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Position paper

18 October 2019

AnimalhealthEurope comments to the EMA advice to the European Commission on the list of variations not requiring assessment

Implementing measures under Article 60 (1) of Regulation (EU) 2019/6 as regards the list of variations nor requiring assessment.

General comments

AnimalhealthEurope thanks the Commission for the opportunity to provide comments on this important implementing act. In particular, we wish to comment on how the EMA advice might be used in the preparation of the implementing act.

We have also taken the liberty to provide AnimalhealthEurope's suggestions for the implementing act and provide comments about closely related topics since these have the potential to have great impact on the final list of variations not requiring assessment. If there are any questions about our comments, please feel free to contact us.

We support the process used by the EMA in preparing the advice and that EMA used Article 60(2) criteria as the basis for determining the variations that do not require assessment.

The place for details is in guidance documents

AnimalheathEurope feels strongly that the implementing act should be prepared in a general, high-level manner to maintain flexibility in the future and minimise the need for revisions to the implementing act. To illustrate this more clearly, we attach here our AnimalheathEurope position paper with our proposal for the list of variations not requiring assessment. We recognize that the EMA advice discusses the need for an "Article 5" type process to add unforeseen variations to the list. Even with such a process a detailed implementing act written without looking to flexibility in the future will require revision more often than is practical. Instead, the details concerning the variations and their conditions and requirements are better contained in a corresponding guidance document (as also mentioned in the EMA advice).

If a general list is not the preferred format for the implementing act and a table similar to that included in the EMA advice is used instead, we contend that the table will need significant revisions and corrections, including for example, the final column in the table which can be replaced by a simple statement. Also, variations that clearly state that they apply only to human medicines are included and are not applicable for this implementing act for veterinary medicinal products. The table also will require additions of variations that were not included. The details of these are included in the specific comments that follow. However, most (if not all) of these issues would be avoided if a general, high-level list is adopted for the implementing act.

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Biologicals – all variations should not be excluded by default

The EMA advice assumes that variations to products having biological active substances should arbitrarily be treated differently (i.e., more stringently) than products with a chemical active substance. In fact, it is noted that for immunological products, no variations have been changed from the existing classification and added to the list of variations not requiring assessment. This is also not consistent with the distinction that is now made between immunologicals and other biologicals in the annex II of the Regulation. The perception is reinforced that everything other than pharmaceuticals needs to be assessed. If the variation does not require assessment as defined in Article 60(2), it should be on list regardless of the type of active substance. This is important for future products in which active substances may be something that does not fit the current classification of "chemical or biological".

Union Product Database should not be a limiting factor

AnimalheathEurope fully supports the statement in the EMA advice that "the practical management of variations not requiring assessment will depend on the functionality of the Union Product Database (UPD) for veterinary medicinal products". However, it is our firm belief and request, central to achieving the targeted reduction of administrative burden, that the list of variations not requiring assessment should not be restricted if the UPD that complies with Article 55 is not available. Instead, the list should be prepared, and the Implementing Act written to comply with the applicable requirements as set forth in Article 60(2). Alternative work-arounds for dealing with a UPD that is not fully functional/compliant when the new regulation comes into force could, if it becomes necessary, be suggested to avoid the need to limit the list of variations not requiring assessment in the implementing act.

GMP compliance – more such variations can be included on the list

In the current variations guidance (and consequentially, in the table included in the EMA advice) many variations are included that relate to GMP requirements for manufacturers and Marketing Authorisation Holders (MAHs). In those cases where GMP compliance systems already cover assessment of such changes, further scientific assessment by the competent authorities or the agency may not be necessary and thus should not be included in the implementing act list. The EMA advice reflects this principle, for example in the entries for changes B.II.c.1 z) and B.II.e.1 z) from 25.07.11, where excipient and packaging material testing frequency is stated to be a GMP issue and such details should therefore be deleted from the marketing authorisation by means of a previously unforeseen variation. The same idea can be applied to other changes already assessed by other compliance systems (such as GMP) and those changes can be included on the list not requiring assessment or considered not to be a variation at all.

