VETERINARY MEDICINES VMD DIRECTORATE

ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

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Mr Nicolas Rossignol
European Commission
DG Enterprise and Industry
Unit F2 Pharmaceuticals
B-1049
Brussels
Belgium

4 January 2008

Dear Nicolas

UK VETERINARY RESPONSE TO THE COMMISSION'S PUBLIC CONSULTATION PAPER: "BETTER REGULATION OF PHARMACEUTICALS: TOWARDS THE SIMPLER, CLEARER AND MORE FLEXIBLE FRAMEWORK FOR VARIATIONS"

Thank you for the opportunity to provide a written response to the Commission's draft proposals for a new Variations Regulation.

The Veterinary Medicines Directorate welcomes the proposals from the Commission and congratulates them on the papers circulated for comment. It is clear that the proposals are designed to achieve a significant reduction in administrative burden, primarily for the pharmaceutical industry but also, to some extent, for national authorities and we fully support this. Our detailed comments are attached.

It is important that the proposals strike the correct balance between the need to reduce administrative burden and the need to ensure that the quality, safety and efficacy of medicines are maintained. Many of the UK's veterinary comments stem from our desire to ensure this balance is correct.

We look forward to discussing these with you when you visit the MHRA on 10 January and also to participating in the more formal discussions in Brussels, which necessarily will have to deal with the practical details.

A copy of this letter goes to Maggie Jackman and David Hook at MHRA.

Yours sincerely

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ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

UK Veterinary comments on public consultation on proposed changes to the Variations Regulations

Introductory Remarks

The VMD welcomes the proposals from the Commission and congratulates them on the papers circulated for comment. It is clear that the proposals are designed to achieve a significant reduction in administrative burden primarily to the pharmaceutical industry, but also to some extent for national authorities and we fully support this.

It is important that the proposals strike the correct balance between the need to reduce administrative burden and the need to ensure that the quality, safety and efficacy of medicines are maintained. Many of the VMD comments stem from our desire to ensure this balance is correct.

The VMD looks forward to participating in the discussions, which necessarily will have to deal with the practical details.

Major Issues

1. Specific to Veterinary Medicines

1.1 Variations to the Pharmacovigilance System

Our understanding is that variations relating to changes in the pharmacovigilance system will now be IB rather than Type II as at present. This is an improvement on the current system. However, it is still not entirely satisfactory as the same pharmacovigilance system relates to every MA in the Marketing Authorisation Holder's portfolio. Consequently a variation such as a change in the qualified person for pharmacovigilance (QPPV) could require a group variation covering a large number of MAs. The preferred option would be for a pharmacovigilance system dossier (i.e. a pharmacovigilance system master file) for each MAH rather than for each MA. This is a procedure currently being considered in proposals to change the pharmacovigilance legislation for human medicines. It is important that the option of a pharmacovigilance system dossier should also be considered for veterinary medicines.

There do not appear to be any examples of pharmacovigilance system variations in the draft guidelines. It would be helpful to have these included.

1.2 Variations to Antigen Master Files or antigens in vaccines for specified diseases

We note that within annex 3 of the proposals (i.e. the draft guidance) the "new" variations include two concerning Antigen Master Files and one concerning the use of new antigens or combination of antigens for vaccines against avian influenza, foot-and-mouth disease or bluetongue. Whilst the concepts of vaccine Antigen Master Files and multi-strain dossiers has been introduced into the draft Technical Annex of Directive 2004/28/EC, this annex has not yet been finalised and scientific and procedural guidance linked to these new processes are yet to be developed by the EMEA. It is therefore difficult to comment in detail on the proposed new variations and in particular on how such changes should be categorised. However, in principle the UK supports the aim of making it easier for companies to introduce changes to vaccines in a timely fashion so that the industry can be more responsive to changing disease situations.

2. Applicable to Human and Veterinary Medicines

2.1 Timing

The proposed timing of implementation of the new Regulation will be critical. The changes involved are substantial and in addition to changes to national legislation, changes to application tracking systems (nationally and CTS) will need to be introduced to support the changes. It is suggested that authorities have a period of at least 24 months in which to put in place the necessary changes to allow the new systems to operate successfully. The option for a national authority to implement certain elements of the changes relating to nationally authorised products at an earlier date should also exist.

