The response of the Netherlands on the consultation on Pharmacovigilance

Introduction

The Medicines Evaluation Board and the Ministry of Health, Welfare and Sports supports the proposed revision of the Pharmacovigilance legislation in general. To provide a simpler, rational and flexible regime for the system of pharmacovigilance for human medicines in the EU such is launched in the public consultation of the European Commission (EC) is welcome.
Overall the realization of a formal Pharmacovigilance Committee would be helpful, however our main concern is that the tasks and responsibilities of and the interaction between this Committee and the CHMP are not entirely clear and should be fine tuned. An overlap of the responsibilities of the two committees should be avoided, as well as duplication of discussions.
The principle of having one "problem owner" for each issue, as is already the case with the (co-) rapporteurship for centrally authorised products and the RMSship for MRP/DCP products, should be strictly maintained and followed as much as possible for nationally authorised products.
The proposed simplification of the reporting of adverse drug reactions and the proposed patient reporting are welcomed as well as the proposed legal basis for the existing initiative of Member States for the periodic safety update reports synchronisation and work sharing. Also the strengthened rules regarding the fulfilment of risk management plans by pharmaceutical companies can be supported.
The Netherlands are in favour of introducing the principle of intensive monitoring, however, prefers to have in place for all medicinal products with a new active substance or new route of administration as long as needed from a public health point of view. Regarding the introduction of a new section with key safety information in the product information it is doubtful whether that will stimulate the safe use of medicines, it may even jeopardize patient compliance. Improved ways of communication to healthcare providers and patients would probably more effective.

Comments on the public consultation

The analysis in this report follows the key item heading of the EC proposal. The Dutch proposals for a change in the future legal framework are made clear in *italics*.

1) Committees and decision-making

Art. 16h (1) (d), third subparagraph Directive 2001/83/EC
It is not clear why the reference to Article 57(2) of Regulation (EEC) No 2309/93, which relates to database and patient leaflets, is made. Instead a relevant reference should be made in Regulation (EEC) No 726/2004.
The coordination of the Herbal Medicinal Product Committee (HMPC) and the CHMP could serve as an example for the appropriate coordination by the Agency of activities in relation to the new Pharmacovigilance Committee and the CHMP.

Article 101k(1)a and 101k(2) of chapter 6 relates to suspending a marketing authorisation. Only marketing and use of MRP and DCP products can be suspended according article 36(2) of the Directive, whereas in articles 101k(1)a and 101k(2) the suspension of the marketing authorisation is also introduced for MRP and DCP products. There seems to be a discrepancy.
Article 101k(3) the notifications under paragraph 1 may relate to individual medicinal products, or to groups of medicinal products identified by the substances they contain *and where applicable by the therapeutic indication(s) and the route(s) of administration.*
Article 101k(7) except when urgent action is required for the protection of public health, the Committee on Pharmacovigilance shall hold a public hearing and marketing authorisation holders and the public may participate by registering following the public announcement.
The added value of a public hearing is questioned and it would easily lead to an (administrative) overburden the Pharmacovigilance Committee.

In **article 101k(10)d and in article 101k(12)** a reference to MAH should be added:

- That the Member States *and/or Marketing Authorisation Holders* need to implement risk minimisation actions and the nature of those actions.
- Unless the opinion of paragraph 10 is that no further evaluation or action is required at Community level, the Commission shall adopt a final decision addressed to the Member States *and the Marketing Authorisation Holders* in accordance with the procedure.

In **article 101k(10)f** changes to the product information of the medicinal products concerned which shall specify specific wording and where such wording shall be placed in the summary of the product characteristics *and the package leaflet.*

Regarding the regulation the Netherlands has some additional remarks.
In Article 61(2)a+b of Regulation (EC) No 726/2004 the role of the Pharmacovigilance Committee is filled in e.g. members and alternates that will represent health professionals and patient associations. To create a flexible pragmatic approach (it may be difficult to find qualified candidates) we propose the following text: The Pharmacovigilance Committee *may* additionally include.

In the following article 62(1) it is stated in general that different types of Committees can make use of the scientific advisory groups. However it is unclear if and how the Pharmacovigilance Committee can make use of those scientific advisory groups.

2) Roles and responsibilities and Good Vigilance Practices
Chapter 2 'Good Vigilance Practice'
Art. 101(b) subparagraph 1 of the Directive 2001/83/EC the Netherlands would prefer a stronger wording "Following consultation with the Agency, Member States and interested parties …the Commission *will* (instead of may) adopt guidelines on good pharmacovigilance practice'.
Art. 101b (1) 3rd indent: the monitoring by the Agency *and Member States Competent Authorities* of the data in Eudravigilance for signals of new or changing risks.

