13 October 2016
EMA/326293/2015
Committee for Human Medicinal Products

Overview of comments received on 'Draft guideline on influenza vaccines: non-clinical and clinical module ' (EMA/CHMP/VWP/457259/2014)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	European Centre for Disease Prevention and Control (ECDC)
2	IFAPP (International Federation of Associations of Pharmaceutical Physicians and Pharmaceutical Med)
3	Medicines Evaluation Board in The Netherlands
4	PPD Inc
5	Trombetta Claudia, Piccirella Simona, Lapini Giulia, Perini Daniele, Montomoli Emanuele (University of Siena and/or VisMederi srl, Enterprise in Life Sciences)
6	Vaccines Europe
7	Therapeutic Goods Administration, Australia

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. General comments – overview

Stakeholder no.	General comment	Outcome (if applicable)
ECDC	ECDC welcomes the new Guideline on influenza vaccines: non-clinical and clinical module addressing regulatory requirements for new seasonal, pandemic, and zoonotic influenza vaccines and updated seasonal influenza vaccines. ECDC notes that the Draft Guideline in its chapter 5.2.3 addressing requirements for influenza vaccines – scientific aspects, strongly recommends the use of the ECDC case-control study protocol to conduct vaccine effectiveness studies for seasonal and pandemic influenza vaccines. Further, if this study design is not feasible other study protocols may also be used, e.g. the cohort study protocol also published by ECDC. ECDC has in collaboration with its Influenza Monitoring Vaccine Effectiveness (I-MOVE) network of researchers in EU/EEA Member States acquired significant experience using the two study protocols and agree with the proposal to use these for future product-specific vaccine effectiveness studies. ECDC is exploring possibilities to support conducting product-specific vaccine effectiveness studies for seasonal and pandemic influenza vaccines and will continue the close collaboration established with EMA on this issue.	Noted
MEB Netherlands	Non-clinical The general structure of the guideline is strongly supported. Under 4 "*Applications for influenza vaccines: dossier requirements*" the specific requirements per vaccine are given, whereas under 5	Noted

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	"*Requirements for influenza vaccines the scientific aspects*" have been spelled out. From a non-clinical point of view MEB's comments are focussed on the scientific aspect, section 5.	
MEB Netherlands	Clinical The current draft guidance on influenza vaccines gives a comprehensive overview of the data needed for registration of the different influenza vaccines. The current scientific knowledge is clearly presented. Where possible recommendations to manufacturers are made, in other cases manufacturers are referred to the regulators for specific advice.	Noted
University of Siena	University of Siena (Molecular Epidemiology Laboratory) and VisMederi srl welcome the opportunity to comment on "guideline on influenza vaccines". The main purpose of comment and suggestion is to improve the standardization of the assays to evaluate a vaccine. Standardization includes validation of the assays, reagents, laboratories and methods used to assess the data. We would like also to highlight the value of Single Radial Haemolysis (SRH) assay in serological field as an established technique, particularly after the appearance of zoonotic avian influenza viruses. Other studies on neuraminidase and antibody kinetics needs to be further improved and supported in order to achieve a better and more comprehensive evaluation of vaccines' immunogenicity.	Noted
Vaccines Europe	Vaccines Europe thanks EMA for the opportunity to provide comments on the EMA draft Guidance on influenza vaccines –Non-	