The proposal to work on the change to the legal basis for national variations via the co-decision procedure in parallel to the work on the details concerning the Variation Regulations is in principle acceptable. However, it is important to understand that it will be very difficult to agree to the change to the legal basis for national variations until the details concerning the changes to the Variation Regulations have been agreed and therefore the impact of the change is fully understood.

2.2 Work Sharing

The information provided on the proposed work sharing element for variations is lacking in detail and therefore it is very difficult to fully understand the proposals and their impact on marketing authorisation

holders, national authorities and the EMEA. In principle the idea of work sharing is supported. However, as national authorisations are involved we consider that the role of co-ordination/evaluation should reside with the national authorities and not with the EMEA. Whilst the EMEA has recent experience in work sharing for a small sub-set of Type II variations, the ability of this system to cope with the potentially vast numbers of applications that might be delivered under these proposals is not obvious. It is the responsibility of the Heads of Agencies to decide on a practical operating system. In any system that is developed it will be essential to address the following points:

- Work sharing should be optional for national authorities.
- The selection of the "lead" assessment country must be fair, take account of national resources and experts, and should include an element of marketing authorisation holder preference.
- National authorities should be suitably re-imbursed for work they undertake.
- The decision reached through the work-sharing assessment should not be binding for National Authorities. Where the proposed variation gives rise to serious public health concerns in a particular country, that country should retain its power to refuse the variation.

In terms of the types of applications suitable for work sharing, it is considered that these in the first place should be restricted to a sub-set of specified Type II variations. Variations that require the data in the existing dossier to be examined to understand their full implications, should be excluded from work sharing as the data may differ between countries and it is not practical to exchange this level of information.

The draft Regulation and associated papers do not provide sufficient clarity in terms of the national phase which will follow the work sharing assessment. This element is not mentioned in the draft Regulation.

2.3 Annual Reporting of Type 1A Variations

The reporting of type 1A variations within 12 months is welcomed. However, we do not believe it is appropriate to leave the decision on the timing of such submissions solely with the marketing authorisation holders. Whilst it is noted that a comment is included to encourage reaching agreement with national authorities on timing, we believe this should be strengthened. Furthermore, for European authorisations, a co-ordinated timing of submission across Europe would be appropriate. The model being created for PSUR work sharing may represent a useful starting point. In this context it would also be appropriate to consider whether those marketing authorisation holders who do not submit variations in a 12 month period should be required to submit a statement

confirming that no changes have been made. One possible approach is to require nil returns from all companies, with the exception of those who have demonstrated they work to the requirements set out in ICH guidelines Q9 and Q10.

The move to annual reporting for certain changes will result in MAs not being completely "current". This may lead to difficulties for GMP Inspectors who use the current MA documentation for some parts of the inspection, (e.g. change in batch release arrangements and quality control testing of the finished product). It is therefore suggested that in addition to annual submission, MAHs submit 1A variations to the Supervisory Authority in advance of a GMP inspection.

Detailed Comments

Chapter I - General Provisions

Under Article 3, Definitions, Paragraph 2 (b) reference to Informed Consent applications (Article 13c) is missing. Is this deliberate? It should be possible to vary products authorised under the Informed Consent basis. A reference to Article 13d is also missing.

Chapter II - Variations to Marketing Authorisations granted by Member States without mutual recognition

Article 9, paragraph 3: According to the proposal a type IB variation is deemed accepted 30 days following the acknowledgement of receipt, unless the applicant has heard from the relevant authority. Taking into account that many more variations will fall into this category, including some that represent higher potential risks to the product safety and efficacy, it is considered more appropriate for the applicant to wait for positive confirmation of approval. In reality we understand this is how industry usually chooses to operate.

Article 10, paragraph 4: According to the proposal no time limit is set for applicants to provide supplementary information. For reasons of efficient operation in the authorities, a maximum time limit should be specified. After this time the applicant would be expected to re-apply for the variation.

Chapter III - Variations to marketing authorisations granted by Member States with mutual recognition/decentralised procedure

Article 13: According to the proposal there does not appear to be an opportunity for CMSs to comment on, firstly, whether or not the change is such that a Type II variation procedure should apply, and secondly, whether they consider that the applicant should provide additional information.

Article 14, paragraph 3: The proposal is that the RMS will prepare an assessment report and a draft decision on the application and this will be sent to the CMSs. The proposal is silent on the CMSs ability to react to these documents and to send

additional questions to the RMS for their consideration. As this element is already part of the existing procedures, it is presumed that this element will be retained.

