NL (I)VMP-assessor's comments on the Draft Commission Regulation, version 24 October 2007 for variations and Public Consultation Paper "Better Regulation of pharmaceuticals: ..".
(Assessor's comment in blue)

The Comments on the proposed revision of Annex II of Commission Regulation (EC) 1084/2003 are also applicable to Annex II of Commission Regulation (EC) 1085/2003.

The Comments focus on the proposed Classification of Changes and the proposed revision of Conditions of the a.m. Variation Regulations and their applicability for Immunological Veterinary Medicinal Products (IVMPs).

General comment.
The text as such is very complicated and not easy to read, mainly due to repetitions on procedures, having much text in common. The small differences do not appear. Definitions on type of variations should be clearly defined and stated as such.

Having regard to:
Annex I of Commission Regulation (EC) No 1084/2003 and Commission Regulation (EC) No 1085/2003 set out the conditions necessary for a given variation to follow either a type IA or a type IB procedure.
The IA and IB procedures are in fact notifications which follow two distinct time tables for validation and acceptance.
The guideline on dossier requirements for type IA and IB notifications in the NoTA Vol 6C, in particular the Documentation sections.
The purpose to give a *precise* definition of minor variations for which no prior evaluation is needed according to Consideration No 7 of the introduction of COMMISSION REGULATION (EC) No 1084/2003 and Consideration No 5 of COMMISSION REGULATION (EC) No 1085/2003

The Dutch Assessor is of the opinion that:
1. The Public Consultation Paper is not written in suitable wordings for changes on IVMPs. The proposed revisions in the Draft Commission Regulation are even worse due to an apparent disregard of the inherent differences between biochemically complex IVMPs and (chemically defined) pharmaceuticals. Although there may be less reasons to distinguish between changes on well defined biological and synthetic pharmaceuticals, a similar approach is not justified for changes on the production and control of more complex product classes to which the IVMPs belong. Indeed, the subtitle of the Consultation Paper "for a better regulation of pharmaceuticals..." does not even refer to IVMPs. Nevertheless, manufacturers, regulatory authorities and assessors have been forced to use the available classification for variation procedures of the current Regulation although neither the described conditions for minor changes nor the listed documentation in Vol6C of the NoTa match satisfactorily with IVMPs.

2. The biochemical composition of the vast majority of active substances of IVMP's is not exactly defined in contrast with the majority of pharmaceuticals of either biological or synthetic origin. It is therefore necessary to discriminate between the IVMPs and pharmaceuticals in a revised Commission Regulation which would be more consistent with the two separate Titles of Annex 1 of Directive 2001/82 as amended by Directive 2004/28/EC (not consolidated) as well as with the different classes of products described in the introduction of the European Pharmacopoeia.
A revised Regulation on Variations should contain adequate descriptions of the minor changes and the relevant conditions for changes on IVMPs for which no prior evaluation is needed (in accordance with the opinion of the Immunological Working Party of the CVMP). It is expected that the list of changes in the production and control of an IVMPs for which a negative influence on the quality, safety and efficacy of production batches could be *a priori* excluded with certainty, will be very short. Therefore, a prior assessment of data to support the conclusion that the proposed change (and/or consequential changes) in the production and control of an IVMP does not have a negative influence on the required minimum quality and/or safety and/or the stated efficacy, will remain essential.

3. The currently used descriptions (biological medicinal products, biological ingredient, biological substance etc.) in Regulations, Guidelines and Notices to Applicants on Variations (category, required conditions, recommended documentation) should be replaced by clear specifications of the class of product (pharmaceutical *or* immunological class) that is meant, i.e. for veterinary use *or* human use. In addition the description of a minor variations should unambiguously refer to either (Biological) Starting Materials, (Biological) Components of Culture Media, Biological Pharmaceutical (Final) Products or Immunobiological (Final) Products.

4. The proposed *deletion* of Conditions with the text "The product is not a biological medicinal Product" appears to be unacceptable or not suitable for IVMPs in a majority of cases.
It is therefore proposed to maintain or amend the text of these Conditions to exclude the described IA or IB notification procedures for IVMPs.

