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Veterinary Medicines Division

Report on the joint EMA/HMA workshop on requirements for the authorisation of vaccines within the EU

Background and approach

On 25 March a joint European Medicines Agency (EMA)/Heads of Medicines Agencies (HMA) workshop was held at the EMA bringing together experts from national competent authorities and industry for exchanging views on requirements for the authorisation of veterinary vaccines in the EU. The aim was to explore how to improve the availability of veterinary vaccines whilst maintaining a high level of protection of animal and public health and the environment. In particular, the objective of the workshop was to consider if the current level of requirements and the way in which they are interpreted remains proportionate to the risks and benefits of this class of products. The workshop explored what constitutes an appropriate level of requirements, whether or not current requirements represent a disincentive to the authorisation of new vaccines, and to identify if a more in-depth reflection on this important topic was needed. A number of aspects were considered including reflecting on the degree of alignment between EU requirements and those of other regions (such as the USA) as well as on other measures that exist to make vaccines available in the event of need/in emergency situations and in the absence of authorised vaccines such as authorisation under exceptional circumstances, use of autogenous vaccines, etc.

The workshop was divided into three sessions. The morning session covered the requirements for marketing authorisation of vaccines in the EU, their impact on availability and the challenges faced by the industry, including Small and Medium sized Enterprises (SMEs). Short presentations were given by speakers representing regulatory authorities (EU and USA) including vaccine experts, the European Commission and industry. In the afternoon there were breakout sessions involving mixed groups of participants debating the main issues around vaccine availability and authorisation requirements. The meeting closed with a presentation summarising the key findings and recommendations of the meeting. The presentations given are available on the EMA website. The morning and closing sessions of the workshop were recorded and are available here.

Discussion and conclusions

The groups discussed a number of issues related to the impact of the existing legal framework on vaccine availability by exploring its different perspectives (i.e. scientific, regulatory, procedural, financial), the challenges the framework poses to regulators and industry, and whether or not it is considered to be sufficiently flexible. Other issues addressed included reflections on the factors that

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drive development and availability of vaccines and if current approaches address availability problems adequately, other particular areas that present challenges, and exploring potential measures that could stimulate the authorisation of more vaccines.

There was general agreement that there is lack of availability for products for Minor Use Minor Species (MUMS)/limited markets and that significant challenges remain in terms of ensuring that authorised vaccines against epizootic diseases are available in the event of emergency situations. In relation to major diseases, the situation was less clear-cut but there was an overall perception that fewer vaccines are available in the EU than in other major regions such as the United States. However it was not evident what impact this has on animal health. Regulatory authorities were of the opinion that if availability is to be promoted for this type of product, the outcome needs to be that more products are available in the market that benefit animal health by expanding the range of diseases that can be effectively prevented, and not just allowing onto the market an increased number of products of uncertain efficacy.

Industry representatives expressed the view that several aspects of the existing legal framework represent a particular challenge to companies seeking to authorise vaccines in the EU as compared to other regions. Prominent among these in their view are a lack of consistency in the approach to management and acceptance of risk and uncertainty, the level of technical requirements and the complexity of administrative procedures. Industry had prepared a tabulation and prioritisation of the factors that they consider constrain the availability of vaccines within the EU (see Annex 2).

The technical requirements for the authorisation of veterinary medicines, together with the available detailed scientific guidance (i.e. guidelines) for demonstrating compliance with these requirements, have led to the perception by some parties that requirements in the EU are higher than in other regions, acting as a disincentive to authorisation of these products within the EU. In that context, it was stated by industry representatives that the high development costs and time to market for veterinary vaccines in large markets as well as the lack of financial incentives for small markets make the EU less competitive compared to other regions. The entirely private nature of the veterinary sector and the lack of support from public health infrastructure services, as exists in the human health sector, mean that significant levels of investment are required from the veterinary industry to operate in the domain of veterinary vaccines.

