role being granted to marketing authorisation holders (read below our General comment to point "E. Signal detection and risk identification"). However, we agree with the minimal requirements for marketing authorisation holders if they are supplemented by our proposals (see answer to Consultation item no. 1 and no. 6), by regular inspections and by dissuasive sanctions.

[2]- "*The marketing authorisation holder shall ensure that information to the public is presented objectively and is not misleading.*"
[3]- Lucian L. Leape "Reporting of Adverse Events" *NEJM* 2002; 347 (20): 1633-1638.

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

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

The quality system for national authorities and EMA should be more precise, in point "18. Compliance management", stating that "*inspections should be carried out without delay in case of doubt about a dysfunction and at least once every 5 years on each pharmacovigilance master file*".

The quality system for national authorities and EMA should include 3 more requirements:

- (f) "*make publicly accessible without delay the detailed agenda and video records of its meetings, accompanied by decisions taken, details of votes and explanations of votes, including minority opinions*" (in accordance with article 126b of the Directive 2001/83/EC);
- (g) "*proactively carry out pharmaco-epidemiological studies to investigate safety concerns*", which complements very effectively spontaneous reports[4];
- (h) "*provide health professionals and patients who reported a suspected adverse drug reaction with information on the outcome of their reports*"[5]. This is essential for encouraging spontaneous reports.

In point "19. Record management", second para, the word "*confidentiality*" must be deleted from the statement "*measure should be taken to ensure data security ~~and confidentiality~~*". It is not compliant with the legal pharmaceutical framework which allows public access to individual reports upon request (*Article 107* bis of Directive 2010/84/EC).

Moreover, pharmacovigilance data are scientific data of public interest, and are therefore to be excluded from the definition of "commercially confidential data" according to Regulation (EC) N°1049/2001 and in line with the repeated decisions of the European Ombudsman asking the EMA to release such information when requested[6].

E. Signal detection and risk identification

General comment:

Pharmacovigilance should mainly be covered by independent competent authorities, not by the marketing authorisation holder.

In fact, many recent examples show that pharmaceutical companies often withhold data or delay their disclosure, so as to delay decisions that would adversely affect sales[7].

---

[4]- In recent years however, a number of serious adverse reactions corresponding to common diseases have been identified, but only after a long delay (breast cancer with hormone replacement therapy, cardiovascular effects with cyclooxygenase-2 inhibitors (anti-inflammatory drugs), bone fracture with proton pump inhibitors (anti-ulcer medication), etc.).
Because these adverse effects correspond to common diseases, they are seldom reported spontaneously, and were often discovered through observational studies or during clinical trials. Proactive pharmacovigilance is needed as a complement to the spontaneous reporting system: the drug regulatory agencies are responsible for analysing clinical trials (meta-analyses) in order to identify and quantify the risks associated with the use of medicines, and for proactively organising observational studies. In France, in 2010, such a study was very effective to show the link between consumption of *benfluorex* (Mediator°) and adverse drug reactions (Weill A et coll. "Benfluorex and valvular heart disease: a cohort study of a million people with diabetes mellitus" *Pharmacoepidemiology and drug safety* 2010; 9999: 1–7.).

[5]- For example: How many reports of the same adverse drug reaction with that medicine have they already recorded? Will further actions be undertaken? etc.

[6]- The US Food and Drug Administration (FDA) already provides this type of information through quarterly data extracts from its Adverse Event Reporting System (AERS) database, as does the national pharmacovigilance centre of the Netherlands.

[7]- For example, in 2000, data from the Vigor trial revealed an increased rate of infarction in patients taking *rofecoxib*. Merck then put forward the hypothesis that the comparator drug used in this trial had a beneficial cardiovascular effect. Between the first results and market withdrawal of the drug, 4 years elapsed and tens of thousands of cardiovascular events occurred that were attributable to *rofecoxib* (Vioxx°), a considerable number of which being fatal. In another example from 2007, Lilly gave tens of thousands of dollars in compensation to each of the 28 000 US plaintiffs who accused it of not having informed them honestly of the adverse effects of the neuroleptic *olanzapine* (Zyprexa°), which can cause diabetes and significant metabolic disorders, a fact which was known to the company. In a further example pharmacovigilance data on *paroxetine* (Deroxat°/Seroxat°) in children was shown to have been withheld (increased suicide risk).