Article 14, paragraph 3: The comments under chapter 2, article 10, paragraph 4 also apply here.

Article 14, paragraph 5: The proposal seems to be silent on the timeline under which the RMS should assess the response and update the assessment report and draft decision. This mirrors the current system. However, the lack of a set timeline at this stage leads to problems and it is suggested this opportunity is taken to introduce a timeline, for example 60 days.

Article 16, Paragraph 1: This could have a significant impact on the work of CMD(v). There is already limited time to discuss products submitted under Directive 2001/82/EC as amended, during the usual plenary sessions. Consideration should be given to the potential numbers involved and the likely impact on resources. For example how will this additional work be funded, including attendance at extended meetings?

Chapter IV - Variations to marketing authorisations granted in accordance with Regulation (EC) No 726/2004

Based on the draft Regulation it is not clear how the CHMP/CVMP and experts from national authorities will be involved in the examination of variations to centralised products. As this is not an area highlighted for change it is assumed that the current procedures will continue to operate.

Article 19: Unlike the chapters on Mutually Recognised products and products authorised through the decentralised system, there appears to be no reference to the production of an assessment report for Type II variations for centrally authorised products. This is unacceptable and as now assessment reports should be produced for such applications.

Article 19, paragraph 4: The comments under chapter 2, article 10, paragraph 4 also apply here.

Article 19: Following a request for supplementary information, the proposal as written gives the Agency complete freedom to decide on the period of time to be taken to assess the response and prepare the draft decision. In line with the suggestions made under article 14, paragraph 5 it is suggested that this opportunity is taken to introduce a timeline for this assessment, for example 60 days.

Chapter V

Section 1 - Closure of Procedures and Implementation

Article 21, paragraph 1.b: In principle the proposed timelines for authorities to amend marketing authorisations are acceptable, and in fact for the VMD would represent a significant relaxation. However, in certain cases the authority's ability to update the

marketing authorisation is dependent upon the marketing authorisation holder to provide certain data to meet national requirements. For example, mock-ups of labels and leaflets in English which reflect the agreed changes and take account of national requirements (such as distribution category) need to be provided. In these cases there should be an obligation for the marketing authorisation holder to provide these within 30 days of being informed of the outcome of the application.

Article 22, paragraph 2: In a parallel to the remark made under chapter 2, article 9; marketing authorisation holders should only implement type 1B variations following a positive confirmation of their approval from the relevant authority. It would appear this is the proposal for variations to centralised authorised products, but it should be applicable equally in the case of variations to national and MRP/DCP products.

Section 2 - Special Procedures

Article 24, paragraph 1: It is not clear whether the "categories" referred to are items 1 to 13 in annex II or items 4 to 13 in annex II. It is considered more appropriate to limit work sharing to certain types of more complicated variations.

Article 24, paragraph 2: The proposal indicates that the application and supporting information should be submitted to the agency. It is considered important that at the same time the relevant authorities also receive this information. The intention would not be to allow each authority to perform an independent assessment, instead this would allow authorities to provide comments should they feel it is necessary to do so.

In the application, in addition to the points set out as a) and b), the applicant should set out any significant differences between the national dossiers which would be relevant to the assessment of the application.

Article 24, paragraph 3: The proposal fails to address how the evaluation will be performed and by whom and how all authorities with a direct interest in the application will be able to contribute to the assessment if they consider this to be appropriate.

Article 24, paragraph 6: In addition to the final opinion, a copy of the final assessment report should be forwarded to relevant authorities.

Article 24, paragraph 7: It is necessary to consider the type of information the member states may be asked to provide. It would not be appropriate to ask member states to provide complete sections of dossiers. Where the Agency requires a significant amount of information from the national authorities, it will be necessary to consider whether the application in question is appropriate to be examined under the work sharing principle, or whether instead it would be more efficient for it to be examined by the national authority in question.

Article 24: The proposal appears to be incomplete as it does not set out how the national phase of the procedure is intended to operate. The "NEW" elements to the draft guideline are clearly of relevance, but these alone are not sufficient to understand how this will operate on a practical level.

Article 26, paragraph 1: In addition to referring to a risk to public or animal health, reference should also be made to a risk to the environment.