Conditions and documentation requirements for variations on the list

The EMA advice seems to imply that current conditions and documentation requirements for variations on the list will simply be carried over and used for these variations under the new regulation. While these conditions and documentation requirements do not have a direct impact on the list of variations to be included in the implementing act, we urge that the accompanying guidance be written to require only the conditions and documentation that will be applicable under the new process of handling variations not requiring assessment, to avoid an increase in administrative burden for the applicant without a clear benefit.

Examples of current conditions/documentation that will likely not be needed are already available. The EMA advice on the UPD considers it as a 'Must' that the UPD uses organisations data from the OMS, implying an interconnection between the two systems. Consequently, the regulatory process for notifying the change in the name of a legal entity could be streamlined by only requiring an OMS

update and no additional submission of a Chamber of Commerce document to be checked for the marketing authorisation change (assuming of course, that any action other than the OMS update is needed at all).

Variation codes system

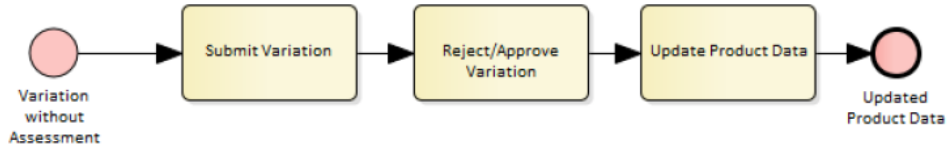
Such a code system is detail that is not necessary for the implementing act. We disagree that the existing variation codes system should be retained. As noted, after Regulation 2019/6 comes into force, the classification guidance will no longer apply to veterinary medicines. It will, however, continue to apply to human medicines. After veterinary and human medicines legislation is decoupled, the regulatory systems will surely diverge and there will be different needs for variations. As new variation codes are needed, retaining a common code system means the two industries will need to adopt codes that may not even apply or be needed – which will only add to confusion and complexity. In the future, human and veterinary medicine industries will have unique, separate legislation and even will have completely different ways of handling variations not requiring assessment – it does not follow that a common code system should be required. The final veterinary code system should be adapted to the final list of variations set forth in the implementing act, to the final UPD, and to other systems that may impact how the variations can most easily be referenced.

Additional recommendations and points to note

AnimalhealthEurope applauds the recommendation in section "Additional recommendations and points to note" stating 'the level of complexity of a variation requiring assessment should be reflected in the assessment timetable with a shorter timetable for less complex variations'. However, we do not feel that this should be used to determine if a variation is included in the list of variations not requiring assessment (i.e., a variation should not be left off the list only because it can be handled in an abbreviated variation procedure).

Process for RMS approval or rejection

For variations not requiring assessment, the new regulation only indicates a MAH shall "record the change in the product database" within 30 days after implementation. However, the regulation also indicates that competent authorities/the agency will notify if the variation is approved or rejected but it is unclear when this determination is made. When the EMA advice on the UPD is reviewed, and specifically the diagram on p.4 describing the business process applying to the 'without assessment', it appears that a two-stage process is being planned (see diagram from p. 4, below). Therefore, it seems that this will need to be clarified in the final Implementing Act that the 30-day timeline following the implementation of the variation for the MAH to record the change in the database applies to the 'submit variation' step and not to the 'Update Product Data' step.



More variations should be considered "not requiring assessment"

It is appreciated that the EMA advice reports an increase of variations not requiring assessment. However, the percentages given at the end of the "Concluding remarks" are relatively low and hardly traceable. But in any case, we urge every possible effort should be taken to reduce administrative burden (more variations being considered "not requiring assessment" but also to consider if any existing variations can be eliminated) and simplify the process for variations not requiring assessment.