The collection of adverse event reports is a critical step in enabling subsequent analysis and reliable interpretation of the data. The Member States' national and regional pharmacovigilance centres rely on the expertise of teams specialised in pharmacology and on their proximity to the population. This proximity, in terms of language and knowledge of local lifestyle, enables easy contact with reporters, usually by telephone. Specialised teams can therefore obtain any additional information that might be required to analyse the data properly.

Consultation item no. 9: For efficiency reasons a 'work sharing' procedure could be appropriate for the monitoring of medicinal products or active substances contained in several medicinal product. However, do you see a risk in cumulating all tasks (for the authorisation, PSUR scrutiny and Eudravigilance monitoring) in one Member State, as thereby the benefits of parallel monitoring may be lost ("peer review" system)?

We do see an important risk in cumulating all tasks (for the authorisation, PSUR scrutiny and Eudravigilance monitoring) in one Member State.

The European Medicines Agency and many National Drug Agencies are funded almost exclusively by pharmaceutical companies, through the fees the companies pay, which creates a financial conflict of interest that prevent them from making the doubts benefit the public in the first place.

Additionally, the committees responsible for the authorisations (CHMP, CMDh and Licensing Committees of the National Drug Agencies) have an intrinsic conflict of interest: having licensed the implicated medicine in the first place, they find it difficult to raise doubts about their original decision, as experience has shown[8].

Work sharing can make sense if the Member State for the assessment of periodic safety report is chosen to be acting as a reference Member State.

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.

We are very worried about the proposal for respective monitoring roles of marketing authorisation holders, national competent authorities and EMA.

In practice, the expected scenario is the following:

- marketing authorisation holders' role would be to decide if a signal seems relevant or not;
- then the competent authorities would have to use "a common methodology" to "determine the evidence contained in a signal" and "validate" the need for further analysis.

With this distribution of tasks, the detection of a safety problem relies largely on the marketing authorisation holder, but its interests is to withhold data or to delay their disclosure, so as to delay decisions that would adversely affect sales. The risk is that a signal will be played down from the start, and that relevant signals will get lost.

Moreover, no timeline is specified: there is a risk that signals could be transmitted late. To avoid such withholding of data, safety concerns should be transmitted without delay to competent authorities whenever a death or a hospitalisation is suspected to be linked to a product, with dissuasive sanctions in case of non-compliance.

---

[8]- Examples include:

- the case of *nimesulide:* after several months of prevarication, the CHMP confirmed the hepatic risks of *nimesulide* (Nexen°), but it contented itself with half-measures, notably limiting the treatment duration to 15 days, leaving European patients exposed to a risk of death that was unjustified, given the large number of existing anti-inflammatory drugs with similar efficacy but which are less dangerous;
- the case of *rimonabant* (Acomplia°): *rimonabant* (Acomplia°) was withdrawn from the European market in October 2008, only 2 years after being granted marketing authorisation in obesity, due to an unfavourable harm-benefit balance (increased suicide risk). The US drug regulatory agency (FDA) on the other hand refused to approve *rimonabant* due to inadequate data on its harms;
- the arbitration procedure on the combination *paracetamol* + *dextropropoxyphene* (Di-antalvic°): this arbitration went on for a year and a half before the drug was finally withdrawn from the market in June 2009 due to its unfavourable harm-benefit balance.

On how signals are picked up, we would like to warn that the use of statistics and quantitative approaches to detect and assess pharmacovigilance signals is often useless if not counterproductive. A series of significant clinical cases are very often sufficient to identify a relevant signal if they are reported to experienced and independent teams.

