French position concerning the reform of the European pharmacovigilance system

I. General comments:

The amendments to Directive 2001/83/EC and Regulation No 726/2004 proposed by the European Commission lie within the framework of the efforts to improve safe use of medicinal products and focus, in general, on increased coherence and harmonisation within the pharmacovigilance system.

Nevertheless, the role played by each actor of the pharmacovigilance system should be clarified in order to avoid complicating access to data and reaction from the aforementioned actors. Thus, pharmacovigilance should continue to rely on dynamic cooperation between Community institutions and national authorities, including national agencies whose natural mission consists in animation, expertise and decision-making.

The latter must therefore maintain easy and rapid access to important safety information as well as a capacity to instruct and react sufficiently, in order to continue playing their fundamental role of close interlocutor and to undertake their responsibilities vis-à-vis any external actors and public opinion.

II. Comments concerning the proposals to modify the texts:

- **Article 1 (11/, 13/ and 16/) of Directive 2001/83/EC**:

The definition of "adverse reaction proposed by the European Commission ("a response to a medicinal product which is noxious and unintended") and the deletion of the definition of "unexpected adverse reaction" tend to widen the field of adverse effects. Thus, any noxious and unintended response associated with a product used without respecting the normal dosage and also in cases of abuse could be considered as an "adverse reaction", given that deletion of the definition of abuse is proposed.

Such a widening of the pharmacovigilance target could entail difficulties in the use of the system. Therefore, the French Authorities are not in favour of the aforementioned changes to the definition. It is essential to keep the definitions currently in force, which form a common basis for all Member States. On the other hand, it would be worth adding a definition for the term medicinal product error and also for misuse. In fact, in order for such type of information to be exploitable at European level, it is essential that all definitions be common to all Member States.

It should also be noted that the term "unexpected" is used in article 101a, where it is indicated that "the Member States may impose specific requirements on doctors and other healthcare professionals in respect of the reporting of suspected serious or unexpected adverse reactions". Therefore, the reference to "unexpected adverse reactions" is not consistent with the deletion of its definition mentioned above. In addition, the Commission does not propose a definition for the term "serious", which would be useful to specify.

- **Article 1 (14) of Directive 2001/83/EC**:

Reference to article 104, in the definition of periodic safety update reports, would have to be modified.

- **Article 1 (15) of Directive 2001/83/EC**:

The Commission is proposing to widen the definition of post-autorisation safety study by replacing "a pharmacoepidemiological study or a clinical trial carried out in accordance with the terms of the marketing authorisation, conducted with the aim of identifying or quantifying a safety hazard relating to an authorised medicinal product" by "a pharmacoepidemiological study or a clinical trial with an authorised medicinal product, conducted with the aim of identifying, characterising or quantifying a safety hazard or confirming the safety profile of the medicinal product." This proposal, in particular, is acceptable because it is better suited to the conditions of post MA, which by definition are not limited to those complying with the terms of the MA.

- **Article 1 (33) of Directive 2001/83/EC**:

The French Authorities are proposing the addition of a definition for "risk management plan", an expression that is commonly used in the "risk management systems" guideline, in order to differentiate this concept of "risk management system". In general, throughout the text, when reference is made to "risk management", the term "system" is used incorrectly instead of "plan" since reference is made to specific actions for a given product (while a "risk management system" is a combination of "pharmacovigilance system" and "risk management plan"). Therefore, this causes confusion.

- **Article 8 of Directive 2001/83/EC**:

With respect to the "pharmacovigilance system master file" (a file that is specific to the pharmacovigilance system): should the items constituting the object of an application for variaton be those contained in the MA ("summary of the pharmacovigilance system") or should they be the latter plus those included in the "pharmacovigilance system master file"?

In article 8 (3) (ia), the term "a summary" should be replaced by "key elements".

- **Article 11 of Directive 2001/83/EC**:

As far as the summary of the product characteristics (SPC) is concerned, it would be more appropriate to develop a more legible and more pragmatic SPC, adapted to the expectations of health professionals, in addition to the regulatory document foreseen by the MA.

The Commission is proposing to establish a public list of medicinal products under intensive monitoring. The French Authorities are questioning the relevance of publishing such a list. In fact, this initiative could give rise to queries and suspicion from patients and health professionals, vis-à-vis these products. On the other hand, it is essential that the criteria for inclusion in this list be precise and validated by all Member States (cf. comments concerning article 101j).