Specific Comments

Page Number	Comment
2 and 3	In the Introduction on page 2, the second bullet mentions the classification guidance and includes the citation to the title as published on 16.05.2013. *'Guidelines on the details of various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures (2012/C/223/01)'* However, on page 3 in the 3rd paragraph starting "For the preparation of the recommendation…" it mentions, and has a link to, the former original version of the classification guidance. *'Classification Guidance on minor variations of type 1A minor variations of Type 1B and major variations of Type II'* It is unclear why the former version of the guidance was used.
3	"The current requirements for conditions and documentation in the variations Classification Guideline should be retained for all assessed and non-assessed variations with new and revised conditions for the type IB variations, which are now classified as not requiring assessment, being introduced. The wording of conditions and documentation requirements for some of the former type IA/IA_{IN} notifications should be clarified for ease of use." Comment: In light of this proposal, we recommend having the opportunity to review the list of conditions and documents and allow for improvements to be made before the proposed guidance is published.
4	As noted in the general comments, it was not considered that any current type II variation warrants inclusion on the list of variations not requiring assessment. For some variations of the existing guideline, being a biologicals/immunological substance leads automatically to a type II variation application while not always justified. Indeed, for some variations, the subcategories "the change refers to a biological/immunological substance…" does not always include the particular phrase "…which may have a significant impact on the quality, safety, efficacy of the product…" - for instance, variation B.I.a.1 All variations not requiring assessment should be on the list regardless of the type of active substance.
4	Changes that do not require variations: In the additional recommendations and points to note it is proposed to add reference to changes that do not require variations. This concept could apply to administrative changes that do not impact the product and for which the change is reported in the database without any need to validate or reject the change.
6	Change A.2.b - change in the invented name of the medicinal product for nationally authorised products - does not require any scientific assessment and thus, should be added. The administrative "assessment" required is not significantly different from that for a centrally authorised product.

6	Change A.4 should be applied to all excipients (where specified in the technical dossier); the word 'novel' can thus be deleted. Also, this change as applied to an ASMF (listed in the next row) and is not a new variation, but the change is in red text.
7	B.I.a.1 - The subcategories related to a change in the manufacturer of a starting material do not concern Immunologicals; the subcategory B.I.a.1.e) "The change relates to a biological active substance or a starting material/reagent/intermediate used in the manufacture of a biological/immunological product" of the current Variation regulation could be added in the list of variations without assessment, in case of equivalent and EP compliant starting materials for example.
7-8	B.I.a.2 - Immunologicals should be included in the sub-category B.I.a.2.a), "Minor change in the manufacturing process of the active substance" (indicated "n.a." for immunologicals in the table) as some changes of process can be considered minor even for immunologicals and these variations do not have negative impact on quality, safety or efficacy. The exclusion of Immunologicals is not justified for the following variations, which are now considered as variations without assessment: - a minor change in the manufacturing process of the finished product (B.II.b.3.a)) - a minor change of an analytical procedure for an in-process control (B.I.a.4.z)) - a minor change to an approved test procedure (B.I.b.2.a)) The same approach should be adopted for a minor change of process. Furthermore, these aspects are already assessed as part of GMP compliance programs.
8	B.I.a.2.e), Minor changes to the restricted part of ASMF should be included in the list since minor changes do not usually require scientific assessment.
8	B.I.a.3.e) The scale for a biological/immunological active substance is increased / decreased without process change (e.g. duplication of line) has not been considered in the list of variations without assessment, whereas it is currently considered as a type IB variation. In the case of this variation, there is no modification of process and no impact on product quality as the increase is only the consequence of a duplication of line; this does not require scientific assessment and should be considered in the list of variations without assessment.
9	B.I.b.1 i), Change in specification from in-house to a non-official Pharmacopoeia or a Pharmacopoeia of a third country should be included in the list. When appropriate conditions are met, the comparability of the Pharmacopoeial specification can be confirmed without a scientific assessment.
9	B.I.c.1 c), Change in immediate packaging of the active substance for a liquid active substance (non-sterile) should be included in the list. The documentation required for this current Type IB is essentially the same as B.I.c.1 a) – which is Type IA – and thus would not be expected to require a scientific assessment.
10	It is proposed to add the current IB variations which have not been retained in the list: • Change in the re-test period/storage period or storage conditions of the active substance where no Ph. Eur. Certificate of Suitability covering the retest period is part of the approved dossier. • B.I.d.1 a).4. Retest period / Storage period: extension or introduction of a re-test period/storage period supported by real time data • B.I.d.1 b).3. Storage conditions, change in storage conditions of the active substance