The collection of adverse events reports is a critical step in enabling subsequent analysis and reliable interpretation of the data. The Member States' national and regional pharmacovigilance centres rely on the expertise of teams specialised in pharmacology and on their proximity to the population. This public expertise should be developed.

Public access to Eudravigilance content (anonymised raw data as well as aggregated data) should be granted so independent team of researchers can analyse the data.

Spontaneous reports should also be complemented by studies using the linkage between social insurance data and hospitalisation data[9].

F. Use of terminology

Use of internationally agreed methodology

Consultation item no. 11: Do you agree with the proposed terminology? Please comment.

We do not agree with the proposed terminology.

Imposing International Conference on Harmonisation (ICH) standards on the data entered into the Eudravigilance database risks stripping them of all clinical significance.

The ICH is an entity composed of representatives of pharmaceutical companies and selected drug regulatory agencies which guide drug policy.

The MedDRA° dictionary (Medical Dictionary for Regulatory Activities Terminology) is supposed to standardise adverse effect reporting. In practice, it requires encoding adverse effects by "symptom" using the "lowest level term", at the risk of making it clinically meaningless. This risk is particularly high since the "symptom" must be linked to one or more "categories" (system organ class, SOC): the data from one patient is therefore spread across several "categories" making the evaluation of cases difficult. Furthermore, some adverse effects could "disappear" if they are linked to the wrong categories. For example, if the symptom "weight gain of 20 kg" is encoded in the "investigations" category, where nobody would think of looking for it, this adverse effect can be concealed.

Use of internationally agreed formats and standards

Consultation item no. 12: Do you agree with the list of internationally agreed formats and standards? Please comment.

See above, the answer to item no. 11.

To be able to investigate medication errors, we require the addition of the investigation criteria for medication error that was proposed in the European Council report (Council of Europe Expert Group on Safe Medication Practices "Creation of a better medication safety culture in Europe: Building up safe medication practices" Internet version accessed 9 September 2009: 275 pages. http://www.edqm.eu/medias/fichiers/Report_2006.pdf).

G. Transmission and Submission requirements

Consultation item no. 13: Is there additionally a need for transitional provisions as regards certain aspects of this implementing measure, especially in relation to the specifications on format and content? Please comment.

No comment

[9]- Following a series of well documented clinical cases, the French Drug Regulatory Agency requested the Social Insurance System to complete a study linking its database with the hospitalisation database in order to quantify a possible increase in the risk of valvular heart disease in diabetic patients treated with benfluorex (Mediator°) in France, Weill A. et coll. "Benfluorex and valvular heart disease: a cohort study of a million people with diabetes mellitus" *Pharmacoepidemiology and Drug Safety* 2010; **19**: 1256-1262).

Annexes

The four Annexes (Annex I – Electronic submissions of suspected adverse reactions ; Annex II – Risk management plans ; Annex III – Electronic periodic safety update reports ; Annex IV – Protocols, abstracts and final study reports for the post-authorisation safety studies) seem complete.

In order to improve transparency of pharmacovigilance data, detailed risk management plans (not only part IV), periodic safety update reports and assessment reports of these PSURs by competent authorities, protocols, abstracts and final study reports for the post-authorisation safety studies should be made publicly available according to Regulation (EC) No 1049/2001.
Adverse effects are suffered by patients. Their reports are public scientific data, not commercial data to be collected by pharmaceutical companies as part of their marketing services. Full transparency of pharmacovigilance data makes it possible to prevent the recurrence of adverse drug reactions and enable authorities to take appropriate decisions.

The International Society of Drug Bulletins

ISDB. International Society of Drug Bulletins (ISDB), founded in 1986, is a world wide Network of bulletins and journals on drugs and therapeutics that are financially and intellectually independent of pharmaceutical industry. Currently, ISDB has 79 members in 40 countries around the world. More info: www.isdbweb.org. Contact: press@isdbweb.org.