5. A *consolidated* text of the new Regulations should be available before the Documentation Sections of the Guideline for Type IA and IB Notifications (Vol6 C, NoTA) can be adequately updated.

6. All variations on the Production and Control of IVMPs involving changes (e.g. replacement, reduction, refinement) in the use of laboratory or target animals in approved tests are major (type II) because a potentially negative influence of these variations on the minimum release quality of IVMP batches can not be excluded.

7. All variations on the use of approved Seed Materials and Cell lines or on approved tests with blood or tissue samples derived from laboratory or target animals are essentially major (type II) because a potentially negative influence on the release quality of an IVMP can not be excluded.

8 An adjuvant or adjuvant mixture of an IVMP is a *key* substance that attributes decisively to the quality, safety and efficacy of an IVMP. It is not justified to describe or even consider the adjuvants as a common excipient like salts/buffer of an IVMP. Consequently all variations on the approved adjuvants or adjuvant components are major (type II) changes which can have a potentially negative impact on the quality (potency, stability), safety and efficacy of an IVMP.

Other remarks:
The only clear reference made in the current Commission Regulations to IVMPs ("vaccine and adjuvant") concerning the examination of variations is Condition No 5 of minor change No 19. Condition 5 of minor change 19 is one of the many which are now proposed to be deleted in the Draft Commission Regulation. The Draft Commission Regulation and The Public Consultation paper seem to ignore completely that IVMPs have been described in a separate Title (II) of Annex I of Directive 2001/82/EC as amended by Directive 2004/28/EC (not consolidated).

[The abbreviations "PXN" and "PxN" in the text of the Consultation Paper and legend of Figure 2 (Today> PXN notification and Proposal > PxN" down to 1) are not understood and should be clarified.

"The procedure "Line Extension" is only mentioned in Guidelines for human medicines and is not defined in any known legal document for the marketing authorisation of *veterinary* medicines. A clear definition should be included in the legislation for veterinary medicines.]

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Assessor's Comment:
SECTION 1
(a) / (b). It is not clear which safety/efficacy characteristics are meant. "Not significantly different" may imply numerous studies to demonstrate.
(c) The way in which "biologically active" is used is not clear. E.g. in Annex I (c) it applies to a pharmacologically active substance (chemicals). Immunobiologicals are usually not characterized on a molecular basis, but hormones (also biologically active) can.

"Slightly different" allows difference in interpretation and should be specified.

SECTION 2 (a) / (b).
Changes in bioavailability and pharmacokinetics is a result of a change (in formulation or route of administration), rather than a change as such.

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7. Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product
a. Secondary packaging for all types of pharmaceutical forms
Conditions: 1,2 (see below) **IA** IAIN
b. Primary packaging site
1. Solid pharmaceutical forms, e.g. tablets and capsules
Conditions: 1,2,3,5 **IA** IAIN
2. Semi-solid pharmaceutical forms
Conditions: 1,2,3,5 **IB** IAIN
3. Liquid pharmaceutical forms (*e.g.* suspensions, emulsions)
Conditions : 1,2,3,4,5 **IB**
c. All other manufacturing operations except batch release
Conditions : 1,2,4,5 **IB**
Conditions:
1. Satisfactory inspection in the last 3 years by an inspection service of one of the Member States of the EEA or of a country where an operational Good Manufacturing Practice (GMP) mutual recognition agreement (MRA) exists between the country concerned and the EU.
2. Site appropriately authorised (to manufacture the pharmaceutical form or product concerned).
3. Product concerned is not a sterile product.
4. Validation scheme is available or validation of the manufacture at the new site has been successfully carried out according to the current protocol with at least three production scale batches.
5. Product concerned is not a biological **or immunological** medicinal product **for human or veterinary use**.