	Reasoning: These changes are based on real time data and are not subject to scientific assessment.
10, 17, and 22	B. I z), B.II z), and C.I z), these "new variations" have been included in the list to allow editorial changes if inclusion in an upcoming procedure is not possible. However, such editorial changes are not currently considered variations at all and should not be considered as variations under the new regulation. If, however, such a variation is determined to be needed, these are prime examples of where a general, consolidated list would allow one rather than 3 separate variations to be listed.
11	B.II.a.3 a) 1., Changes in the composition (excipients) of the finished product: addition, deletion or replacement of components of the flavouring or colouring system is currently a Type IA variation and, when appropriate conditions are met, is a minor change that does not require scientific assessment. While it has been announced that one or two Type IA variations were left off the list in the EMA advice due to previous experience of the NCAs/agency, such experience is not familiar to AnimalheathEurope for this variation. We request that this be included in the list in the implementing act.
11	B.II.b.3 f), Change in the manufacturing process of the finished product, including an intermediate used in the manufacture of the finished product - Minor change in the manufacturing process of an aqueous oral suspension should be included in the list. When appropriate conditions are met and documentation provided, such minor changes would not always require a scientific assessment.
12	B.II.b.4 b), Change in the batch size (including batch size ranges) of the finished product, down-scaling to 10-fold for the pharmaceutical form medicinal gas (issued 17.10.2016). It is unclear why this has been listed separately. This change is already included in the general description of the variation (as would be expected in the implementing act list). It would only need to be addressed in the future variations guidance by including the pharmaceutical form in the current guideline condition 2.
12	B.II.b.4 f), The scale for a biological/immunological medicinal product is increased / decreased without process change (e.g. duplication of line) should be included in the list. Similar to our comment for B.I.3 e), for this variation, there is no modification of process and no impact on product quality as the increase is only the consequence of a duplication of line. (Note: a general list as we propose would consolidate these specific changes into one variation in the list for the implementing act.)
12	B.II.b.5 z) from 27.09.10), Change to in-process tests or limits applied during the manufacture of the finished product. The text for the subcategory for this variation is a perfect example of why the table in the EMA advice cannot be used verbatim and a general list of variations not requiring assessment should be written. If included as written, this variation would only apply if an applicant also wishes to change hardness in-process limits from 65-85N to 45-85N.
13 and 15	B.II.c.1 z) and B.II.e.1 z), both from 25.07.11, are good examples supporting our general comment that assessments as part of GMP and other compliance systems can be used to avoid the need for NCAs/the agency to do an additional scientific assessment – or, as in these examples, delete the information from the dossier and thereby eliminating the need for variations. (Note: A general list as we propose would consolidate these 2 changes into one variation in the list.)
13	B.II.c.1 g), Change in the specification parameters and/or limits of an excipient, change in specification from in-house to a non-official Pharmacopoeia or a Pharmacopoeia of a third country should be included in the list. Similar to our comment for B.I.b.1.i), when applicable

	conditions are met, the comparability of the Pharmacopoeial specification can be confirmed without a scientific assessment. (Note: a general list as we propose would consolidate these specific changes into one variation in the list.)
13	B.II.c.2, There should be an additional change not requiring assessment for a change in method when the pharmacopoeial method used to control a non-pharmacopoeial excipient changes drastically and we are following that change e.g. the MLT to MET change that could not be covered by the "current edition of Ph. Eur. test" disclaimer.
13	B.II.c.3 a) 2., For excipients or reagents used in the manufacture of a biological / immunological active substance or in a biological /immunological medicinal product should be included in the list. A new change B.II.c.3. z) has been included in the list presumably because the change is to a material unlikely to present TSE risk and the same approach can be applied to B.II.c.3.a.2). The current documentation requirement for an equivalence study can be replaced by requiring a confirmation/declaration that the new excipient/reagent has no impact, thus eliminating the need for any level of scientific assessment.
13	B.II.d.1 a), Change in the specification parameters and/or limits of the finished product, tightening of specification limits. It is unclear why the second entry of this change (from 20.12.10) is included in the table. It seems that this somewhat specialized case is already included in the table – it is still a tightening of limits. (Note: a general list as we propose could consolidate all tightening of limits changes into one variation in the list.)
14 and 15	B.II.d.1 h) and B.II.d.2 f) included in the subcategory column is an "*" but this is not footnoted anywhere in the document (we recognize that this is a result of copy/pasting directly from the current guidance and the footnote concerns the explanation that no variation is needed when pharmacopoeia monographs are updated if reference is made to the current edition of the monograph). While this is valuable information, it is not pertinent to the list for the implementing act. If the table is used verbatim in the implementing act, these asterisks would cause confusion.
16	B.II.e.7 a) has a second entry including a recommendation from 22.11.10. However, it is unclear why this is included in the table since deletion of a supplier (as recommended) is already covered by the first entry for that variation.
16	B.II.f.1 b) 1., 2., 3., and 5, Change in the shelf-life or storage conditions of the finished product, Extension of the shelf life of the finished product. These changes should be included in the list. They apply to various aspects of the final product shelf-life that are currently classified as minor Type IB changes. All are based on real-time data or (in the case of biological/immunological products) on an approved stability protocol. Therefore, when appropriate conditions are met a scientific assessment would not be necessary. (Note: a general list as we propose would consolidate these for minor shelf-life extension changes into one variation in the list.). The title of B.II.f should also include bulk products.
18	B.III.1 a) 5., Submission of a new or updated Ph. Eur. certificate of suitability for a non-sterile active substance that is to be used in a sterile medicinal product, where water is used in the last steps of the synthesis and the material is not claimed to be endotoxin free should be added to the list. When appropriate conditions are met and documentation/confirmation provided, no scientific assessment would be required.
18	B.III.1 b) 5., Submission of a new or updated European Pharmacopoeial TSE certificate of suitability for an active substance/starting material/ reagent/intermediate/or excipient: New/updated certificate from an already approved/new manufacturer using materials of human or animal origin for which an assessment of the risk with respect to potential