Article 101d
For a Centrally Authorised Products (CAP) signal detection in Eudravigilance should be a task for the Agency, for MRP/DCP products it should be a task for the RMS, for purely nationally authorised products it could be in hands of the leading Member State as defined in article 101f-4(e).
In paragraph 2 dealing with Eudravigilance it is stated that the Agency, in collaboration with the Member State Competent Authorities, shall monitor the data in Eudravigilance for signals of risks of medicinal authorised products. In the event of a change being detected, the Agency shall inform the marketing authorisation holder, the Member States and the Commission of these findings.
However the future Pharmacovigilance Committee should be included here, because this Committee will be established based on it's expertise to evaluate such signals of risk.

Chapter 7 "Responsibilities and tasks"
In **Article 101L (1)e** an extra text is proposed:

- As documented in the risk management system assess *through its committees* updates to the risk management system *relating to centrally authorised products* or any data resulting from the measures contained therein.

In addition a new provision should be made in **article 101L(2):**

- *As documented in the risk management system assess updates to the risk management systems relating to non-centrally authorised products or any data resulting from the measures contained therein.*

Article 101L(2)f reads: "Monitor data in Eudravigilance for signals of new or changing risks and for changes to the risk benefit balance of medicinal products for which it is the competent authority and where no reference member state exists."
In cases where no reference member states exists work sharing as for PSURs as provided for in article 101f(4)e is possible. See also Article 101d(2).

In **article 116** of the directive 2001/83/EC it is stated that the competent authorities shall suspend, revoke, withdraw or vary marketing authorisation if the view is taken that the risk-benefit balance is not *considered to be favourable* (in stead of *positive* to bring it in line with the wording of Article 26) under normal conditions of use , or that its qualitative and quantitative composition is not as declared.

In **Article 125 in** the third subparagraph suspension of the marketing authorisation is not mentioned. The Netherlands therefore proposes to add a new formulation, namely the Decisions to grant, *suspend or* revoke a marketing authorisation shall be made publicly available as well as decisions to suspend the marketing and use.

Regulation (EC) No 726/2004 in **article 8(2)**
A point which in our opinion should be included is the possibility to require a GCP or PhV inspection during the evaluation phase.

Regulation (EC) No 726/2004 in **article 57(1)(d)**
An additional point the Netherlands would like to draw attention to the fact that this provision should be made compatible with new Article 101d(3) of the Directive. Article 57(1)d currently reads "ensuring the dissemination of information on adverse reactions to medicinal products authorised in the Community, by means of a database permanently accessible to all Member States; health-care professionals, marketing authorisation holders and the public shall have appropriate levels of access to these databases, with personal data protection being guaranteed", whereas the proposed article 101d(3) states that the public must submit a request to get information on each individual adverse reaction report. The latter creates a hurdle to the public and will also add to the administrative burden.

3) Company Pharmacovigilance System
Art. 8 (3)(i)a Directive 2001/83/EC
The Netherlands fully supports a less detailed description of the pharmacovigilance system, to avoid that every change to description will automatically be a type II variation.

In **article 101L (4)** reads: "In addition to the general responsibilities for monitoring the benefit risk balance of the product, for notifying new information including clinical trial results and keeping product information up to date pursuant to Article 23, …… the Marketing Authorisation Holder shall…".Nevertheless, is it the intention to extend the responsibilities of the QPPV to clinical trials?

4) Rationalise risk management planning
Art. 21(1) of Directive 2001/83/EC It is proposed to annex the risk management system to the marketing authorisation. However it would be less complicated to annex to the marketing authorisation only the key elements of the RMP instead of the complete RMP. In line with administrative simplification preference goes out to an annex of key elements.
Article 21(3) of Directive 2001/83/EC
The competent authorities shall make publicly available the marketing authorisation together with the summary of the product characteristics *and the package information leaflet* for each medicinal product which they have authorised.
However if a RMP should be made public it should be included here. For transparency reasons the Netherlands is in favour to make also the (key elements of) RMP public.
In **article 21(4)** a reference is made to the assessment report what will contain the update whenever new information becomes available which is of importance for the evaluation of the quality, safety or efficacy of the medicinal product concerned. The Netherlands would prefer to replace "safety or efficacy" with " or the risk-benefit balance" in order to be consistent in terminology.