The main challenges in relation to vaccines for emergency use were identified as the lack of an incentive for pre-epizootic investment together with the different data requirements that are perceived to apply at national level across the EU. In addition, industry stated that different risk management decisions are sometimes made for the same product based on the same or similar dossiers. It was noted that regulatory response times at European level are often slower in comparison to those made at national level. Although a direct comparison of requirements is not appropriate between emergency and routine situations, the workshop noted that a paradoxical situation exists with respect to vaccines against epizootic and endemic diseases. Vaccines against epizootic diseases for a particular region or geographic area, representing a high risk, are accepted based on lower emergency requirements with high tolerance to risk and uncertainty combined with quick decision making at national level. In comparison, vaccines against endemic diseases normally representing a lower risk are characterised by a defined high level of requirements, a lower tolerance to risk and uncertainty and slow decision making. The meeting noted that it may be helpful to develop an approach in which vaccines are grouped on the basis of inherent risk (live vs. inactivated), risk tolerance (companion animal vs. livestock) and need (endemic vs. epizootic). In a second step it may then be possible to tailor requirements and approaches to the particular groups of vaccines identified.

In terms of how much flexibility the existing guidelines provide, there were mixed views. Some expressed the view that there is not enough inherent flexibility whereas others considered that flexibility exists and guidelines are open to interpretation. The latter group highlighted instead the need for more harmonised interpretation and promotion of a pragmatic approach by both regulators and the industry. Considering the above, and in order to bring consistency in terms of assessment, there were suggestions to use the Network Training Centre to further enhance the training of assessors ensuring similar understanding and interpretation of the guidelines. In addition, possibilities should be explored for joint training between regulators and industry, as well as establishing other forms of cooperation that could result in achieving better understanding of issues and requirements. Industry offered to provide the network with practical examples of how guidelines have been applied based on actual experience.

A number of concerns and issues were voiced by the industry highlighting differences between the EU and other regulatory regions and the impact that these differences might have. Several speakers from industry spoke in favour of the phased approach to assessment carried out in USA whereby there is a step-wise approval process for the different studies in the dossier prior to final submission of the application for licensing. The industry considers that the requirement to demonstrate the correlation between serology and protection has to be more rigorously demonstrated in the EU as compared to other regions (i.e. requiring challenge trials to demonstrate duration of immunity, compatibility, etc.), impacting on the cost and time to authorisation. Industry therefore proposed that serology should be more readily accepted as a marker or surrogate of efficacy in the EU, if applicable and meaningful. Industry also advocated allowing more readily the use of field trials from other regions or the use of existing experience (pharmacovigilance) in countries where a product is already licensed in a submission for approval in a new country. This would act as a high incentive promoting better availability of vaccines, as the cost would be reduced. As an example, the industry stated that field efficacy trials are not required for products for food producing species in other regions (i.e. USA, Australia) provided that laboratory efficacy is adequately demonstrated, questioning whether a similar approach can be considered in the EU or whether such studies could be generated post-authorisation. In addition, independent input from experts in academia and research institutes could contribute in resolving some scientific questions in terms of what constitutes a proportionate level of data requirements and results for particular aspects of authorisation such as field efficacy trials, extrapolation of serology data and the usefulness of other biomarkers.

Industry cited the slow process for change of European Pharmacopoeia monographs as a concern and highlighted the demanding nature of certain monographs, particularly the efficacy requirements in some cases. Industry urged that better use be made of pharmacovigilance data to support existing authorisations and proposed holding early discussions with risk managers so that companies can address in advance any potential risks. Industry and regulators felt that there was scope to explore how remaining area of uncertainty could be addressed by making them more clear to the end user in the product literature (e.g. stating that the duration of immunity (DOI) is unknown when no DOI studies have been performed rather than the lack of such studies preventing authorisation). Industry also urged that consideration be made to developing a registry of approved vaccine strains.

Several speakers also highlighted a number of factors to consider in terms of improving availability and managing the risks related to the current situation. These included developing the concept of conditional marketing authorisations for special circumstances, harmonising the rules for manufacture of autogenous vaccines, post-approval follow-up of old vaccines, and exploring ways to move some requirements from the pre- to post-authorisation stage. Recognising that vaccine development is more and more carried out by SMEs, it is important to establish good communication links with SMEs and find a way to reach out to them, even before they are identified as potential developers of

veterinary vaccines. Furthermore, regulators proposed to reflect further on the possibility to develop positive incentive to authorisation of vaccines ('pull' incentives) such as advertising of vaccines to end users and allowing the sale of vaccines as part of clinical trials.

The current benefit risk assessment framework was also discussed and a number of proposals were made trying to address the extent to which this can be reshaped specifically for veterinary vaccines by making any data gaps more transparent, whilst also highlighting both the direct benefits gained from the authorisation of products as well as reflecting on any 'lost opportunity' risks from not authorising.