Assessor's Comment:
Change Nr.7b1 and Nr.7b2: Not Applicable to IVMPs.
Change Nr.7b3: Not Applicable to inactivated IVMPs for parenteral use (Conditions 3 and 5) or live IVMPs (Condition 5).
Change Nr.7b3 should be classified as Type II for an IVMP.
Condition 5 should be amended as indicated:
5. Product concerned is not a biological or immunological medicinal product for human or veterinary use.

8. Change in batch release arrangements and quality control testing of the finished product
a. Replacement or addition of a site Conditions: 2, 3, 4 (see below) **IA where batch control/testing takes place**
Conditions: 2, 4 (see below) ***IB***
b. Replacement or addition of a manufacturer responsible for batch release
1. Not including batch control/ testing Conditions: 1, 2 **IA** IAIN
2. Including batch control/testing Conditions: 1, 2, 3, 4 **IA** IAIN
Conditions: 1, 2, 4 ***IB***
Conditions:
1. The manufacturer responsible for batch release must be located within the EEA.
2. The site is appropriately authorised.
3. Product concerned is not a biological **or immunological** medicinal product **for human or veterinary use**.
4. Method transfer from the old to the new site or new test laboratory has been successfully completed.
5. Product concerned is not an immunological medicinal product for human or veterinary use.

Assessor's Comment:
Not Agreed.
Present: Change Nr.8b2 is classified as a type II for IVMPs because of Condition 3.
Proposed (alternative condition and classification): 1, 2, 4 IB): Change Nr.8b2 is classified as type IB.
The transfer of batch control/testing (including: in vivo assays) of an IVMP should remain classified as a major variation (type II).

Attention:
If Change Nr.8b2 as type IB will be accepted for a pharmaceutical biological medicinal product, an amended condition (5) should be added to exclude IVMPs as follows:
5. Product concerned is not an immunological medicinal product for human or veterinary use.
Conditions to be fulfilled: 1, 2, 5 IB.
Condition 3 should be amended as indicated:
3. Product concerned is not a biological or immunological medicinal product for human or veterinary use.

Change No 9*: No Comment*

10. Minor change in the manufacturing process of the active substance IB
Conditions:
1. No change in qualitative and quantitative impurity profile or in physico-chemical properties.
2. The product concerned is not a biological **or immunological** medicinal product **for human or veterinary use**. ~~active substance is not of biological origin.~~
3. The synthetic route remains the same, i.e. intermediates remain the same. In the case of herbal medicinal products, the geographical source, production of the herbal substance and the manufacturing route remain the same.

Assessor's Comment:
Change Nr.10 is not applicable for IVMPs.
Conditions 1 and 3 are not applicable to an IVMPs.
Condition 2 should be amended as indicated to exclude IVMPs.

11. Change in batch size of active substance or intermediate
a. Up to 10-fold compared to the original batch size approved at the grant of the marketing authorisation
Conditions: 1,2,3,4 (see below) **IA**
b. Downscaling Conditions: 1,2,3,4,5 **IA**
c. More than 10-fold compared to the original batch size approved at the grant of the marketing authorisation
Conditions: 1,2,3,4 **IB**
Conditions:
1. Any changes to the manufacturing methods are only those necessitated by scale-up, e.g. use of different sized equipment.
2. Test results of at least two batches according to the specifications should be available for the proposed batch size.
3. The product concerned is not a biological **or immunological** medicinal product **for human or veterinary use.** ~~active substance is not a biological substance.~~
4. The change does not affect the reproducibility of the process.
5. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.

Assessor's Comment:
Changes in the batch size of an IVMPs must be classified as Type II. Condition 3 should be amended as indicated.