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	clinical and Clinical module" (EMA/CHMP/VWP/457259/2014) Our general comments regarding the matter of vaccine effectiveness studies are as follows: 1. Vaccines Europe considers that "type " (e.g. non-adjuvanted trivalent vaccine) vs "brand" specific effectiveness data would improve the feasibility of addressing the guideline requirements in the current environment and existing infrastructures (see below the feasibility considerations to collect brand data). In addition, this would be better aligned with the current scientific questions related to influenza vaccine effectiveness 2. Collecting vaccines effectiveness data would require close collaboration with public authorities. Therefore Vaccines Europe suggests that more consideration is given to the role of the public health agencies currently performing surveillance to establish stronger collaboration between EMA and them. In addition, consideration should be given to the current limitations of collaboration between pharmaceutical industry and public health agencies making it difficult to establish public private collaborations. There should be acknowledgement that these studies will be impossible to implement without support of national and supranational public health authorities 3. Vaccines Europe supports the Vaccine Working Party recommendation, given at the meeting on Nov 27th 2014, where it was said that this guideline will only refer to vaccine effectiveness methodological requirements and that an agenda will be set up separately between the different	1. Difficulties in collecting brand-specific effectiveness data in the current environment and existing infrastructure are acknowledged, however brand-specific data are required from a regulatory perspective in view of benefit/risk considerations, which are product-specific. 2. The elements mentioned are acknowledged. 3. noted

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	stakeholders to roll out a Public Private Partnership platform, which will be tasked with supervising the collection of these data 4. The text should better clarify the objective of generating this data. It is Vaccines Europe's understanding that this data would be used from a public health point of view to increase knowledge on the performance of the vaccine and not necessarily have a regulatory impact 5. In the Guideline, broad vaccine effectiveness framework requirements are established for manufacturers. How will it be determined that manufacturers' proposals are acceptable in meeting these requirements and that no additional request will be raised by reviewers (such as reference Member States), on a case by case basis, leading to inequity in proposal review? <u>Feasibility considerations</u> 1. The number of subjects needed each year to evaluate brand-specific effectiveness is very high, and currently, existing networks are not able to collect such high numbers. In the 2012-13 influenza season the iMOVE project recruited almost 800 GPs in 7 countries for a total study population of almost 6500 subjects, but despite the operational scale across multiple countries, the conclusion of the report was that the sample size was too small to allow analyses across age or even at a vaccine type level, let alone brand 2. The tender market in many EU countries is such that it is not possible to know sufficiently in advance where a given vaccine will be used in time to set up an effectiveness	4. The text has been clarified. 5. As MSs have endorsed the guideline, it is expected that it will equally apply to NAPs. <u>Feasibility considerations</u> noted, the guideline has been modified.

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	evaluation and ensure that information is captured for all brands each season. 3. Given the distribution of influenza vaccines in Europe with relatively low vaccination rates and a market fragmented between many different manufacturers and different brands, Vaccines Europe believes that any single manufacturer cannot conduct sound brand specific effectiveness studies 4. The cost and feasibility of conducting a vaccine effectiveness study annually will be challenging, particularly for smaller pharmaceutical companies where a significant increase in costs could result in a less than favourable business case for marketing in the EU 5. Vaccines Europe supports the guideline's consideration that "*data from other regions may be acceptable if extrapolation to the EU population can be justified'*. For companies with a small market share in Europe, it will be important to maintain flexibility and be able to conduct effectiveness studies outside of the EU *6.* Several seasons are probably required in order to collect sufficient cases to estimate brand specific vaccine effectiveness with a reasonable confidence interval. An approach in which the data of the new season is combined with that of previous seasons on a strain level would be considerably more informative, and more in line with the spirit of the new guidance (effects of strain changes, etc.) 7. It is understood that age and other subgroup differences will be assessed and taken into account by stratification of the analysis of the vaccine effectiveness but studies will NOT be	