The current text on exceptional circumstances of **Article 22** of the Directive 2001/83/EC should remain in place. This provision is necessary to authorise orphan drugs or drugs for which it is not possible to perform the normally required studies due to ethical reasons.

The Netherlands supports the provision as stated in the public consultation, however it should be included in the article on conditional approval (namely article 14 (7) of Regulation 726/2004/EC) and a similar provision (e.g. a new Article 22a) should be included in Directive 2001/83.

Article **101p (1)** it should be possible to require an Risk Management Plan (RMP) for a product authorised before the entry into force of this directive and also for a product authorised after the entry into force of this directive when a safety issue is detected post authorisation.

5) Post authorisation safety studies and risk management plans

In **article 101h(1)e** the Netherlands favours a stronger wording: The competent authority or the Committee, as appropriate, may give a recommendation on the submitted protocol within 60 -days. The marketing authorisation holder shall take this recommendation into account *and should amend the study protocol accordingly* before commencing the study.

In subparagraph i some precise wording is suggested: 'The marketing authorisation holder (MAH) shall consider whether the results of the study impact on the product *information* and submit an application to vary the product *information* to the competent authorities *where appropriate*.' Nonetheless a more principal question is whether this applies only the MAH and if this is a task for the MAH solely?

j) In addition to any reporting requirements in the study protocol, the marketing authorisation holder shall submit an abstract of the study results, *also in case of an early termination of the study,* to the Committee.

l) Competent authorities and marketing authorisation holders shall take account of the recommendations for the product information. The Netherlands prefers the new wording as proposed in the fourth subparagraph of Article 23 of the Directive, which is more stringent i.e. the MAH shall insure that product information is kept up to date with the current scientific knowledge including assessment conclusions to made public via the European medicine safety web-portal.

6) Adverse Drug Reaction reporting

In the first article of the directive 2001/83/EC, namely **article 1(12)** the definition of a serious adverse reaction lacks the concept of 'medically important/significant'.

In **article 59** of Directive 2001/83/EC it is mentioned that all suspected adverse reactions in relation to products under intensive monitoring should be reported to the marketing authorisation holder. It becomes not clear why the reporting should be done exclusively to the MAH.

In article 59(1) the Netherlands suggest to add an extra subparagraph:

Information on how patients can report directly to the competent authority.

The proposal in **article 101e(2) of the Directive** that non-serious adverse reactions shall in the near future be reported to Eudravigilance can be supported. However the Netherlands would like to make a distinction between serious and non-serious cases and therefore proposes that those serious cases are reported within 15 -days and non serious cases within 30 days.

In **article 101e (3) in the 2nd subparagraph** reference is made to reporting of adverse reactions by healthcare professionals and patients via national websites which shall be linked to the European medicines safety web -portal (also referred to in Article 101i). Member States have to transmit their reports to Eudravigilance. What is meant by the link to European medicines safety web-portal? In case of direct reporting by health care professionals and patients to the European medicines safety web portal the Netherlands is not in favour, because the routing is via the national competent authorities.

In **paragraph 5 of article 101e** states that the Agency shall monitor medical literature for reports of adverse reactions to medicinal products and the Agency shall publish the list of publications subject to this monitoring plus enter the publications into Eudravigilance.

However this provision should not discharge the MAHs from their responsibilities to check medical literature which are relevant for their products and to take actions where needed.

7) Periodic Safety Update Reports

The Netherlands is in favour of linking the initial validity of marketing authorisations to the date of first marketing of the relevant product. Therefore the proposal is to change **article 24 of Directive 2001/83/EC** as follows;

1. Without prejudice to paragraphs 4 and 5, a marketing authorisation *ceases to be valid five years after the date of the initial placing on the market referred to in Article 23a, first subparagraph.*
2. The marketing authorisation may be renewed after *five years of the date of initial placing on the market* on the basis of a re-evaluation of the risk-benefit balance by the competent authority of the authorising Member State.

To this end, the marketing authorisation holder shall provide the competent authority with a consolidated version of the file in respect of quality, safety and efficacy, including *the periodic safety reports in accordance with Article 101f(1) covering a period of at least four years after the date of actual marketing in the Community and* including all variations introduced since the marketing authorisation was granted, at least six months before the marketing authorisation ceases to be valid in accordance with paragraph 1.

In **Article 101f (1) of the Directive** it is only mentioned that MAHs shall submit periodic safety update reports to the Agency, but depending on the route of authorisation of the relevant product it can also be the Competent Authority of Member State.