12. Change in the specification of an active substance or a starting material / intermediate / reagent used in the manufacturing process of the active substance

a. Tightening of specification limits

Conditions: 1,2,3 (see below) **IA**

Conditions: 2,3 **IB**

b. Addition of a new test parameter to the specification of

1. An active substance Conditions: 2,~~4~~,~~5~~ **IA [IB]**

2. A starting material/intermediate/ reagent used in the manufacturing process of the active substance

Conditions: 2,4 **IA [IB]**

Conditions:

1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a Type II variation procedure).
2. The change should not be the result of unexpected events arising during manufacture.
3. Any change should be within the range of currently approved limits.
4. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

~~5. The active substance is not a biological substance.~~

Assessor's Comment:

Agreed. Change Nr.12 is a compilation of variations but a tightening of approved specifications or the addition of a new test parameter (no replacement!)does not have a potentially negative impact on the quality (potency) of an IVMP.

13. Change in test procedure for active substance or starting material, intermediate, or reagent used in the manufacturing process of the active substance

a. Minor change to an approved test procedure

Conditions: 1,2,3~~,5~~ (see below) **IA**

b. Other changes to a test procedure, including replacement or addition of a test procedure

Conditions: 2,3,4,5 **IB**

Conditions:

1. The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method); no new impurities are detected.
2. Appropriate (re-)validation studies have been performed in accordance with relevant guidelines
3. Results of method validation show new test procedure to be at least equivalent to the former procedure.
4. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.
5. The active substance, starting material, intermediate or reagent is not a biological substance.

Assessor's Comment:

Not agreed.

Change Nr.13b: The deletion of Condition 5 is invalid.

Change Nr.13a and 13b: Condition 5 must be maintained as indicated to exclude IVMPs because the described changes (except the addition of a test procedure) in (e.g. in vivo) test procedures can have a potentially negative impact on the approved quality, safety and efficacy of an IVMP.

Assessor's Comment:

Change No 14

Condition 4 should be amended as follows.

4 The product concerned is not a biological or immunological medicinal product for human or veterinary use

Change No's 15-16: ***No Comment***

17. Change in :

a. The re-test period of the active substance

Conditions: 1,2,3 (see below) **IB**

b. The storage conditions for the active substance

Conditions: 1,2 **IB**

Conditions:

1. Stability studies have been done according to the currently approved protocol. The studies must show that the agreed relevant specifications are still met.
2. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.
3. The active substance is not an immunobiological substance (vaccine strain or antigen)

Assessor's Comment:
Not Agreed.
Change Nr.17a: Not Applicable to active substances of IVMPs.
Change Nr.17b: Unacceptable proposal for IVMPs.
Condition 3 should be amended to exclude IVMPs as indicated:
3. The active substance is not an immunobiological substance (vaccine (production) strain or antigen).

18. Replacement of an excipient with a comparable excipient

a. The replacement leads to a change in the Summary of Product Characteristics

Conditions: 1, 2, 3, 4, 5 (see below) **IB**

b. The replacement does not lead to a change in the Summary of Product Characteristics

Conditions: 1,2, 3, 4, 5 ***IA***

Conditions:

1. Same functional characteristics of the excipient.
2. The dissolution profile of the new product determined on a minimum of two pilot scale batches is comparable to the old one (no significant differences regarding comparability cf. Note for Guidance on Bioavailability and Bioequivalence, Annex II; the principles contained in this note for guidance for medicinal products for human use should still be taken into account for veterinary medicinal products, if relevant). For herbal medicinal products where dissolution testing may not be feasible, the disintegration time of the new product is comparable to the old one.
3. Any new excipient does not include the use of materials of human or animal origin for which assessment is required of viral safety data. For excipients in a veterinary medicinal product for use in animal species susceptible to TSE, a risk assessment has been carried out by the competent authority.
4. The product concerned is not a biological medicinal product. ~~It does not concern a medicinal product containing a biological active substance.~~
5. Stability studies in accordance with the relevant guidelines have been started with at least two pilot scale or industrial scale batches and at least three months satisfactory stability data are at the disposal of the applicant and assurance that these studies will be finalised. Data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).

Assessor's Comment:
Not agreed
Replacement of a key excipient like the adjuvant of an IVMP results in principle in a new product (replacement is not an extension). The chemical structures of the adjuvant complex should be functional comparable (e.g. replacement of mineral oil by vegetable oil) in order to qualify the change as type II
Condition 1: The functional characteristics of an adjuvant are not sufficiently defined. The described change could have a potentially negative influence on the quality (potency, stability), safety and efficacy of the IVMP.
Condition 2: Not suitable for an IVMP.