Based on the above it is clear that the issues affecting vaccine availability are complex and interdependent and therefore require a range of actions covering administrative and technical as well as scientific requirements. In addition, recent developments in technology and indications, such as vaccines against hormones and tumour antigens, mean that the 'classic' paradigm for vaccine authorisation may no longer be relevant in some cases. In order to improve availability without compromising high standards of protection of animal and public health, the actions required can be differentiated into those on which there is consensus and which can therefore be implemented immediately from those for which further reflection is needed in order to identify what actions are required and by whom.

Recommendations

The interactive session of the workshop engaged participants in discussions on various issues mentioned above relating to the availability of vaccines and to the level of requirements for their authorisation. The workshop identified several opportunities to be explored and further developed, and concluded with the following key recommendations:

1. Develop proposals to increase communication, cooperation and transparency in the development of scientific and administrative guidelines at early stages so that they better achieve the desired objective of increasing predictability without increasing requirements. In addition, explore the use of independent experts to provide independent scientific advice on specific topics or in situations where regulators and industry have expressed divergent views in order to agree on a proportionate level of data requirements, such as the use of serology as a surrogate marker for efficacy and the need for field efficacy trials for vaccines.
2. Identify and propose specific training for assessors to enhance consistency of assessment and share experience in order to define and promote an appropriate level of pragmatism in the interpretation of guidelines. Explore possibilities for joint training between industry and assessors to achieve better understanding of issues and requirements. Industry can add value by supplying examples for case-based training based on real situations.
3. Develop lists of diseases for which vaccines are not available, and therefore required, together with clear expectations of what would be needed for their authorisation such as where requirements could reasonably be reduced or where alternative approaches to risk tolerance or risk management would need to be developed. To develop such list it may be helpful to tailor requirements according to the characteristics of the vaccine (e.g. live vs. inactivated), the disease (epizootic vs. endemic) or the target species (companion animal vs. livestock) and to outline plans as to how to address unmet needs. The impact of this approach on the structure of the benefit risk assessment for vaccines should be explored taking into account the risk management approach.
4. Examine in more depth the list of factors prepared and prioritised that industry consider constraining the availability of vaccines within the EU.
5. CVMP should maximise the existing opportunity of the revision of the MUMS guidelines to explore reduction of data requirements for this type of product.
6. The opportunity of the current revision of the legislation governing veterinary medicines should be taken to reflect if there are lessons to be learnt from other regulatory areas in terms of the approach to assessment of vaccines and the level of requirements that should apply.

Next steps

The above recommendations, considerations and suggestions made during the workshop will be considered by EMA, through the CVMP, and HMA to decide if they could form the basis for a joint EMA/HMA action plan to improve the availability of vaccines within the EU. Subject to the agreement of EMA and HMA, the recommendations arising from the workshop will be developed into a series of short, medium and long-term goals. Through new workshops involving small numbers of experts from national competent authorities, CVMP and industry, the actions necessary to achieve each goal will be identified. The regulators will then decide on the implementers, milestones and timelines.

Disclaimer

The views expressed in this report are the views of the participating experts and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its Committees or working parties.

Annexes

Annex 1: Programme

Joint EMA / HMA Workshop on requirements for the authorisation of veterinary vaccines in the EU

25 March 2015, European Medicines Agency (EMA), London

PROGRAMME		
OPENING SESSION		**Chair: David Mackay**
9.00 – 09.05	Introduction and welcome	Andreas Pott
9.05 – 09.10	Setting the scene	Anja Holm
9.10 – 09.15	Introduction on the background, rationale and expected outputs for the meeting	Jean-Pierre Orand
9.15 – 09.20	European Commission - The risk manager's perspective	Agnieszka Kasperek
SESSION 1:	**Requirements for marketing authorisation of vaccines in the EU and impact on availability**	**Chair: Esther Werner**
9.20 – 9.40	**1.1 Review of requirements for vaccines in the EU and their evolution since the start of Community legislation on medicines**	Carmen Jungbäck
9.40 – 9.45	Moderated plenary discussion	All
	1.2 National experience of application of the requirements for marketing authorisations and other ways of making vaccines available	
9.45 - 10.05	Small MS's perspective	Jiří Bureš
10.05 – 10.25	Large MS's perspective	Jean-Claude Rouby
10.25 - 10.30	Moderated plenary discussion	All
	COFFEE BREAK (10.30 – 10.50)	
	1.3 Perspective on challenges meeting the requirements for authorisation of vaccines in the EU	
10.50 – 11.10	Industry perspective	Jacques Léchenet
11.10 – 11.30	Perspective of veterinary SMEs	Rhona Banks
11.25 – 11.30	Moderated plenary discussion	All