Article 101f (4)a addresses the rules which shall apply to the submission and assessment of periodic safety update reports. The Netherlands propose an alternative provision (see below), because the PSUR schemes are already linked to the date of initial marketing (see article 101f-2 (c)
(a) the Committee on Pharmacovigilance referred to in Article 56(a)a of Regulation EC(No) 726/2004 may determine the European reference dates and frequency of submission for periodic safety update reports for medicinal products *containing a certain active substance f*or human use authorised in the Community. For the purposes of this provision, *the Committee shall take into account the date of initial placing on the market of the first medicinal product containing the relevant substance, if known.*

Article 101f (4) c reads as follows: MAHs for medicinal products requiring periodic safety update reports may submit requests to the Committee on Pharmacovigilance to change the European reference date or submission schedule for periodic safety update reports. Two remarks should be made, namely the Netherlands would like to avoid changing the European reference date for PSURs. Secondly requests for changing the submission schedule of PSURs should be excluded from the Regulation on Variations.

In **Article 101f(4) d**
The Committee may request a periodic safety update report for products referred to such as generics, herbals. However t*hese reports should be submitted with the competent authorities who granted the relevant marketing authorisations.*
(h) The assessment conclusions shall be made public including any recommendations for the product information by the Agency via the European medicines safety web -portal referred to in Article 101i. *See also Article 21(4) which says that the full assessment report (AR) should be made public; this is preferred.*
(i) Competent authorities and marketing authorisation holders shall take account of the recommendations for the product information. *The wording in Article 23, fourth subparagraph, is much stronger and therefore preferred.*

8) Transparency and Communication

In **Article 21 Directive 2001/83/EC** it is mentioned that the competent authorities shall make public the assessment report, together with the reasons for their opinion, after deletion of any information of commercially confidential nature.

PSURs are new information which is of importance for the evaluation of the risk-benefit balance and, therefore, the assessment report of the concerned medicinal product should be updated and be made publicly accessible. Thus, PSUR assessment reports (AR) should also be made public. However, Article 101f (4)(h) states that only the conclusions and recommendations should be made public. It is preferred to make the full PSUR ARs publicly accessible.

The current **articles 102 of the directive and article 26 of the Regulation** both include that information is permanently accessible to all Member States and without delay to the public, whereas article 57(1)d of regulation is more specific: that the public shall have access on appropriate levels. However in the new **Article 101d (3)** it is stated that individual adverse reaction reports held on the Eudravigilance database can only become public on request. This would create a hurdle for the public and a case by case administrative burden for the authorities.

Article 101i (1)d in chapter 5 on communications

Instead of using Risk Management Plans it would be more consistent to use Risk Management System throughout the text. The Netherlands is in favour of making only the key elements available to the public.

New **Article 101i(1)f** requires that the name of the QPPV, including Member States in which they reside, is publicly know. The Netherlands does not support this provision because it may jeopardize is personal safety of the QPPV.

Article 101i(2) requires medicines safety web -portals on national level to be set up which have to linked to the European medicines safety web-portal (as referred to in paragraph 1). By means of the national medicines safety web-portals, the Member States shall make public at least the following information:

(a) Agreed risk management systems *or only key elements?* pursuant to Articles 22 and 101p for medicinal products authorised in accordance with the procedures of this directive.

An extra indent is needed, namely:

(c) Information about how to report suspected adverse reactions to medicinal products and forms for their web -based reporting by healthcare professionals and patients.

9) Clearer safety warnings

Article 11(3) b of the Directive 2001/83/EC

In the summary of the product characteristics it is mentioned that is shall contain key safety information about medicinal product and how to minimise risks. There is a concern that SPC are expanding which will not stimulate the SPCs to be read by the prescribers. The real issue is that SPCs are hardly read by prescribers.

For medicinal products included on the European list of intensively monitored products referred to in Article 101j however a definition is not formulated. All new products containing a new active substance, new indication or with a new route of administration should fall under the requirements of intensive monitoring. The requirements of intensive monitoring can be lifted based on marketing experience and fulfilment of RMP requirements to be decided by the Competent Authority.

10) Inaccuracy

In relation to the proposal to Pharmacovigilance System Master File the reference to 2309/93 both **article 6 (1) and article 8 (1)** should be 726/2004.

Article 111 (2) of the Directive 2001/83/EC currently reads "Member States shall take appropriate steps to ensure that the manufacturing processes used in the manufacture of immunological products are properly validated and attain batch -to-batch consistency." Manufacturing processes of all medicinal products should be properly validated!

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