19. Change in specification of an excipient

a. Tightening of specification limits Conditions: 1,2,3 (see below) **IA**

Conditions: 2,3 **IB**

b. Addition of a new test parameter to the specification

Conditions: 2,4 ~~,5~~ **IA [IB]**

Conditions:

1. The change is not a consequence of any commitment from previous assessments (e.g. made during the procedure for the marketing authorisation application or a Type II variation procedure).
2. The change should not be the result of unexpected events arising during manufacture.
3. Any change should be within the range of currently approved limits.
4. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

~~5. The change does not concern adjuvant for vaccines or excipient of biological origin.~~

Assessor's Comment:

Agreed. A tightening of approved specifications or the addition of a new test parameter (no replacement!) for an excipient, does not have a potentially negative impact on the quality (potency) of an IVMP.

20. Change in test procedure for an excipient

a. Minor change to an approved test procedure

Conditions: 1,2,3,5 (see below) **IA**

b. Minor change to an approved test procedure for a biological excipient

Conditions: 1,2,3 **IA [IB]**

c. Other changes to a test procedure, including replacement of an approved test procedure by a new test procedure

Conditions: 2,3,4,5 **IB**

Conditions:

1. The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method); no new impurities are detected.
2. Appropriate (re-)validation studies have been performed in accordance with relevant guidelines.
3. Results of method validation show new test procedure to be at least equivalent to the former procedure.
4. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.
5. Product concerned is **not** an excipient of an immunological medicinal product for human or veterinary use.

~~The substance is not a biological excipient.~~

Assessor's Comment:

Not Agreed

The described conditions are not suitable for IVMPs.

The nature and function of the excipients are not sufficiently described. Changes in the test procedures for adjuvant(s), and preservatives of an IVMP could have a potentially negative effect on the quality for release.

Condition 5 should be amended as indicated to exclude IVMPs:

5. Product concerned is not an excipient of an immunological medicinal product for human or veterinary use.

Change No's 21-23: *No Comment*

Change No 24

Assessor's Comment:

Condition 2 should be amended as follows.

2 The finished product is not a biological or immunological medicinal product for human or veterinary use

25. Change to comply with Ph. Eur. or with the national pharmacopoeia of a Member State

a. Change of specification(s) of a former non-European pharmacopoeial substance to comply with Ph. Eur. or with the national pharmacopoeia of a Member State

1. Active substance Conditions: 1,2 (see below) **IA [IB]**

2. Excipient Conditions: 1,2 **IA [IB]**

b. Change to comply with an update of the relevant monograph of the Ph. Eur or national pharmacopoeia of a Member State

1. Active substance Conditions: 1,2 **IA**

2. Excipient Conditions: 1,2 **IA**

Conditions:

1. The change is made exclusively to comply with the pharmacopoeia.
2. Unchanged specifications (additional to the pharmacopoeia) for product specific properties (e.g. particle size profiles, polymorphic form), if applicable.

Assessor's Comment:
This change has been written for starting materials and pharmaceuticals.
All changes to comply with revised general and specific monographs for veterinary and human IVMPs (vaccines and sera)and which involve the in house validation of new mandatory in vivo or in vitro should be excluded by adding Condition 3 as indicated:
3 The change does not include mandatory tests for an immunological medicinal product for human or veterinary use

Change No's 26-30: ***No Comment***

31. Change to in-process tests or limits applied during the manufacture of the product

a. Tightening of in-process limits Conditions: 1,2,3 (see below) **IA**

Conditions: 2,3 **IB**

b. Addition of new tests and limits Conditions: 2,4 **IA [IB]**

Conditions:

1. The change is not a consequence of any commitment from previous assessments (e.g. made during the procedure for the marketing authorisation application or a Type II variation procedure).
2. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.
3. Any change should be within the range of the currently approved limits.
4. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

Assessor's Comment:
Agreed A tightening of in process limits or the addition of new tests and limits do not have a potentially negative impact on the quality of an IVMP.