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	powered for subgroup specific estimates. This applies also for subtype specific analyses. What stratification is the most important: age, strain or brand?	
	Public health perspective 1. Vaccine effectiveness is a result of the combination of various factors: product characteristics, vaccine program/recommendations, herd immunity, seasonal strain coverage, etc. The non-product related factors can lead to significant differences in vaccine effectiveness while there may be no difference within a similar setting. Conversely, these factors can also limit the ability to show actual differences in vaccine effectiveness between different types of vaccines where these differences are expected. This should be highlighted in the guidance.	Public health perspective 1. Accepted.
	2. Investigation of vaccine effectiveness should be routinely performed, understanding that this effectiveness can vary over time based on various factors. Is it practical or realistic to have an open ended annual vaccine assessment? If a consistent picture about brand specific VE emerges after 5 years, would brand specific estimates or annual estimates continue to be needed?	2. Vaccine effectiveness should be routinely evaluated as a monitoring tool of vaccine performance over the years in light of annual changes in vaccine composition. This is without prejudice of future discussions at CHMP based on what will be learned.
	3. How will severity of the clinical endpoint be taken into account when considering vaccine effectiveness estimation? For example 30% VE against influenza hospitalization is not equivalent to 30% VE against medically attended influenza outpatient visits.	3. Noted, no need of entering into details deemed necessary at this stage.
	4. Mid-season estimates are not feasible due to logistical challenges (centralised testing by batch, time for data entry	4. Partly accepted, text modified to allow some flexibility.

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	and analysis, quality control, etc.)	
Vaccines Europe	**SCOPE OF THE GUIDELINE** Vaccines Europe would like to confirm its understanding that this guideline: • Will apply to: – New clinical/non-clinical Variations to existing MAs (for which development has not yet started) – New MA Applications (But transition phase should be foreseen to allow completion of on-going development programmes – see below) • Will not apply to: - Existing MAs - On going developments (N.B. studies that are part of on-going development programmes have been designed according to the established criteria)	Accepted The guideline also applies to existing MAs with regard to post-authorisation requirements, e.g. annual strain update. As for ongoing developments, a pragmatic approach may be considered on a case by case basis. If critical issues are anticipated by companies, it is recommend that scientific advice is sought or that the Agency is contacted as soon as possible.
Vaccines Europe	**CLINICAL SEROLOGICAL TESTING** Vaccines Europe has major comments with clinical serology testing: Number of serological assays (HI, SRH, VN, CMI, anti-NA, …) • Guideline too open on number of assays to be used, long term storage of samples and possibility of retesting. • Unclear whether expectation is that all tests should be carried out for licensure purposes, or whether some are only	Partly accepted. The guideline was modified to clarify the choice of assay to be used and expectations. Concerning long term storage and retesting, it was not considered possible to be more prescriptive than what is currently proposed.

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	"recommended" (i.e. for exploratory scientific investigation) • Unclear whether all tests are required in all subjects and in all age ranges • Recommendations: – EMA should select one preferred assay for licensure – Guideline should be more explicit on intended use of blood sera and CMI testing for the purposes of understanding vaccine responses. Questions/Concerns about the relevance/added value: • Added-value of carrying out <u>all</u> of the tests listed in the guideline? • Not clear how to interpret results (no threshold of protection) • Ethical considerations for children: • Amount of blood samples required, Number of tests, Long term storage of blood samples and possibility of Retesting • This might create conflicts with process of informed consent of subjects. *(N.B. informed consent documents, expected to document intended use of blood samples)* • Feasibility and relevance of certain tests is questionable; • e.g. CMI: • No standardized assay and no correlation between	Given the assay variability and the differences among assays, it is considered that there is added value from conducting different assays, e.g. proving consistency across testing. It is not possible, based on the current knowledge and the need for further research into correlates of protection, to indicate a strict antibody threshold for regulatory purposes, which should be proposed and discussed by the Applicant. Children: difficulties with testing in children are acknowledged. However it is considered that this data is needed.

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	CMI and clinical efficacy • Difficult to perform in children "Single Designated Laboratory" for all HI and SRH assays : Although it would be ideal, this is not possible in practice: • unrealistic since clinical development can take 5-10 years • lab workload sometimes unsustainable and tests have to be contracted out to other labs, • not feasible for global development (e.g. some countries like China require testing lab in their country) Persistence studies / follow-up • Should not be a criteria for licensure • The benefit of assessing 12 months persistence for seasonal vaccines is questionable (persistence studies for 6 months would already give meaningful information for a vaccine against seasonal influenza) • Unclear: o in which age groups persistence studies are expected? o which assays are expected to be carried out? o would persistence studies be expected in population subset(s) only? • Conducting persistence studies are challenging due to subjects leaving the study (hence can no longer be followed)	The comments on the single designated laboratories are partly accepted. The guideline was modified to clarify and allow some flexibility. Partly accepted. The guideline was modified to clarify the cases for which the provision of persistence data is considered of particular interest, and when this data should be obtained.