Finally, the addition of the statement "all suspected adverse reactions should be reported", both to the SPC and the package leaflet of certain medicinal products under intensive monitoring, could give rise to confusion, in the sense that it could imply that this is not the case for other medicinal products. Moreover, this statement is not consistent with the proposals concerning the definition of the adverse reactions to be reported by health professionals, that is, any serious or unexpected adverse reactions, given that the field of the aforementioned statement is larger on the one hand and that, on the other hand, the definition of unexpected adverse reactions has been eliminated. In any case, the recipients of such a notification should be specified or a reference should be foreseen, as is the case in the stipulations of articles 54 (o) and 59 (ba) (name and address of the marketing authorisation holder in the Member State where the marketing authorisation hold er will receive suspected adverse reaction reports).

- **Article 22 of Directive 2001/83/EC**:

The Commission's proposal, which aims to abolish MAs granted under exceptional circumstances is not satisfactory. It could, potentially, apply to any application for a MA provided the applicant undertakes to submit all required pharmacovigilance details. Such MAs, however, should continue to be reserved, under exceptional circumstances, for applicants that are not able to provide complete information on the efficiency and the safety under normal conditions of use. In fact, with respect to the evaluation of the efficiency and the tolerance of a given

medicinal product, the Commission's proposal tends to deal with incomplete MA files in the same way as it does with complete files which, however, require pharmacovigilance monitoring (RMP).

The French Authorities are not in favour of advance issuance of MAs on the basis of a robust pharmacovigilance system only, as the proposal for review tends to suggest. Advance MAs cannot be based on a risk management plan and sustained pharmacovigilance; it should include regular review of the benefit-risk balance. The proposal for review of article 22 should therefore be reconsidered accordingly.

- **Article 23 of Directive 2001/83/EC**:

In the 4th paragraph, the words "including results of clinical trials" should be replaced by "including non-clinical results and results of clinical trials and studies", given that this information is just as important. It would also be useful to add "positive and negative results".

The sentence "Marketing authorization holders should supply annually the updated pharmacovigilance master file to the competent authorities and the Agency" should be added before the last sentence of this article. That would allow for an annual summary statement for the system, which would be a precious tool for deciding on initiating inspections in particular, and also for preparing inspections in advance.

- **Article 26 of Directive 2001/83/EC**:

The Commission is proposing, without any justification, to eliminate "the therapeutic effect of the medicinal product is insufficiently substantiated by the applicant" as a ground for refusing a MA.

The French Authorities are not in favour of this proposal and wish to keep the current phrasing of article 22 in its entirety. In fact, it is important to ensure that the medicinal product does actually have a therapeutic effect and that it is the applicant's responsibility to prove so. Granting MAs without proof of therapeutic effects would discredit the entire authorisation procedure.

- **Articles 31 and 36 of Directive 2001/83/EC**:

The circumstances under which articles 31 and 36 shall be implemented, in relation to the list of criteria defined in article 101k, should be clarified. On the other hand, clarifications are necessary for the "criteria listed in article 101k": do they correspond to those of paragraphs 1 ("A Member State shall notify the other Member States, the Agency an the Commission and shall thereby initiate the procedure of this article where :…") and 2 ("Where urgent action to protect public health is necessary…") of this article or only to those of paragraph 1?

- **Article 59 of Directive 2001/83/EC**:

The Commission is proposing to add a prompt for spontaneous notification in the package leaflet, by stressing, for products subject to intensive monitoring, in particular, the necessity to report adverse reactions to the MA holder.

The establishment of such a reporting mechanism appears to be complicated and it would be preferable for the national authorities to set up websites allowing for reporting by health professionals and patients. Moreover, it would be preferable for patients to report adverse reactions to the national authorities only and not to the holders of MAs. In any case, national authorities at least should be the recipients of all alerts originating from patients.

The Commission should also provide for the establishment of a "Border Black Box" for presenting information on safety data. The French Authorities are more in favour of improving the current package leaflet, a wish expressed in fact by patients' organisations and the patients themselves.

- **Article 101 a:**

-Second subparagraph: the term "unexpected" should be defined.

-Third subparagraph: The proposal provides that through the methods of collecting information and where necessary through the follow up of adverse reaction reports, the Member States shall ensure that any biological medicinal product prescribed and dispensed in their territory which is the subject of an adverse reaction report is identifiable. What does the term "identifiable" mean exactly?

- **Article 101 b:**

The Commission is proposing to widen the field of the Good pharmacovigilance practices.

How will these Good practices be linked to volume 9A? Will this volume disappear?
Furthermore, how will they be linked to the Good practices of national pharmacovigilance systems?