32. Change in batch size of the finished product

a. Up to 10-fold compared to the original batch size approved at the grant of the marketing authorisation

Conditions: 1,2,3,4,5 (see below) **IA**

b. Downscaling down to 10-fold Conditions: 1,2,3,4,5,6 **IA**

c. Other situations Conditions: 1,2,3,4,5,6,7 **IB**

Conditions:

1. The change does not affect the reproducibility and/or consistency of the product.
2. The change relates only to standard immediate release oral pharmaceutical forms and to non-sterile liquid forms.
3. Any changes to the manufacturing method and/or to the in-process controls are only those necessitated by the change in batch-size, e.g. use of different sized equipment.
4. Validation scheme is available or validation of the manufacture has been successfully carried out according to the current protocol with at least three batches at the proposed new batch size in accordance with the relevant guidelines.
5. ~~The product concerned is not a biological medicinal product. It does not concern a medicinal product containing a biological active substance.~~

The product concerned is not an immunological medicinal product for human or veterinary use
6. The change should not be a result of unexpected events arisen during manufacture or because of stability concerns.
7. Relevant stability studies in accordance with the relevant guidelines have been started with at least one pilot scale or industrial scale batches and at least three months stability data are at the disposal of the applicant. Assurance is given that these studies will be finalised and that the data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).

Assessor's Comment:
Not agreed.
Changes in the batch size of an IVMP must be classified as Type II. Condition 3 should be amended as indicated.
Neither the conditions nor the recommended documentation in the NoTA is applicable to IVMPs.
Condition 5 should be amended as indicated:
5. The product concerned is not an immunological medicinal product for human or veterinary use

33. Minor change in the manufacture of the finished product IA [IB]

Conditions:
1. The overall manufacturing principle remains the same.
2. The new process must lead to an identical product regarding all aspects of quality, safety and efficacy.
3. ~~The product concerned is not a biological medicinal product does not contain a biological active substance.~~ 3. The product concerned is not an immunological medicinal product for human or veterinary use.
4. In case of a change in the sterilisation process, the change is to a standard pharmacopoeial cycle only.
5. Relevant stability studies in accordance with the relevant guidelines have been started with at least one pilot scale or industrial scale batches and at least three months stability data are at the disposal of the applicant. Assurance is given that these studies will be finalised and that the data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).

Assessor's Comment:
Not agreed
Minor changes are not defined. Neither the conditions nor the recommended documentation in the NoTA is applicable for IVMPs.
Condition 3 should be amended as indicated:
3. The product concerned is not an immunological medicinal product for human or veterinary use

Change No's 34-36: *No comments*

37. Change in the specification of the finished product

a. Tightening of specification limits Conditions: 1,2,3 (See below) **IA**
Conditions: 2,3 **IB**
b. Addition of a new test parameter Conditions: 2,4,5 **IA [IB]**

Assessor's Comment:
Agreed. A tightening of the approved specifications or the addition of a new test parameter (no replacement!) because these changes do not have a potentially negative impact on the quality (potency) of an IVMP.

38. Change in test procedure of the finished product

a. Minor change to an approved test procedure
Conditions: 1,2,3,4,5 (see below) **IA**

b. Minor change to an approved test procedure for biological active substance or biological excipent
Conditions: 1,2,3,4,5 **IA [IB]**
c. Other changes to a test procedure, including replacement or addition of a test procedure
Conditions: 2,3,4,5 **IB**
Conditions:
1. The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method).
2. Appropriate (re-)validation studies have been performed in accordance with relevant guidelines.
3. Results of method validation show new test procedure to be at least equivalent to the former procedure.
4. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.
5. Product concerned is **not** an immunological medicinal product for human or veterinary use.

