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07 November 2011

By email: sanco-pharmaceuticals@ec.europa.eu

Directorate-General for Health and Consumers
Unit SANCO/D/3
BE-1049
Brussels
Belgium

Dear Sirs,

Re: PCIM/11/01 – Public Consultation on Implementing Measures for Pharmacovigilance

Aptalis Pharma would like to submit their response to the concept paper submitted for public consultation on the '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)'.

Aptalis Pharma is a recently formed pharmaceutical organisation from the merger of two entities (Axcan Pharma and Eurand) holding a number of marketing authorisations in the EEA. Aptalis Pharma does not meet the definition of a SME. Aptalis does agree to the publication of their comments, together with their details on the public health website.

A. Pharmacovigilance System Master File (PVSMF)

> (6) A description of the process, data handling and records for the fulfilment of pharmacovigilance in the following aspects:
> (e) Process for communicating safety concerns and safety variations to the summary of product characteristics and package leaflet to patients and health professionals.

Aptalis Pharma request additional information is provided in subsequent guidance documents or templates on the level and type of information expected to be provided in the PVSMF when describing processes for communication of safety concerns and safety variations.

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

Aptalis Pharma does not believe there are any additional processes that require description.

(7) A description of the quality system for the performance of pharmacovigilance activities including:
(b) A description of the resource management for the performance of pharmacovigilance

Aptalis Pharma request additional information on the new concept of resource management is provided in subsequent guidance documents or templates, including development of standardized measures of adequate resources.

4. Maintenance
The information in the pharmacovigilance system master file should be succinct, accurate and reflect the current system in place. It shall be continuously kept up to date and, where necessary, shall be revised to take account of experience gained, technical and scientific progress and amendments in the legislative requirements.

Aptalis Pharma request subsequent guidance documents and templates provide an expectation of the frequency of updates to the PVSMF. Aptalis Pharma also requests clarification of the nature of 'experience gained, technical and scientific progress', as the context of these triggers for updates to the PVSMF is ambiguous.

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? If so, how should this be done? Should the master file contain a date when it was last reviewed?

Aptalis Pharma suggests a definition of significant changes is formalized, should this become a trigger for submission of updates to competent authorities. Aptalis Pharma agrees the PVSMF should contain a date of last review.

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6. Delegation
Copies of the signed agreements shall be included in the master file.

Aptalis Pharma believes maintaining a duplicate copy of each agreement in the PVSMF is a significant resource issue with potential for incorrect versions to be provided and a new process for reconciliation with legal departments required. Aptalis Pharma strongly opposes this requirement and recommends providing a description of the location of the agreements only within the PVSMF.

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.

Aptalis Pharma believes additional clarification should be provided, e.g. confirmation of whether agreements with clinical trial CROs should be included, or whether agreements where Aptalis is not the marketing authorisation holder or the manufacturer should be included.

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?

Aptalis Pharma strongly opposes the inclusion of audit reports and findings in the PVSMF. Aptalis Pharma believes the section in the proposed PVSMF requiring inclusion of audit findings will significantly reduce the effectiveness of internal audit programmes as there is likely to be reluctance to be candid. Currently audit reports can be explicit in the knowledge they are internal confidential documents, and a softening of approach and language will be an inevitable consequence of making the findings and/or reports available to agencies.

Aptalis Pharma recommends developing audit standards if this requirement is implemented, as industry standards vary widely, e.g. CAPA may only be required for critical findings in some organisations.

Finally, Aptalis Pharma would like clarification on whether agency inspectors can request previous versions of PVSMF. If inspectors can request these, then removing findings from PVSMF becomes a redundant activity.

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

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Aptalis Pharma objects to the inclusion of audit findings, CAPA status and audit reports in the PVSMF. Aptalis Pharma would like development of standards and procedures for compliance measurement to assist with the audit section of the PVSMF.

B. Quality Systems for the Performance of Pharmacovigilance Activities – Common Obligations

> *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.

Aptalis Pharma would appreciate clarification of whether the two year audit is expected to be a complete audit of the entire pharmacovigilance system, or a targeted audit of individual components of the pharmacovigilance system determined on a risk-based approach.

> *10. Audit*
> A report of the results of each quality audit, and reaudit(s) where taken, shall be made and such reports shall be reviewed by management having responsibility for the matters audited.

Aptalis Pharma would appreciate clarification of the level of management expected to review audit reports, i.e., those who directly manage the function only or higher level managers who have accountability, e.g. Vice-Presidents, Chief Executive Officers, etc.

> *11. Performance indicators*
> Where indicators are used to continuously monitor the good performance of pharmacovigilance activities, those indicators and their results shall be documented. For marketing authorisation holders this shall be done in an annex to the pharmacovigilance system master file.

Aptalis Pharma requests clarification the performance indicator results themselves are required to be included in the PVSMF. Aptalis believes a description of the process alone is more appropriate and is concerned about the resource to duplicate results in the PVSMF and to develop reconciliation processes with the main compliance documentation.

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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.

Aptalis Pharma would appreciate guidance on methods to assess if a sufficient number of personnel are available. Is monitoring typical performance indicators adequate or are additional activities required?

> *13. Resource management*
> 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.

Aptalis Pharma requests clarification of how to measure the knowledge of the Qualified Person for Pharmacovigilance, and if a minimum number of years of experience and specific types of experience is required.

> *13. Resource management*
> The resource management shall be documented in the pharmacovigilance system master file.