PROGRAMME		
	1.4 Requirements for vaccines in other regions	
11.30 – 11.50	Licensing requirements for vaccines: US perspective	Larry R. Ludemann
11.50 – 12.10	Requirements for vaccines in other regions of the world: Industry considerations	Vaughn Kubiak
12.10 - 12.15	Moderated plenary discussion	All
	LUNCH BREAK (12.15 – 13.30)	
SESSION 2:	**Setting data requirements as part of balancing benefits and risks when authorising vaccines**	**Chair: David John**
13.30 – 15.00	Breakout groups of mixed composition will discuss the following topics 1. To what extent can the challenges to availability of vaccines be addressed within the existing legal framework (not just MAs but also other ways)? 2. What are the particular areas that present challenges to industry and to regulators? 3. How to define and promote an appropriate level of flexibility and pragmatism in application of existing guidance? 4. What measures could stimulate the authorisation of more vaccines (reducing data requirements? If so, in what area? Other measures?)?	Groups
	COFFEE BREAK (15.00 – 15.20)	
SESSION 3:	**General discussion and conclusions**	**Chair: Anja Holm**
15.20 - 16.30	Feedback from the breakout session	Rapporteurs
16:30 - 17:00	General conclusions and recommendations addressing the question: 'Are requirements for marketing authorisation of vaccines in the EU proportionate to the benefits and risks of this type of product?'	David Mackay

List of speakers

Anja Holm	Danish Health and Medicines Authority; Chair of the Committee for Medicinal Products for Veterinary use (CVMP), EMA
Jean Pierre Orand	Head of ANMV – French Agency for Veterinary Medicines
Agnieska Kasperek	DG Sante – European Commission
Carmen Jungbäck	Head of Section Veterinary Virology 1 in the Veterinary Department at the Paul-Ehrlich-Institut (PEI), Germany; IWP member
Jiří Bureš	Institute for State Control of Veterinary Biologicals and Medicaments, Czech Republic; CVMP member
Jean-Claude Rouby	French Agency for veterinary medicinal products, France; CVMP member
Jacques Léchenet	Regulatory Affairs, MERIAL
Rhona Banks	Veterinary Biologicals Consultant at RA-Elect
Larry R. Ludemann	Section Leader, Bacteriology, Center for Veterinary Biologic, Policy, Evaluation, and Licensing - USA
Vaughn Kubiak	Responsible for Biological Regulatory Affairs, Zoetis Inc.

Session chairs

David Mackay	Head of Veterinary Medicines, European Medicines Agency
Esther Werner	Paul-Ehrlich-Institut - Chair of the CVMP Immunological Working Party (IWP-V) at European Medicines Agency
David John	Technical Manager at IFAH-Europe
Anja Holm	Danish Health and Medicines Authority; Chair of CVMP, EMA

Programme Committee

David Mackay	Head of Veterinary Medicines, European Medicines Agency
Anastasia Kesisoglou	Scientific Administrator, European Medicines Agency
Jean-Pierre Orand	Head of ANMV – French Agency for Veterinary Medicines
Anja Holm	Danish Health and Medicines Authority; Chair of CVMP, EMA
Esther Werner	Paul-Ehrlich-Institut - Chair of the CVMP Immunologicals Working Party (IWP-V) at European Medicines Agency
David John	Technical Manager at IFAH-Europe

Annex 2: Requirements for the authorisation of vaccines in the EU *(prepared by industry)*