On the other hand, to the extent that their object should be to define the role of each actor involved in the issue, should they not also define the role of health professionals?

It is suggested that, after consulting with the EMEA, Member States and stakeholders, and in compliance with the procedure of article 121(2), the Commission could adopt guidelines for Good pharmacovigilance practices. The French Authorities are proposing the adoption of a wording that is similar to that of article 47 of the Directive, which refers to Good manufacturing practices (GMP) for medicinal products: The principles and guidelines for Good pharmacovigilance practices could be adopted in the form of a Directive, in accordance with the procedure referred to in Article 121(2) (therefore binding for all Member States); then, detailed guidelines in line with these principles would be published by the Commission, taking also into account that the principles, guidelines and detailed guidelines would be derived from the current volume 9A.

In the first subparagraph, the words "quality management system rules" should be added after "including technical rules". If that cannot be added in this Directive, the "quality management system" aspect should be mentioned in the principles of Good pharmacovigilance practices.

For consistency with other draft stipulations, it is suggested that the following be added to the third indent: "the monitoring by the Agency, in collaboration with Member States, of the data in Eudravigilance …".

- **Article 101d:**

-paragraph 2:
It is essential that any signals be evaluated by the Committee on Pharmacovigilance, before informing the holders of MA licenses.

It is important to recall that the establishment of the EudraVigilance network does not reduce the responsibility of national authorities as regards the detection of signals on their territory.

- **Article 101 e:**

On page 7 of the Commission's document submitted for consultation, a distinction is made between the methods of notification used by patients, depending on whether the product in question is subject to intensive monitoring or not. This is not included in the text of this article but it is worth pointing out that it will be difficult to apply in practice.

-paragraph 1:
Direct reporting of adverse reactions by patients is a wish that has been repeatedly expressed by the patients themselves and also by patients' organisations. In fact, this appears to be useful for the detection of signals.

Nevertheless, no matter how patients report any adverse reactions, only cases fulfilling the same requirements as those imposed by reports made by health professionals should be integrated in EudraVigilance, that is, any cases whose evaluation allows to establish a causal relationship based on chronological criteria at least. On the other hand, a system should be established in order to avoid duplication of signal reporting (parallel reporting of signals by a patient and a health professional). Statement of cases by patients should not prejudice any interaction between health professionals and patients, in order to ensure medical confirmation of cases on the one hand, and suitable treatment of any adverse reactions observed in patients on the other.

The wording suggests that patients are able to analyse a causal relationship and consider it to be a reasonable possibility. It should therefore be amended.

On the other hand, the French Authorities are questioning the evaluation methods applied by the EMEA to cases reported directly via the EMEA portal. Finally, it could be envisaged that in such situations each Member State shall be responsible for documenting any cases observed on their territory.

It is important to underline that cases that have not been medically validated could "pollute" EudraVigilance and give rise to false signals. Thus, should one ensure that "patient" data can be integrated in the EudraVigilance data base while keeping its "patient notification" identity, which would allow analysing "patient" data and "health professional" data separately and also better evaluating of the complementarity between these two sources? In this respect, clarification is required.

-paragraph 2:

Since access to EudraVigilance is not functional, it would be desirable for MA holders to report domestic cases both to EudraVigilance and also to Member States. It would be useful to clarify the ways in which the EudraVigilance system functions and also the link with each Member State in particular. A transition period should therefore be defined in the Directive.

It should be reminded that in order to ensure optimum pharmacovigilance and health safety, national authorities should have access to data in real time in order to ensure evaluation thereof.

-paragraph 3:

First subparagraph: it is noted that Member States shall continue to transmit to MA holders any cases brought to their attention. For consistency with the previous paragraph, why no provision is made for MA holders to consult EudraVigilance themselves while guaranteeing, however, that they cannot change the contents (read-only access).

In this respect, it would be useful to provide more clarifications on EudraVigilance access authorisation and especially the data accessibility levels for each authorised body.

Third subparagraph: The methods to be used for reporting and exchanging medicinal product errors (concept to be defined) are not clear. Specifically, should one transmit all medicinal product errors or only those where presentation of the medicinal product is being questioned (which would eliminate medicinal product errors associated with the circulation of medicinal products or any practical problems)? This new provision assumes that new reporting and exchange systems have already been established at national level.