Aptalis Pharma requests subsequent guidance and template documents provide a framework for documentation of the new concept of resource management. This is an area that is not clearly defined and is subjective, so a framework for measurement and documentation of this area will ensure a consistent approach across the industry that is in line with agency expectations.

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?

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In general, Aptalis supports the addition of quality procedures as described. With regards to detection of duplicates in EudraVigilance, Aptalis believes this should be an Agency activity rather than a marketing authorisation holder activity, in light of the Agency's enhanced access to and knowledge of EudraVigilance.

15. 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.

Aptalis Pharma would be interested in the source of these recommendations given their difference to other ICH regions. Aptalis Pharma is concerned about the ability to comply with these recommendations when products and/or organisations go through acquisition procedures. Aptalis Pharma recommends document retention requirements are aligned with other ICH regions to facilitate the operations of international organisations having to comply with multiple requirements.

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

Aptalis Pharma notes a number of increased requirements for pharmacovigilance quality systems that will require additional resource to execute. Aptalis Pharma requests clarification on whether industry is expected to have staff dedicated to pharmacovigilance quality systems. In addition, Aptalis Pharma would appreciate clarification of whether staff focussed on quality systems can be members of the pharmacovigilance department, or whether this would be discouraged as not being sufficiently independent of pharmacovigilance operations.

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E. Signal Detection and Risk Identification

22. Methodology
The Pharmacovigilance Risk Assessment Committee shall perform a regular review of the methodology to be used and publish recommendations, if appropriate.

Aptalis Pharma supports clarification of what methodology should be used and how frequently. Aptalis Pharma requests that any guidance is sufficiently flexible to take into account differing technology and personnel resource available to the industry and differing volumes of activity.

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)? Additionally, it may be envisaged to extend 'work sharing' to all medicinal products (including all centrally approved products) and to appoint a lead Member State in addition to EMA (Article 28a(1)(c) of Regulation (EC) No 726/2004). Please comment.

Aptalis Pharma acknowledges the possibility of bias being introduced to the safety monitoring performed by agencies, and questions whether a conflict of interest could be created by one agency conducting all tasks, e.g., generation of regulatory fees through requesting excessive safety variations.

26. Signal detection audit
The national competent authorities and EMA shall keep an audit trail of their signal detection activities in Eudravigilance and of the relevant queries and their outcomes. The audit trail shall allow traceability of how signals have been detected and how validated signals have been investigated.

Aptalis Pharma would support marketing authorisation holder's access to these audit trails and visibility of agency activities in general.

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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.

Aptalis Pharma believes publication of guidance on signal detection by the Pharmacovigilance Risk Assessment Committee is a high priority item that will greatly assist the industry in standardizing its approach to this activity. Solutions for smaller organisations with minimal technological ability will be of particular importance.

F. Use of Terminology

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

Aptalis Pharma agrees with the proposed terminology.

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

Aptalis Pharma agrees with the formats and standards.

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.

Aptalis Pharma would strongly support a transitional period for implementation of the revised requirements for ICSR expedited submissions, risk management plans (RMP) and periodic safety update reports (PSURs), particularly for products with current marketing authorisations. Aptalis Pharma requests clear, unambiguous templates for PSURs and RMP, and a transitional timeframe to convert existing PSUR & RMP to the new format following the release of the templates.

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Aptalis Pharma requests clarification of the different objectives of the PSUR and RMP, due to the increasing duplication of information in the revised formats of these documents, creating multiple redundancies within each document.

Aptalis Pharma has the following additional comments on the Annexes describing the following:

PSURs

3. PSURs shall provide an accurate estimation of the population exposed to the medicinal product including all data relating to the volume of sales and volume of prescriptions. This accurate estimation of exposure will be accompanied by a qualitative and quantitative analysis of actual use including how it may differ from indicated use based on all data available to the Marketing Authorisation Holder including the results of observational or drug utilisation studies.

Aptalis Pharma requests clarification on the methodology to be used to obtain qualitative and quantitative analysis of actual use, given that few products have observational or drug utilization studies. Is there an expectation that other databases should also be used, e.g. claims databases? Is it acceptable to not provide any database information for older products that have no parallel activities likely to generate this type of data?

5. Estimated Exposure 5.1. Cumulative Subject Exposure in Clinical Trials 5.2. Cumulative and Interval Patient Exposure from Marketing Experience

Aptalis Pharma would like clarification if clinical trial exposure data should be included if no studies are ongoing during the period of the PSUR and/or have not been conducted for several years.

6. Data in Summary Tabulations 6.1. Reference Information 6.2. Cumulative Summary Tabulations of Serious Adverse Events from Clinical Trials 6.3. Cumulative and Interval Summary Tabulations from Spontaneous Data Sources

Aptalis Pharma requests that subsequent guidance and template documentation clarifies if data from clinical trials should be included even if no clinical trials have taken place during the

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period of the PSUR. It should also be clarified if both serious and non-serious information should be provided in cumulative summary tabulations, for both clinical trial and spontaneous sources.

17. Benefit Evaluation 17.1. Important Efficacy and Effectiveness Information 17.2. Newly Identified information on Efficacy and Effectiveness

Aptalis Pharma requests that guidance is given as to the nature and structure of efficacy and effectiveness information that should be provided, with an explanation of expectations for this new section.

Aptalis Pharma also requests the possibility of implementing a step-wise risk-based approach to these changes as opposed to a wholesale approach for July 2012.

Do not hesitate to contact Aptalis Pharma if clarification on any comment is required.

Yours sincerely

Miranda Dollen BSc (Hons)
EEA Qualified Person for Pharmacovigilance
OptumInsight, on behalf of Aptalis Pharma

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