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	→ would require initial recruitment of larger numbers of subjects to compensate.	
Vaccines Europe	**CLINICAL REQUIREMENTS** Vaccines Europe would like to seek further clarification regarding the recommendation of studies in subsets: • Unclear recommendations re. immunological testing parameters – Rationale for requesting VN assays in all studies and all subjects? (N.B. If several studies conducted in the same age population, then VN in ALL studies and ALL subjects would represent redundant testing in all subjects) → wording should be adapted (e.g. "representative subsets" of the population intended for use) • Unclear recommendations re. studies in subsets of populations (e.g. immunocompromised)	Not accepted. The guideline was considered sufficiently clear.
Vaccines Europe	**IMMUNOGENICITY CRITERIA FOR APPROVAL** • The new guideline moves away from the current "CHMP criteria" – As the draft guideline is not specific regarding the criteria for assessing immunogenicity endpoints, will previously mandated endpoints still be acceptable? – Not clear what the criteria for MA approval will be in the future – Guideline requires *"pre-defined and appropriately justified*	It is not possible, based on the current knowledge and the need for further research into correlates of protection, to indicate a strict antibody threshold for regulatory purposes, which should be proposed and discussed by the Applicant.

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	threshold level" for immunogenicity studies : → Unclear o How companies are expected to justify threshold levels? o Consistency of threshold levels across manufacturers?	
Vaccines Europe	**NON CLINICAL REQUIREMENTS** Vaccines Europe has major comments wrt to non-clinical requirements: • Non-alignment between EMA guideline and WHO guideline in particular: – Investigation of risk of immunological toxicity, hypersensitivity reactions and autoimmunity reactions (no models available, no recommendations can be made at this time regarding specific nonclinical studies to be conducted) – Interval between doses for repeated dose toxicity studies (a 3-4 week interval as indicated in the EMA guidance will considerably impact timing for completion of studies) • Not realistic to request MAH's to use the same strain for Non clinical testing and Clinical testing • Many of the requested non clinical endpoints (CMI, Th1/Th2, Antibody persistence etc.) are of limited predictability for humans Non-clinical section 5.1 should be specific on what is expected for	Accepted.

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	each type of vaccine *(i.e. trivalent seasonal, quadrivalent seasonal, adjuvanted, zoonotic, pandemic, etc.)*	
Vaccines Europe	**CLINICAL EFFICACY: CLINICAL ENDPOINT** Vaccines Europe acknowledges and is very pleased to see that EMA offers some flexibility to discuss potential alternative efficacy endpoints. • Acceptance Criteria – Need to define acceptance criteria for absolute and relative non-inferiority efficacy trial design. • Conduct of efficacy studies – Not feasible to conduct efficacy studies by age and by sub populations or risk groups (for ethical or sample-size reasons) – Inclusion of subjects in pivotal efficacy study stratified by condition compromise overall results • Immunogenicity and efficacy requirement for MAA for seasonal inactivated vaccines in paediatric populations: – EMA should make clear that an efficacy study in older paediatric population (3- 9y) will not be requested if results of efficacy study in the 6-36 mths population are not conclusive. – Unclear what the impact will be on SmPC for 3-9y population if efficacy study in 6-36 mths population is not conclusive	Partially accepted. It is considered that the guideline should not define a priori the non-inferiority margins for efficacy trial (guideline modified) Partially accepted. The stratification into age categories or other subgroups is recommended in order to ensure that a representative cross-section of the population is studied. However it is not expected that the study is powered to demonstrate efficacy in subgroups (guideline modified). Partially accepted. The guideline has been modified for improved clarity but it is not possible to define a priori recommendations for cases where efficacy trials in the 6-36 month-olds are inconclusive.