-paragraph 5:

It is stipulated that a literature review, and also registration in the EudraVigilance data base of individual pharmacovigilance cases originating from the literature, be conferred upon the EMEA. The objective of this initiative is to avoid duplications in EudraVigilance. In fact, the majority of articles concern active ingredients and not a given proprietary medicinal product. Nevertheless, this initiative raises a number of questions:

- Will MAHs always have to conduct a literature scan in order to include, in the data used for signal detection purposes, any relevant pharmacovigilance cases or does this new stipulation totally exempt the parties from carrying out this review? It should be noted that until now the review of national literature is conducted by the subsidiaries of MAHs in Member States.

  The first option should be adopted unless market authorisation (MA) holders have access to the results of literature scans conducted by the EMEA and they can include these in the data used for detecting signals themselves. Therefore, this point should be clarified.

- Will the EMEA have the resources that are necessary to conduct a review of publications and ensure translation thereof?

On the other hand, this suggestion assumes high reliability and handling for the EudraVigilance data base, especially so that all MAHs are able to retrieve any pharmacovigilance cases concerning their proprietary medicinal products, which is not the case currently. On the other hand, it risks giving rise to delays in signal detection and therefore any health safety decisions that are necessary for the protection of the population.

Finally, it is desirable that any cases in the literature be integrated in the PSUR by MAHs and that the EMEA ensures control of their completeness.

- **Article 101 f:**

-paragraph 1:
The Commission is proposing that MAHs address PSURs to the EMEA only.
The French Authorities believe that these documents should necessarily also be transmitted to Member States in which the medicinal products have been authorised and which are responsible for supervision. Moreover, what is the relevance of submitting all PSURs (in particular those concerning medicinal products with a purely national MA) to the EMEA?

The French Authorities are also questioning the supervision methods applicable to "old established products". Will a list of such products be drawn-up and if yes, by which body? It should be noted that for these products there will no longer be a five-year update or a PSUR. As a consequence, it will be necessary to ensure that MAHs continue to carry out their pharmacovigilance duties for these products (by setting up an efficient system for signal detection in particular), and that they fulfil the notification requirements for any changes regarding the risk-benefit balance and updating product information, through in-depth and regular pharmacovigilance inspections in particular. That would significantly increase the work load for inspectors, unless other control methods are foreseen. Thus, an alternative solution would be to review the periodicity of PSURs and to return to a 5-year submission cycle for all products.

Also, what is the relevance of mentioning the data to be included in a PSUR, in particular those concerning the volume of sales, given that these requirements have already been detailed in other guidelines (volume 9A, unless it is to be deleted?).

-paragraph 2:
Submission of PSURs in paper format should remain possible.

-paragraph 4a:
According to the Commission's proposals, the Committee on Pharmacovigilance will have to establish the PSUR timeframes for "certain" medicinal products. This proposal should be further clarified.
The medicinal products concerned should also be defined.

-paragraphs 4c, e, f, g:
These provisions are unclear. The PSUR evaluation methods, the choice of rapporteurs, exchange and taking into account of comments, and also final validation require clarification.

- **Article 101 g:**
Amendments to safety study protocols should also be evaluated.

- **Article 101 h:**

To facilitate reading, the article should consist of the following 3 parts:
1- Field of application (current first subparagraph)
2- Underlying PASS principles (current sections a and b)
3- Procedures and deadlines: current sections d to l, to be subdivided into 3 parts (initiation of study, new information, end of study).

With respect to the field of application (part 1):

- Post MA studies carried out by institutions (academic studies) are not included in the field of application. Only studies that are initiated, managed and financed by MAHs are taken into account. However, if a register of these studies is to be created, it would be useful to include studies carried out by institutions.
- The term "financed" should be clarified: does it include studies for which the only thing an MA holder does is provide the product?

Regarding the principles (part 2):

- In addition to points a) and b), some of the principles of article 3 of Directive 2001/20/EC should be reproduced. It should also be noted, as a matter of principle, that the level of information regarding safety, which is sent to the competent authorities, is at least equivalent to that of information provided within the framework of pharmacovigilance.
- Submission of such study protocols to an ethics committee should be mandatory.
- The obligation for prior registration of studies in public registers, if such is the case (clarify however whether registration provided for by article 101 i 1 (h) is prior), and the fact of foreseeing methods for informing/obtaining consent from patients in the protocols should be discussed.

Regarding the procedures and deadlines (part 3):

Initiation of study

- d): the current text provides a possibility for the authorities to refuse studies in two cases only; studies considered promotional or studies considered interventional. The authorities should also be able to refuse studies for other reasons (futility or without scientific interest, major deficiency in the design of the study as regards the achievement of the objective…).
- e): the recommendations of the competent authorities and the Committee on Pharmacovigilance should be transformed into requests for amendments that are binding for the applicant.

