IFAH-Europe response to the Commission proposed draft Regulation concerning the examination of amendments to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products - Version: 24 October 2007

Final, 10 January 2008

IFAH-Europe very much welcomes the Commission proposed draft Regulation concerning the examination of amendments to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products, together with its detailed consultation paper and draft detailed guidelines for classification of variations.

We further wish to thank the Commission for having organised the workshop on 3rd December 2007, which was a unique opportunity to gain clarification on some of the items of the proposal and allowed us to refine our response below.

IFAH-Europe fully supports the main concepts introduced in the draft Regulation, especially 'Do and Tell', 'Default to Type IB', the option to group variations and work-sharing, which all align with the Commission 'Better Regulation' agenda.

Though we appreciate the willingness to finalise this project for rapid entry into force that will also benefit industry, we wish to stress that due to the short consultation period, our comments below focus on the Regulation and Annexes, i.e. pages 1 to 26 of the proposal, and not the Guidelines. A longer consultation period should therefore follow to further reflect on the Guidelines on classification of variations.

Articles of the Regulation on which IFAH-Europe has major comments are highlighted in yellow.

All the comments below have been further inserted in the draft Regulation using 'track changes' mode - see attached IFAH-EU-TrackChanges-Jan08.pdf.

CHAPTER I: GENERAL PROVISIONS

- ***Article 3 - Definitions***

§ 2 b) should also refer to Articles 13 c) and 13 d) of the amended veterinary Directive for Informed consent and Immunological Veterinary Medicinal Products with reduced data package applications, respectively.

With regard to informed consent, this should be further included in the list of Type IA 'Do and Tell' variations so they can be processed automatically following approval of any changes to the first marketing authorisation.

§ 6. Major variations

A major variation is defined as follows: "'Major variation of Type II' means a variation, which is not an extension, and which has a substantial potential to have a negative impact on the quality, safety or efficacy of the medicinal product concerned."

Where a potential negative impact on the product may occur, a change would not be investigated and we propose replacing: *'have a substantial potential to have a negative impact*' with: … *'which has a potential to have a highly significant impact*' as follows: '*Major variation of Type II' means a variation, which is not an extension, and which has a* ~~substantial~~ *potential to have a* ~~negative~~ ***highly significant impact*** *on the quality, safety or efficacy of the medicinal product concerned*.

§ 3 - Minor Type IA

Similarly, we propose amending the definition for Minor Type IA variation as follows: "*'Minor variation of Type IA' means a variation which is not expected to have any* ~~negative~~ ***potential significant impact*** *on the quality, safety or efficacy of the medicinal product concerned*."

- ***Article 4 - Classification***

IFAH-Europe welcomes § 2 that reads that a variation "*whose classification is not laid down in the detailed guidelines shall be considered a minor variation of Type IB*."

- ***Article 5 - Scientific recommendation on unforeseen variation***

IFAH-Europe recommends that the timing for the Agency to deliver a recommendation should be reduced from 60 to 14 days, especially as we understand from the Commission that such recommendation would not be binding.

- ***Article 6 - Guidelines***

IFAH-Europe welcomes that the conditions for classification of variations will be listed in guidelines and no longer annexed to the Regulation. This will indeed provide the necessary flexibility to amend these guidelines, where necessary.

- ***Article 7 - Grouping of variations***

IFAH-Europe very much supports the introduction of a 'may provision' to group variations that solely depends on the applicant's choice and must be accepted by all the authorities concerned. The grouping options are given as follows:
§ 2 (c) for multiple changes to one marketing authorisation;
§ 2 (d) for one or multiple changes to several marketing authorisations that will lead to the work-sharing.

Though the two paragraphs above seem to provide an appropriate level of flexibility in the option to group variations, multiple changes are linked to Annex II of the Regulation. As this Annex focuses on 'consequential variations', it will limit the option to group variations. We therefore recommend amending Annex II to allow more flexible grouping (see also comments to Annex II on page 6).

Also § 2 (d) limits the option to group by 'the same holder'; this should be extended to include all the subsidiaries of this holder.

CHAPTER II: VARIATIONS TO MARKETING AUTHORISATIONS GRANTED BY MEMBER STATES OTHER THAN MUTUAL RECOGNITION/DECENTRALISED PROCEDURE

CHAPTER III: VARIATIONS TO MARKETING AUTHORISATIONS GRANTED BY MEMBER STATES WITH MUTUAL RECOGNITION/DECENTRALISED PROCEDURE

CHPTER IV: VARIATIONS TO MARKETING AUTHORISATIONS GRANTED IN ACCORDANCE WITH REGULATION (EC) N^{O} 726/2004

Delay in the processing of variations is a major issue of the current system for industry; we therefore suggest introducing set times at the following time points in the procedures.