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		Not accepted. as above.
Vaccines Europe	**CORE SmPC/PL** • As announced in the EMA's *'Explanatory note on the withdrawal of the Note for guidance on harmonisation of requirements for influenza Vaccines and of the core SmPC/PL for inactivated seasonal influenza vaccines '*: – The CHMP and the CMDh agreed that the core SmPC and PIL should be withdrawn from the CMDh website – Unclear <u>when</u> this new guideline will be final and effective – Further guidance is needed on practical implementation – Position from VE: Core SmPC <u>should remain applicable at least</u> for the next NH campaign (2015-2016), given time constraints: – Hence too late to submit necessary SmPC variation with an expected approval in time for upcoming vaccination season. • The draft Explanatory Note indicated that « further recommendation from EMA shall include a listing of the most relevant standard statements and warnings that can still be considered applicable to all influenza vaccines" – VE would like to receive some recommendation from EMA on this matter. VE queries whether standard wording will still be acceptable for certain sections of the SmPC	The Clinical and non-clinical Module of the revised influenza guideline will become effective 6 months after publication It is not expected that MAHs of existing vaccines revise the SmPCs due to the withdrawal of the core SmPC. Approved SmPCs should from now on be tailored to product-specific data as new data become available. The Explanatory note is replaced by the Guideline on Influenza Vaccines Non-clinical and Clinical Module

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Vaccines Europe	**STRUCTURE AND USER FRIENDLINESS OF THE GUIDELINE** Guideline is complex to read and assimilate due to unclear structure (e.g. some repetitions between sections 4 'dossier requirements' & 5 'scientific aspects', etc.). Vaccines Europe suggests to re-structure: • section 4 as 'Non clinical' (with sub-headers 4.1 'dossier requirements' and 4.2 'scientific aspects') section 5 as 'Clinical' (with sub-headers 5.1 'dossier requirements' and 5.2 'scientific aspects')	Accepted.
Vaccines Europe	**REQUIREMENTS FOR APPLICATION TO CHANGE VACCINE COMPOSITION** Can EMA clarify/define 'change vaccine composition'. To which changes is reference made? - Only HA strain changes and not excipient/adjuvant system/residuals & contaminant changes? - If only HA strain changes: is reference made to changes of strains within the same subtype of pandemic strains (e.g. changes of the H5N1 clade, e.g. Vietnam to Indonesia)? - Or would HA strain changes also cover changes in pandemic strain with different subtypes of pandemic strains (e.g. HA strain changes from H5N1 to H7N9, etc)? Vaccines Europe understands that no GLP tox studies will be required for such a 'change in vaccine composition' in this draft EMA guideline. Proposed change: Please clarify throughout the guideline and make it	Accepted.

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	consistent	
Vaccines Europe	**Term "similar construct":** Can EMA clarify/define 'similar constructs'. How is this defined? (see also comment on Section 4.1 - Line 134) See also line 158-160: does this mean similar manufacturing process? 'Similar' needs to be defined. Also, in the following sentence: *"The authorisation of a new inactivated non-adjuvanted seasonal influenza vaccine that is manufactured and has a final HA content similar to that of an EU-authorised inactivated non-adjuvanted vaccine may be based on comparative studies of safety and immunogenicity in some population sub-groups as detailed below."* " Final HA content to be clarified (comparison QIV vs TIV)?	Accepted.
Vaccines Europe	**Enhanced surveillance of vaccine safety:** With regard to enhanced safety there is a current discussion between EMA/VWP/PRAC and MAH thus the most recent outcomes of this discussion should be taken into account.	Noted.
TGA Australia	The TGA submits that: -a proposed requirement that each seasonal influenza vaccine product should have annual vaccine-effectiveness studies may under-rate the methodological and logistic challenges involved; -that the requirement for product-specific vaccine effectiveness studies for seasonal vaccines is not included in the protocol recommended in the draft Guideline may lead to confusion on the	Noted. As already stated above, difficulties in collecting brand-specific effectiveness data in the current environment and existing infrastructure are acknowledged, however brand-specific data are required from a regulatory perspective in view of benefit/risk considerations, which are product-specific.