New information during the study

- f): substantial amendments (to be defined) should be the object of an implicit authorisation system by the authorities, with a 35-day deadline during which the MAH will not be able to begin the study.
- g) and h): the level of information regarding the reporting of adverse reactions observed during trials should be equivalent to that required for the current use of medicinal products (see principles). This requirement could be recalled in point h) and provisions could be defined for such a reporting with respect to tolerance. As for the final study report at the end of the trial, it would preferable to describe the provisions concerning this report in a separate section (see below).

End of study

- h): a deadline, after the end of the trial, should be set for submission of the final study report.
- j) and k): the term “competent authority” should be added whenever the word “Committee” is mentioned.

- **Article 101 i:**

This article should be reviewed by taking linguistic requirements into account.

Paragraph 1:

- a): add external experts too;
- b) evaluation reports should be published in the form of an “executive summary” in order to facilitate translation;
- c) it is essential that health professionals and patients in the various Member States have access, via the European portal, to the websites of national authorities so that all available information can be obtained in their own language, including recommendations concerning the methods of reporting adverse reactions;
- e) and f): will the list mentioned be updated by the EMEA or by the Member States?
- h) it would be useful to clarify whether it is actually a question of publicising protocols (which would be more than a simple register of studies). If this is the case, it is essential to define at which point in time they will be publicised. The French Authorities are not in favour of publishing protocols prior to the end of studies.

- **Article 101 j:**

The French Authorities are questioning the relevance of drawing up and making **public** a list of products under intensive/special monitoring. This initiative could give rise to queries and suspicion from patients and health professionals, vis-à-vis these products (cf article 11).

- **Article 101 k:**

Besides the comments concerning articles 31 and 36:

- 5th paragraph: add "and Member States / Committee on Pharmacovigilance" after "the Member State shall make available to the Agency".

- 6th, 7th and 8th paragraph: what is the relevance/added value of the public hearings foreseen?

- **Article 101 l:**

-paragraph 1: The full meaning of "monitor the outcome of risk minimization measures" of point d) should be clarified.

In addition, according to point f), the role of the EMEA should be specified as regards communications on safety of drugs registered under the national procedure, the mutual recognition or the decentralised procedure.

-paragraph 2:

Although the French Authorities are not against regular pharmacovigilance audits, the proposed frequency is too close and therefore unworkable from a practical point of view, given that the requirements will be greater and require a host of additional resources.

On the other hand, concerning the concept of "supervisory authority" (cf. proposal for an article 18(3) of Regulation (EC) n°726/2004), foreseen for carrying out inspections of centralised procedures only and designating the Member State in which the qualified person for pharmacovigilance resides:

What about pharmacovigilance inspection for medicinal products subject to a mutual recognition or decentralised procedure, which is the object of arbitration?

It would then be useful to define the role of this "supervisory authority": will the authority have a coordinating role or will it actually get involved in pharmacovigilance inspection for products concerned in all Member States? This last option would be difficult to accept in terms of workload and would lead to inspection duplication given that, in general, companies register products through different types of procedures and could therefore be inspected twice (inspection for products registered through the centralised procedure and inspection for other products) in each Member State.

The following stipulations should be clearly specified: this "supervisory authority" shall coordinate inspections of global pharmacovigilance (location at which the qualified person operates and location in a third country) and the competent authorities in the other Member States shall inspect pharmacovigilance conducted on their territory and shall report their activity and the results of inspection to the EMEA and/or the "supervisory authority" concerned by the products registered through a centralised procedure. In this case, another term should be used to designate this "supervisory authority", for example, "coordinating authority" in order to avoid confusion with the term "supervisory authority" of each Member State mentioned in article 101 l 2 b.

Finally, there is a consistency problem between the 1st and the 2nd paragraph: at point a) of the 1st paragraph, it is indicated that a Member State may delegate their pharmacovigilance tasks to another Member State or to the EMEA; on the contrary, the last subparagraph of the 2nd paragraph states that only a Member State may delegate all pharmacovigilance tasks to another Member State. This should therefore be corrected or further clarified, along with the responsibilities of each party in particular.

-paragraph 3:

Same comments as for paragraph 2, with respect to the proposed frequency of reporting.

- **Article 101 o:**

The link between this provision and Commission Regulation No. 658/2007 of 14 June 2007 should be specified.