- ***Articles 9, 10, 13, 14, 18, 19 and 24***

We recommend introducing deadlines for acknowledging receipt of an application within 10 working days.

- ***Articles 10.4, 14.4(c) and 19.4 - Type II 'Tell, Wait and Do'***

Where supplementary information is required, extension of the assessment time must be limited to an additional 30 days and not a '*further period'* to be determined by the relevant competent authority. This comment also applies to Article 24 'Work-sharing'.

- ***Articles 9, 13 and 18 - Type IB 'Tell, Wait 30 days and Do'***

In the three articles referred to above, § 5 provides a 'safeguard clause' for the competent authority assessing the change to switch from a Type IB to a Type II timeline, where it is of the opinion that the change has a *'substantial potential to have a negative impact*'. We have the following remarks:
- To ensure that this clause is applied only in exceptional circumstances, a guidance recommending the assessing competent authority to justify its opinion for 'high significant impact' and a comprehensive list of Type II variations will have to be established;
- Where this clause is applied, the procedure must not restart at day 0, i.e. § 5 must not cross-refer to § 2 to 5 of Article 10, 2 to 6 of Article 14 or 2 to 6 of Article 19, but only **extend the assessment time up to a maximum of 60 days**.
- As for Article 3 Definitions, *'substantial potential to have a negative impact'* must be replaced with: '*which has a potential to have a* ***highly significant impact***';

CHAPTER III: VARIATIONS TO MARKETING AUTHORISATIONS GRANTED BY MEMBER STATES WITH MUTUAL RECOGNITION/DECENTRALISED PROCEDURE

- ***Article 16 - Co-ordination group and arbitration***

§ 1 currently refers to Articles 12 to 15, i.e. it includes Type IA and IB variations. However, a Type IA variation does not require assessing and can not lead to a disagreement. Also a Type IB is a change, which does not have a high significant impact; therefore the assessment made by the Reference Member State must be endorsed by all the concerned member states and should never then lead to arbitration. § 1 should therefore read: "*Where, during the course of the procedures laid down in Articles ~~12~~ **14** to 15 …*"

CHAPTER V

SECTION 1 CLOSURE OF PROCEDURES

- ***Article 21 - Closure of procedure***

The closing of Type IA procedures appears too lengthy and a new paragraph (1) for closing of Type IA should be introduced as follows: ***'Where reference is made to this paragraph, the relevant authority, the competent authority of the reference Member State or the Agency shall forthwith notify the holder that the MA has been amended within two months'***.
Reference to this new § 1 should be added to Articles 8, 12 and 17 on Type IA 'Do and Tell'.

In all subsequent paragraphs, the time for a competent authority to amend a marketing authorisation should be reduced from 6 to 2 months for all variations.

- ***Article 22 - Implementation by economic operators***

IFAH-Europe welcomes the following provisions for implementing variations:
§ 1: a Type IA can be implemented at any time.
§ 2: a Type IB or Type II may be implemented once deemed accepted.

SECTION 2 SPECIAL PROCEDURES

- ***Article 24 - Work sharing procedure***

§ 1 provides the option for an applicant to follow the work sharing procedure, which IFAH-Europe welcomes.

§ 3 reads: "*The Agency shall issue an opinion on the valid application referred to in paragraph 2 within 60 days following receipt of the valid application…*"

Comment: IFAH-Europe supports this paragraph in principle, though we feel it requires some refinements to ensure an efficient work-sharing procedure. Such refinements may be described in Guidelines and be as follows:
- Where a Centrally Authorised Product is involved: the Centralised Procedure Rapporteur could be responsible for assessing the change;
- Where a MRP/DCP product is involved: the RMS could be responsible for assessing the change;
- Where purely national authorisations are involved: the EMEA could be responsible for appointing a Rapporteur, following the applicant's recommendation.

§ 6 reads: "*Where it reaches a final opinion on the application referred to in paragraph 2, the Agency shall send it to the holder and to all relevant authorities, together with a list of all the marketing authorisations concerned*."

Comments

A provision must be added to ensure that the opinion delivered by the assessing authority is endorsed by all other concerned authorities.

The work-sharing procedure must also be closed either by referring to Article 21 or introducing an additional paragraph.

ANNEX I: EXTENSIONS OF MARKETING AUTHORIARIONS

The proposed Annex reads under 1. *Changes to the active substance(s)*

"(a) *Replacement of a chemical active substance by a different salt/ester complex/derivative, with the same therapeutic moiety, where the efficacy/safety characteristics are not significantly different*;

(b) *Replacement by a different isomer, a different mixture of isomers, of a mixture by an isolated isomer (e.g. racemate by a single enantiomer), where the efficacy/safety characteristics are not significantly different*;"

Comment: Article 13 of Directive 2001/82 as amended reads that 1 (a) and (b) are in fact considered to be the same active substance, i.e. such replacement cannot be an extension and shall be removed from Annex I.