Chapter VI - Final Provisions

Article 28: The proposal appears to correspond to a 5 year post implementation review, rather than to a date for examining the national implementation of the revised Regulations. This should be clarified.

Annex II - (Work sharing variations)

Point 4: Labels and leaflets are primarily a matter for the national authorities. With the additional complications surrounding linguistics, the benefits of including such variations in the work sharing exercise are not clear.

Point 6: It is not entirely clear what types of changes are intended to be covered by this point. One possible interpretation is that the changes are intended to include those linked with the ICH guidelines Q8, Q9 and Q10. It will be necessary to make point 6 more clear and transparent.

Point 7: Most variations to the pharmacovigilance system are likely to be group variations and as such they could fit well into work sharing. However, if this is agreed it should be co-ordinated with the requirements of the national authorities.

Point 10: This point needs to be clarified as periodic safety update reports (PSURs) are part of pharmacovigilance and any changes relating to the system would be included under point 7. Any changes required as a result of a PSUR, could also be required after receipt of serious adverse event reports. It is not clear why PSURs have been specified. It is likely that where proposals are made to modify SPC/labels/leaflets as a consequence of concerns arising from the assessment of a PSUR (which are the subject of a current work sharing pilot trial) these will be discussed by the Pharmacovigilance Working Party with agreement being reached on the form of words. A similar situation is also likely to apply in the case of serious SARs observed in a number of countries. In these circumstances, as the information has been assessed and the wording agreed, it would seem unnecessary and inappropriate to work share the remaining element which would simply be dealing with national changes to SPC/labels/leaflets.

Annex III

Draft detailed guideline referred to in article 6(1) (a): Conditions for classification of variations.

It would be helpful if in the introductory paragraphs to the guideline it was indicated that where a variation is not listed in the table, it would usually be expected to be submitted in the first place as a Type 1B variation. There would then be the possibility that the relevant Authority would be able to switch the variation to a Type II procedure within 30 days following receipt of the variation.

It would also be helpful to include within the guideline the definition of a minor variation i.e. a change that does not have a substantial potential to have a negative impact on the quality, safety or efficacy of the medicinal product.

Change No. 29.b: It is considered this should remain categorised as a type IB variation.

Change No 41.2: It is considered this should remain categorised as a type IB variation.

"NEW" changes: It is noted that for many of these conditions are yet to be elaborated. It is assumed this is a reflection that the guidance document is an early draft and that the intention is to develop appropriate conditions for each of these new changes.

8(a) and 8(b)2: The proposal to move this from a Type II to a IB variation is not acceptable. Whilst a successful method transfer is one of the conditions, it is not possible to establish if this condition is met without assessment. Test methods such as ELISAs can present difficulty in validation therefore full assessment is required.

13 (a) The proposal for biological products to move this from a Type II variation to a Type 1A variation is not acceptable. However, it may be possible to accept this type of change as a Type IB variation.

13 (b) The proposal for biological products to move this from a Type II variation to a Type 1B variation is not acceptable. This type of change should remain as a Type II variation in view of the need to assess the data, which may be significant if a biological test is to be replaced or a new test added.

For variations 16 (a) and 22 (b) it is proposed that these are dealt with as Type 1A variations even in the case of products intended for administration to TSE susceptible species. We do not consider this proposal to be appropriate. It is important that, for TSE susceptible species, these continue to be dealt with as Type 1B variations. It would be unacceptable to identify after a 12 month period that a product has been on the market that represents a risk of transmission of TSEs in animals.

12 (b), 19 (b) and 37 (b): All of these variations relate to additional test parameters. It is necessary to more clearly define what is intended by test parameters. We assume it relates to either additional specification limits applying to an existing test method or relates to additional specification limits which are established using an additional test method.

20 (b) The proposal to change this variation to a Type 1A variation cannot be accepted. It is necessary for the equivalence of data to be assessed and therefore this should remain as a Type 1B variation.

20 (c) For biological products this type of change should remain a Type II variation. This is based on the requirement to assess equivalence and the fact that this could be a complete replacement of a test rather than just a minor change.

38 (b) This should remain as a Type 1B variation. These types of changes require assessment.

38 (c) For biological products this should remain as a Type II variation. The change could result in a change of test/replacement of test which requires extensive validation. As an example, as written this could relate to a complete change in the potency test which in turn could have an impact upon the efficacy of the product.

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