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	part of manufacturers and regulators. Background. The TGA notes that the Guideline states in Section 4.2 Clinical requirements, subsection 4.2.1: Requirements for applications to change vaccine composition (seasonal strain update): “In principle, there is no need to provide clinical data to support seasonal strain updates. Vaccine performance should be monitored by means of product-specific effectiveness studies and enhanced safety surveillance that should be included in the RMP. The reactogenicity profile of influenza vaccines after annual strain updates should be investigated in the population indicated for each vaccine (including children if applicable) in order to confirm acceptable tolerability of the newly recommended strain(s).” This section cross-references to: Annex I on Enhanced safety surveillance; Section 5.2.3 on Vaccine effectiveness; Section 5.2.5 on Post-authorisation pharmacovigilance requirements. The EMA, in response to a TGA enquiry, confirmed that “product-specific” relates to products of individual manufacturers. “Product-specific” would seem to be generally synonymous with “brand-specific”. The TGA notes that the “ Section 5.2.3 Vaccine effectiveness” states that “Considering the diversity of seasonal influenza vaccines (trivalent and quadrivalent vaccines, split, subunit and whole virion	

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	vaccines, egg or cell culture derived vaccines, virosomal vaccines and vaccines with and without adjuvants), product-specific effectiveness data are necessary" and should be included in the RMP. The proposed Guideline strongly recommends the use of the European Centre for Disease Prevention and Control (ECDC)Protocol for case-control studies to measure pandemic and seasonal influenza vaccine effectiveness. The TGA notes that while the ECDC protocol requires the collection of brand name of vaccine for seasonal vaccine studies there is a contrast between the prescribed analyses of studies of pandemic and seasonal vaccines. For pandemic vaccine the protocol's Analysis and Stratified Analysis sections include analysis by vaccine brand. These sections do not require analysis by vaccine brand for seasonal vaccines. The TGA is of the view that studies of the vaccine effectiveness of individual brands of seasonal vaccines are desirable, but there are practical barriers, especially where multiple brands are used within a geographic region. Case-control studies of vaccine effectiveness using a methodology similar to that in the ECDC protocol have been conducted in Australia. In a recent study report the investigators noted that there were six different trivalent inactivated influenza vaccines licensed in Australia in 2012. Data were not collected on specific vaccines used and it was assumed that all vaccines had the same effectiveness (Sullivan SG et al. Influenza Vaccine Effectiveness During the 2012 Influenza Season in Victoria, Australia: Influences of Waning Immunity and Vaccine Match. 2104. J.Med.Virol. 86: 1017-1025.).	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
8-18	Vaccines Europe	Comment: Please clarify whether the following guidances will be replaced by this guideline: • CHMP Recommendations for the Pharmacovigilance Plan as part of the Risk Management Plan to be submitted with the Marketing Authorisation Application for a Pandemic Influenza Vaccine (EMEA/359381/2009) • Standard Paediatric Investigation Plan for non-adjuvanted or adjuvanted pandemic influenza vaccines during a pandemic (EMA/185099/2010) • Guideline on submission of marketing authorisation applications for pandemic influenza vaccines through the centralised procedure (EMEA/CHMP/VEG/4986/03)	The guidelines that will be replaced by the Non-Clinical and Clinical Module of the Guideline on influenza vaccines are listed in page 1 of the mentioned Module. The “Guideline on submission of marketing authorisation applications for pandemic influenza vaccines through the centralised procedure” (EMEA/CHMP/VEG/4986/03) was replaced by the “Guideline on influenza vaccines – submission and procedural requirements - Regulatory and procedural requirements module” (EMA/56793/2014) The CHMP Recommendations for the Pharmacovigilance Plan as part of the Risk Management Plan to be submitted with the Marketing Authorisation Application for a Pandemic Influenza Vaccine (EMEA/359381/2009) is not in force anymore. Please see the GVP Module P.I on pharmacovigilance for vaccines and the Non-Clinical and Clinical Module of the Guideline on influenza vaccines (page 31). The pandemic-related documents are currently under revision.
55	PPD Inc	Comment: Proposed change: annual rapid safety assessment and ongoing requirements for effectiveness assessments, both of which are included in this guideline, are also for existing vaccines as well as new vaccines.	Accepted