Assessor's Comment:
Not agreed:
Change Nr.38a and Nr.38b:
IA is not an acceptable classification of the described changes for IVMPs. The minor changes and the tests are undefined; any change could have a potentially negative impact on the approved quality, purity and safety of IVMP batches for release.

Condition 1 is not applicable to IVMPs.
An amended Condition 5 as indicated is necessary for change 38a to exclude IVMPs.
An amended Condition 5 should be added as indicated for change 38b to exclude IVMPs

Change Nr.38c:
IB is not an acceptable classification of the described change for IVMPs. The changes and tests are undefined; any change (except the addition of a new test procedure) could have a potentially negative impact on the approved quality, purity and safety of IVMP batches for release.
An amended Condition 5 as indicated is necessary for change 38c to exclude IVMPs.

The replacement of any test procedure of the finished product of an IVMP must be classified as a major change (type II) because the change of any test procedure could have a potentially negative impact on the approved quality, purity and safety of IVMP batches for release.

Condition 2: Too facile description. The tests (in vivo or in vitro), the type of (re)validation study and relevant guidelines should be specified to understand the impact of a change of a test procedure of batches of IVMPs for release.
Condition 3: The equivalence of a new test to the former test of a new test is not an unambiguous requirement and not applicable to for in stance the replacement of an in vivo potency test by an in vitro potency test. This is a major change (type II) and the tests are not equivalent.

Change No's 39-41: ***No Comments***

42. Change in :
a. The shelf-life of the finished product
1. As packaged for sale Conditions: 1,2,3 (see below) **IB**
2. After first opening Conditions: 1,2 **IB**
3. After dilution or reconstitution Conditions: 1,2 **IB**
b. The storage conditions of the finished product or the diluted/reconstituted product
Conditions: 1,2, 4 **IB**
Conditions:
1. Stability studies have been done according to the currently approved protocol. The studies must show that the agreed relevant specifications are still met.

2. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.
3. The shelf life does not exceed five years.
4. Product concerned is not an immunological medicinal product for human or veterinary use.

Assessor's Comment:
Change Nr.42a1,a2:
Remark:
This change requires an assessment by an expert familiar with the vaccine specific stability parameters (e.g. immunogenic potency, upper and lower limits.
Change Nr.42a3 is not a separate category mentioned in the stability section of the SPC for an IVMPs, relevant is the in-use stability for the always preceding Change 42a2: (after first opening)
Change Nr.42b:
Not agreed with the deletion of Condition 4. Condition 4 has to be amended as indicated, to continue to classify this change as major (Type II) for IVMPs because of the potentially negative impact on the quality or the approved (cor)relation between the product specific minimum potency and the claimed efficacy.

Change No's 43-48, New Change No´s 1 and 2: *No comments*

NEW 3. Replacement or addition of a new master seed virus for a veterinary vaccine against avian influenza, foot-and-mouth disease or bluetongue.
II
Assessor's Comment:
Major change: Type II classification or an Extension
The evaluation of the conditions depends on the result of the current consideration of the scientific and legal issues of the Multi Strain Dossier as part of the proposed change of Annex I of Directive 2001/82 as amended by Directive 2004/28 (no consolidated text available; according to the information given to delegates of the 2nd Annual Conference on Veterinary Vaccines, Cologne 3-5 December 2007 a consolidated text may be published at the end of 2008)

NEW 4. Replacement or addition of a new antigen or combination of antigens derived from approved master seed viruses in the case of a veterinary vaccine against avian influenza, foot-and-mouth disease or bluetongue.
II

Assessor's Comment:
Major change: Type II classification or an Extension
The evaluation of the conditions depends on the result of the current consideration of the scientific and legal issues of the Multi Strain Dossier as part of the proposed change of Annex I of Directive 2001/82 as amended by Directive 2004/28 (no consolidated text available; according to the information given to delegates of the 2nd Annual Conference on Veterinary Vaccines, Cologne 3-5 December 2007 a consolidated text may be published at the end of 2008)

NEW Change No´s 5-8: *No comment*