No.	Suggestions for reductions	Grouping	Priority	BREAK-OUT SESSION NO.:	Example of over-regulation	Change required in			
						Directive; Regulations	EU GLs	Ph. Eur	Attitude
2	Abandoning field efficacy study requirement (restrict field studies to safety only), unless claim can only be proven by field efficacy study.	**CHANGES NEEDED IN DIRECTIVE (+/- EU GUIDELINES)**	1	4		X	X	X	
14	Easier acceptance of serology instead of challenge for efficacy studies. Clear protocol needed to determine when serology can be accepted a surrogate marker for efficacy	**CHANGES NEEDED IN EU GUIDELINES**	1	3	X		X		X
15	Associated use: acceptance of serology instead of challenge to proof lack of immunological interference, also if data on correlation between serology and protection are not available; in particular with regard to DOI	**CHANGES NEEDED IN EU GUIDELINES**	1	3	X		X		X
1	Reductions that can be clearly laid down in written rules, authorities and manufacturers can refer to equally well	**GENERAL**	2	1		X	X	X	
7	Reconsideration of presently proposed legislation (Directive Art. 119) for administrative procedure for (repeat-)MRP for older products: more acceptance of field experience as proof of product's quality/safety/efficacy	**CHANGES NEEDED IN DIRECTIVE (+/- EU GUIDELINES)**	3	4	X	X			
19	Acceptance of field studies from other geographical regions (acceptance of US data)	**ACCEPTANCE OF NON-EU STUDIES NOT FULLY COMPLIANT WITH EU RULES**	3	4		X ?			
23	(Restricted) extrapolation possible for setting maximum pre-inactivation titre	**CHANGES NEEDED IN PH. EUR.**	3	3			X	X	X

No.	Suggestions for reductions	Grouping	Priority	BREAK-OUT SESSION NO.:	Example of over-regulation	Change required in			
						Directive; Regulations	EU GLs	Ph. Eur	Attitude
28	Application of MUMS applications as intended, i.e. more flexibility and not requiring commitments for providing a full package later.	**CHANGES NEEDED IN ASSESSORS' ATTITUDE**	3	3,4	X		X		X
37	Improvement of assessment consistency, assessors' capacities to judge alternatives to guidance; by assessor training (joined training with RA managers ?), peer review	**CHANGES NEEDED IN ASSESSORS' ATTITUDE**	3	2					X
5	Step-wise submission: first package only containing quality data (with stability data for R&D batches), lab safety data, OOI efficacy data. Stability data of production batches, validation of QC tests, field safety data and DOI efficacy data to be provided in later phase(s).	**CHANGES NEEDED IN DIRECTIVE (+/- EU GUIDELINES)**	4	3,4		X			X
	Make SPC less complex, more straightforward. Limit to OOI and DOI. Do not provide details on field results, sero-negative/positive animals.	**CHANGES NEEDED IN DIRECTIVE (+/- EU GUIDELINES)**	4	3					
3	At license application, only stability data from R&D batches; further stability data to be provided later	**CHANGES NEEDED IN DIRECTIVE (+/- EU GUIDELINES)**	5	3		X	X		
11	GLP requirement only for single dose/overdose/repeated dose, increase in virulence and dissemination in animal studies	**CHANGES NEEDED IN DIRECTIVE (+/- EU GUIDELINES)**	5	4		X	X		
12	Acceptance of different methods of administration as targeting one route: o.n. (live poultry vaccines)	**CHANGES NEEDED IN EU GUIDELINES**	5	4			X		
18	Comparison of US and EU dossier requirements section by section and defining best practice	**ACCEPTANCE OF NON-EU STUDIES NOT FULLY COMPLIANT WITH EU RULES**	5	2					

No.	Suggestions for reductions	Grouping	Priority	BREAK-OUT SESSION NO.:	Example of over-regulation	Change required in			
						Directive; Regulations	EU GLs	Ph. Eur	Attitude
27	Benefit/risk assessment methodology that includes available data plus experience in other countries/regions with the product, which may substitute for lacking data.	**CHANGES NEEDED IN ASSESSORS' ATTITUDE**	5	3			X?		X
30	Acceptance of 1 vaccination for booster; no need to proof that 2 vaccinations are not necessary	**CHANGES NEEDED IN ASSESSORS' ATTITUDE. Change in Guideline.**	5	4	X		X		X
35	Not starting a re-evalution of old approved data when dealing with new changes	**CHANGES NEEDED IN ASSESSORS' ATTITUDE**	5	3			X ?		X
36	MRPs and repeat-MRPs not leading to reduction of originally licensed claims or new studies due to changed monographs (acceptance of original assessment)	**CHANGES NEEDED IN ASSESSORS' ATTITUDE**	5	3,4	X				X
13	Acceptance of cell-culture-derived antibiotic residues in vaccines (no animal/human health risk)	**CHANGES NEEDED IN EU GUIDELINES**	6	2,3	X		X		X
16	Simplification of requirements for strain addition/replacement (this includes GL for equine influenza vaccine strain update)	**CHANGES NEEDED IN EU GUIDELINES**	6	2	X		X		X
33	Acceptance of PV data to replace field efficacy when licensing older products in new countries	**CHANGES NEEDED IN ASSESSORS' ATTITUDE**	6	3			X ?		X
8	One instead of a group of variation categories for production transfers	**CHANGES NEEDED IN DIRECTIVE (+/- EU GUIDELINES)**	7	2,3	X	X			
10	Different level of requirements for companion *versus* food-producing animals (individual *versus* herd protection)	**CHANGES NEEDED IN DIRECTIVE (+/- EU GUIDELINES)**	7	3		X	X		X