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111-122	Vaccines Europe	Comments: Vaccines Europe understand that this is a EMA guidance, and as such, cites other EMA guidelines in this section; however, Vaccines Europe suggest that the WHO guidelines on nonclinical assessment of vaccines (WHO Technical Report Series, No. 927; not cited at all in document) and on adjuvants and adjuvanted vaccines (mentioned in line 494) should also be listed in this section. Proposed change: Please add the following to the list of guidelines: • WHO guidelines on nonclinical evaluation of vaccines (WHO Technical Report Series, No. 927, 2005: Annex 1) • Guidelines on the nonclinical evaluation of vaccine adjuvants and adjuvanted vaccines. WHO 2013 (as referenced on page 14)	Partially accepted. Section 3 of the guideline can only refer to EU or CHMP-adopted guidelines, however the guideline has been modified to improve clarity (section 4).
151-153	Vaccine Europe	Comment: Vaccines Europe would welcome the clarification on the process in the submission and procedural guidance (3rd module)	Noted. The “Guideline on influenza vaccines – submission and procedural requirements - Regulatory and procedural requirements module” (EMA/56793/2014) is now published
174-196	Vaccines Europe	Comments: Comment 1: Clinical requirements for paediatric population: Vaccines Europe questions the chronology of clinical studies as stated in the guideline and asks EMA to clarify this chronology. First the younger population 6-	1. Not accepted. The guideline is sufficiently clear.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		36 months followed by older age groups is in contrast to normal development where efficacy is first demonstrated in older age groups before moving down to younger subjects. Proposed change: pending clarification from EMA, paragraph to be reworded Comment 2: Vaccines Europe refers to the sentence in the paragraph b) on children aged from 3 years up to approximately 9 years, indicating that “authorisation should be based on demonstrating that the immune responses to the selected dose and regimen are at least as good as those observed in children aged 6-36 months in whom efficacy has been demonstrated.” It is not clear for Vaccines Europe whether the comparison between age groups needs to be made within one study or whether it can be done between studies. Proposed change: EMA should specify how the comparison can be made. Comment 3: Vaccines Europe refers to the sentence in the paragraph c) on use from approximately 9 years, indicating that “The comparison could be made against immunogenicity data obtained with the candidate vaccine in older age groups (e.g. young adults)”. It is not clear for Vaccines Europe whether the comparison between age groups needs to be made between age	2. Accepted 3. Accepted groups within one study or whether it can be done by comparing results from different studies? Proposed change: EMA should specify how the comparison should be made.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
174 and lines following ones (Paediatric population)	IFAPP	Comment: we recommend to use the standard age groups in which the paediatric population of patients is usually divided. Using different age interval creates confusion. Proposed change: Use the standard age groups	Not accepted. The age groups identified in the guideline do not refer to the standard paediatric groups but to the presumed priming status at baseline.
198-213	Vaccines Europe	Comments: Clinical requirements: immunocompromised individuals: Studies in immunocompromised individuals should be optional and linked to the sponsors desire to gain an indication in immunocompromised subjects. If the MA holder is willing to perform studies in immunocompromised children, it is likely that these studies could be performed after a marketing authorisation has been successfully obtained for the vaccine in healthy children or children with co-morbidities. Therefore, to avoid unnecessary regulatory burden studies in immunocompromised children should not be specified in the PIP but should be managed as PAMs or missing information in the RMP. It would be difficult to conclude anything from a comparison of immunogenicity data for immunocompromised children with age-matched healthy children until correlates of protection are established.	