"(c) *Replacement of a biological active substance with one of a slightly different molecular structure where the efficacy/safety characteristics are not significantly different, with the exception of*:
- Replacement of an antigen by another antigen derived from an approved master seed virus in the case of veterinary vaccines against avian influenza, foot-and mouth disease or bluetongue."

Comment: in the context of the introduction of multi-strain dossier, we propose the following amendment:

- Addition *(or replacement) of* ***a new antigen to a multi strain dossier*** ~~*by another antigen derived from an approved master seed virus*~~ *in the case of veterinary vaccines against avian influenza, foot-and mouth disease or bluetongue."*

This comment should be linked to the Commission's proposed new Type II, to also be amended as follows: *Addition (or replacement) of a new antigen to a multi strain dossier for a veterinary vaccine against avian influenza, foot-and-mouth disease or bluetongue.*

This should further be linked to the review of Annex I to the Directive - Title IV B. Multi Strain dossier, which should be made available prior to finalising the Variations Regulation. The Annex I should read that for certain immunological veterinary medicinal products (i.e. Foot and Mouth disease, Avian Influenza and Blue Tongue) and by derogation from the provisions of TITLE II, PART 2 Section C on active substances the concept of the use of a multi-strain dossier is introduced. A multi-strain dossier shall mean a single dossier containing the relevant data for a unique and thorough scientific assessment of the different options of strains/combinations of strains permitting the authorisation of vaccines against antigenically variable viruses. Scientific and procedural guidance for the submission and evaluation of multi-strain dossiers will be developed by the Agency.

We further propose amending sections 2. "*Changes to strength, pharmaceutical form and route of administration*" and 3. "*Other changes*" to allow the applicant to submit some of these changes either as a line extension that would benefit from additional Data Protection, or as a Type II variation:

Extension or Type II variation

Changes to the active substance(s)

1. Replacement of the active substance(s) by a different salt/ester complex/derivative (with the same therapeutic moiety) where the safety, efficacy or PK characteristics are significantly different;
2. Replacement by a different isomer, a different mixture of isomers, of a mixture by an isolated isomer (e.g. racemate by a single enantiomer) where the safety, efficacy or PK characteristics are significantly different;
3. A new ligand or coupling mechanism for a radio-pharmaceutical;
4. Change to the extraction solvent or the ratio of herbal drug to herbal drug preparation where the efficacy/ safety characteristics are not significantly different.

Changes to the strength

1. Change of bio-availability;
2. Change of pharmaco-kinetics e.g. change in rate of release;
3. Change or addition of a new strength/potency.

Extension application for which the Data Protection would be extended from the date the extension is obtained:

1. 'Other changes' to the Active Substance or the strength listed above, where the Applicant chooses to apply for a line extension;
2. Change or addition of a new pharmaceutical form;
3. Change or addition of a new route administration;
4. Change or addition of target species for ***all*** veterinary medicinal products, i.e. not only those to be administered to food-producing animals.

ANNEX II

In this Annex, the word 'consequential' variations must be deleted as it is too restrictive and leads to disharmonised interpretation amongst competent authorities. More flexibility must be introduced to allow grouping Type IB and/or Type II, whether consequential or not.

GUIDELINES

IFAH-Europe supports the principle to list conditions for variations in Guidelines, which makes it easy to amend/update, where necessary. From a first preliminary assessment, here are the points we wish to raise:

Type IA

The introduction reads: *'A variation which is classified in this guideline but which does not fulfil all the necessary conditions laid down in the relevant subcategory shall be considered to be of Type II*: this is totally unacceptable as it goes against the default to Type IB concept. Such variations should therefore be a Type IB.

IFAH-Europe proposed NEW Type IA:

- Any change to an 'Informed consent application', so these can be notified once the variations to the first licence are approved.
- Any change to the 'Description of the Pharmacovigilance system', pending the introduction of a Master File concept that will allow companies to maintain on site a detailed file on their Pharmacovigilance System ("Pharmacovigilance System Master File"), i.e. the description will no longer be part of the dossier; such Master File will be submitted to the authorities upon request or viewed at the time of a pharmacovigilance inspection.

More detailed comments on the Guidelines will be done during the official consultation on Guidelines, which we recommend be 6 months minimum. Meanwhile, you may also refer to the IFAH-Europe first proposal on 'Classification of variations with conditions' submitted in May 2007.

OTHER POINTS TO CONSIDER

Throughout document: reference should be made to Directive 2001/82 ***as amended.***

IFAH-Europe further recommends the development of an all-electronic application system for variations (link to the E-submission TIG group activities).