	contamination with adventitious agents is required should be included in the list despite it being currently considered a Type II variation. If the submission of a new/updated CEP for materials of animal origin does not impact the conclusions of the viral and TSE risk assessment conducted for the IVMP, it can be considered that the risk related to the use of such materials is unchanged. This assessment should be available upon request from authorities. Furthermore, if a CEP is issued for the starting material of animal origin, it also means that the BSE/TSE risk has already been assessed by EDQM and that the compliance to EP and TSE regulations has been demonstrated and approved.
20	C.I.3 a) The description of this change was copied into this table with the text "…of human medicinal products…" although this advice is intended for an implementing act set forth in the new veterinary regulation. While this change number had been accepted by NCAs and the agency in the past, it has now been replaced by the C.I. z) change listed on page 21.
21	C.I.z As noted above this has been adopted for veterinary medicinal products in place of C.I.3 a) and is in common use now. Both are not necessary for the table. Also, this is not actually a new variation as the red text implies.
21	C.I.5 a), Change in the legal status of a medicinal product for centrally authorised products, for generic/hybrid/biosimilar medicinal products following an approved legal status change of the reference medicinal product should be added to the list. When appropriate conditions are met, a scientific assessment would not be necessary.
21	C.I.8 a) Introduction of, or changes to, a summary of pharmacovigilance system for medicinal products for human use. As indicated in the description, this variation applied to human medicinal products and thus, should not be included in the table. Another change from the current guidance mentioning human products (C.I.10) was not included in the table and consistency is needed.
21	C.I.9 a), b), c), and d) are all listed in the table separately but deal with DDPS which will no longer exist under the new veterinary regulation. It has been explained that the pharmacovigilance variations were included in the table (even though no DDPS will apply) to avoid forgetting them because the implementing act for pharmacovigilance is on a different time-line. We also understand that a supplemental EMA advice will be provided to address pharmacovigilance matters. However, Regulation 2019/6 (at Article 8, § 1. (c)) only mentions "a summary of the pharmacovigilance system master file" as part of the data to be submitted with the application. If one assumes that the system established for the veterinary pharmacovigilance master file will be separate from the product dossiers and that any change to the master file will be assessed separately under that system, the list of variations not requiring assessment can and should include only one pharmacovigilance related variation: Changes to the summary of the pharmacovigilance system master file.
22	C.II.2 b), Deletion of a food producing or non-food producing target species, deletion not resulting from a safety issue should be added to the list. Such deletions are usually made for administrative/business reasons and a justification only needs an administrative check to confirm it is not related to safety issue – thus, no scientific assessment is necessary.
22	The Art 5 recommendation-like process variation is new but is not included in the table as red text
6 through 22	If the decision is made to write the implementing act list in the form of the table in the EMA advice, the last 4 columns are not applicable to a list of variations not requiring assessment.