No.	Suggestions for reductions	Grouping	Priority	BREAK-OUT SESSION NO.:	Example of over-regulation	Change required in			
						Directive; Regulations	EU GLs	Ph. Eur	Attitude
20	No absolute GLP requirement for laboratory safety studies (acceptance of US data)	**ACCEPTANCE OF NON-EU STUDIES NOT FULLY COMPLIANT WITH EU RULES**	7	4		X ?			
24	To subject the development sections of Ph. Eur. monographs to evaluation (some are too demanding; examples: Salmonella, fowl pox, ILT, coccidiosis, IB-inac.)	**CHANGES NEEDED IN PH. EUR.**	7	4				X	
31	For field studies in day-old chicks: no requirement to study both broilers and layer/breeders	**CHANGES NEEDED IN ASSESSORS' ATTITUDE**	7	4					X
34	More use of PV data to support product's efficacy	**CHANGES NEEDED IN ASSESSORS' ATTITUDE**	7	3			X ?		X
38	Investigation of pros and cons of the use of Vaccine Antigen Master File	**NO CHANGES NEEDED**	7	2,3					
9	Establishment of pan-EU legislation/regulation for autogenous vaccine	**CHANGES NEEDED IN DIRECTIVE (+/- EU GUIDELINES)**	8	2,4	**under-regulation**	X	X		
21	No sterility required for non-injectables (for avian as well as other species)	**CHANGES NEEDED IN PH. EUR.**	8	1,4	X			X	
4	Conditional licensing as standard system	**CHANGES NEEDED IN DIRECTIVE (+/- EU GUIDELINES)**	9	3,4		X	X		X
17	Reduced safety and efficacy requirements for cell line replacement if FPC requirements and results remain the same (EMA/CVMP/IWP/37620/2014)	**CHANGES NEEDED IN EU GUIDELINES**	9	2,3,4	X		X		
22	Abandoning absolute sterility requirement for wing web vaccines (otherwise no product anymore; too high costs)	**CHANGES NEEDED IN PH. EUR.**	9	4				X	

No.	Suggestions for reductions	Grouping	Priority	BREAK-OUT SESSION NO.:	Example of over-regulation	Change required in			
						Directive; Regulations	EU GLs	Ph. Eur	Attitude
26	Leave GMP-related subjects/issues to GMP inspectorates	**CHANGES NEEDED IN ASSESSORS' ATTITUDE**	9	2					X
29	More priority/better acceptance for 3Rs-based changes proposed by MAHs	**CHANGES NEEDED IN ASSESSORS' ATTITUDE**	9	3					X
32	Use of PV data not only for increase but also for decrease of safety warnings	**CHANGES NEEDED IN ASSESSORS' ATTITUDE**	9	1					X
8	Establish a Vector Vaccine Regulatory Platform for vector vaccines that are build the same way but where you change the inserted gene(s); this could be established for changes of the same gene from a more recent strain (updates: AI, Bluetongue) or going further depending on the vector for any changes, once the vector is accepted.	**CHANGES NEEDED IN DIRECTIVE (+/- EU GUIDELINES)**	10			x			
25	Exclude IVMPs from QP Declaration requirement	**CHANGES NEEDED IN ASSESSORS' ATTITUDE**	11	3			X ?		X
41	No omission of reduced sampling requirements for sterility test from Ph. Eur. monograph 0062	**NO CHANGES NEEDED**	11	2				X	
6	Abandoning sunset clause	**CHANGES NEEDED IN DIRECTIVE (+/- EU GUIDELINES)**	12	3,4					
39	Extraneous agents testing only on starting material (e.g. seeds), not as in-process controls (e.g. on antigen harvest, control cells)	**NO CHANGES NEEDED**	12	2					
40	Ongoing stability data to be provided for actual shelf life, not for shelf life + 3 months	**NO CHANGES NEEDED**	12	2					