- **Article 101 p:**

This article appears to concern the possibility for a health authority to impose a "risk management system" after granting a MA, i.e. at any time during the life of a product. If this is in fact the case, it is important to avoid limiting this possibility to authorised medicinal products after this Directive has entered into force. The first sentence should therefore be drafted as follows: "The competent authority which granted a marketing authorisation may require a marketing authorisation holder to submit a risk management system if there are concerns about the risks affecting the risk-benefit balance of an authorised medicinal product."

- **Article 101 q:**

This is article 121(2) and not article 121(2a).

- **Article 111:**

This article deals with "GMP" and pharmacovigilance inspection at the same time, which makes reading of the article difficult. It would be desirable to amend this article in order to improve the definition of the "Member State concerned" concept within the context of "pharmacovigilance" inspections.

In this sense, the following could be proposed: that the Member State concerned shall be the Member State in which a pharamacovigilance activity is carried out on the one hand, and that the "supervisory authority" mentioned in article 101 l 2 c (the Member State in which the qualified person for pharmacovigilance exercises his/her duties) on the other hand is established for all products or at least for those products registered through the decentralised procedure or the mutual recognition procedure with reference to article 101 l 2 c. This type of organisation would allow for better coordination of the inspection activities between all Member States. This proposal could also be implemented directly in article 101 l 2 c.

- paragraph 8: this paragraph stipulates that the Member State shall send inspection reports to the EMEA systematically and for cases where the "pharmacovigilance master file" and title IX have not been respected, to the other Member States, the Commission and the EMEA. It would also be desirable to send a summary of the findings of inspection to the EMEA on the one hand and to the Member State in which the "supervisory authority" mentioned in article 101 l 2 c is located. Moreover, it would be desirable to rectify the following: the effective, proportionate and dissuasive penalties are mentioned in article 101 o and not article 101 n.

Finally, it would be more justified to require that the qualified person "shall perform their duties in a Member State" rather than "shall reside in a Member State". This comment also applies to articles 101 and 103.

- **Articles 116 and 117:**

The Commission is proposing to amend the grounds for suspension, revocation and amendment of an MA, as well as withdrawal from the market, as follows:

"The competent authorities shall suspend, revoke, withdraw or vary a marketing authorisation if the view is taken that the risk-benefit balance is not positive or that its qualitative and quantitative composition is not as declared" instead of "The competent authorities shall suspend, revoke, withdraw or vary a marketing authorisation if the view is taken that the product is harmful under normal conditions of use, or that it lacks therapeutic efficacy, or that the risk-benefit balance is not positive under the normal conditions of use, or that its qualitative and quantitative composition is not as declared".

There would be no objection to such an amendment, if the lack of therapeutic efficacy systematically gave rise to an unfavourable risk-benefit balance, which remains to be proven. On the other hand, deletion of "under normal conditions of use" from point a) of the proposed article would facilitate supervision of medicinal product use and allow to apply measures that would take any misuse into account.

Finally, the French Authorities are not in favour of adding the following sentence: “The competent authority may limit the prohibition to supply the product to new patients”, on the grounds that is scope is not clear and that its application is not feasible nor controllable.

- **Article 56 of Regulation 726/2004:**

The French Authorities are in favour of setting up a Committee on Pharmacovigilance that will have more transversal responsibilities than those of the pharmacovigilance working party (PhWP). Nevertheless, a number of points require clarification in order to avoid role confusion or reduced efficiency or reactivity, which would prejudice public health:

-the location of this Committee in charge of a number of files, to be subsequently reviewed by the Committee for Medicinal Products for Human Use (CHMP);

-the role of this Committee, within the framework of the implementation of article 101 k in particular;

-interactions with the CHMP and the Co-ordination group for mutual recognition and decentralised procedures (CMDh), for example as regards re-evaluation of the risk-benefit ratio or the choice of rapporteurs.

-the means put at its disposal for carrying out the important new coordination activities in relation to those carried out by the PhWP, in particular, timeframe management for periodic safety update pharmacovigilance reporting (PSURs), management of PSURs and systematic review of post-authorisation safety studies.

Moreover, risk evaluation without considering benefits has its limits. The stress should therefore be placed on possible adverse reactions in cases where recommendations made by the Committee on Pharmacovigilance disagree with the opinion of the CHMP. The contribution of the future Committee on Pharmacovigilance for safety analysis should be reconsidered within the more general framework of risk-benefit ratio analysis which is and should continue to be the responsibility of the CHMP.