Partially accepted. Although it is agreed that, notwithstanding paediatric requirements, sponsors may decide which population they intend to develop a vaccine for and may subsequently investigate that population, it has to be acknowledged that immunocompromised individuals represent an important target for influenza vaccine recommendation in the EU, for which relevant data would be expected. Indeed it would be for the RMP to discuss the need to investigate any missing information. Due to lack of validated immune correlates of protection specific for children, the difficulties in establishing the exact clinical relevance of immune findings are acknowledged. However it is believed that a small size comparison of immunocompromised vs. healthy children, ideally aiming at improving dosage or regimen, could support further the evaluation and appropriate use of a new product in this target population.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			The guideline has been modified for improved clarity.
214-222	Vaccines Europe	Comments: Clinical requirements: patients with co-morbidities: Can EMA clarify if a control group is needed in studies of patients with co-morbidities? Comment: It is not clear from the text whether immunogenicity studies in patients with co-morbidities are required only for specific indications for use in such patients, if only recommended or encouraged, or (if required) when such studies should take place relative to licensure.	Partially Accepted. There is openness to discuss different study design (text not modified). The text was amended to clarify that immunogenicity studies in patients with comorbidities are not required at the time of the marketing authorisation.
224	Vaccines Europe	Comments: **Clinical requirements: pregnant women:** The guideline should make it clear that “considerable data” on the use during pregnancy refers to data generated across inactivated unadjuvanted vaccines and should remain a base to support a general statement in the product information. It should be recognized that collecting effectiveness data in infancy to assess maternal immunization is very challenging. It is Vaccine Europe’s understanding that the topic of maternal immunisation is currently being discussed across products at WHO level.	Partially Accepted. The paragraph on pregnancy was modified for improved clarity. The difficulties in generating effectiveness data in infancy are acknowledged, however a modification of the guideline was not considered needed.
228	PPD Inc	Comment: What superiority in immune response would be	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		considered appropriate? Would the intention be for a larger proportion of elderly subjects to achieve given threshold values for SRH, GMTs and/or seroconversion or would a greater magnitude of immune response in the same proportion of the study population also be considered a superior response?	
228-242	Vaccines Europe	Comments: Seasonal inactivated adjuvanted vaccines: While superior immune responses are preferred, individual health outcomes and positive population health outcomes may be based on other criteria (such as increased breadth of coverage, duration, use of less antigen). Consider including these aspects in this section. Proposed change: Include after 2nd sentence, line 231 - Improved immune responses could also include increased breadth or duration of response. Other benefits, such as use of less antigen for a non-inferior response, may also be considered.	Accepted.
231	Vaccines Europe	Comments: This statement is in conflict with earlier statement on line 172 that states "in which the comparator(s) is/are not approved in the EU" and reflects that use of a non-EU approved vaccine is acceptable, pending prior discussion with EMA. Recommend that the document is consistent in this allowance throughout.	Not accepted. The guideline was considered consistent throughout.

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244-246	Vaccines Europe	Comments: LAIVs: This statement seems too definitive. For inactivated vaccines the draft guidance states that no confirmed immunological correlate of protection exists (line 161). Proposed change : Suggested addition: For authorized vaccines immunological bridging studies may be considered for changes in formulation or delivery device	Accepted.
281	PPD Inc	Comment: What is meant by "efficacy" here? By definition, the vaccine strain contained in a pandemic preparedness vaccine is not one that is circulating in the human population and therefore vaccine efficacy cannot be assessed in humans. Is this referring to a requirement to demonstrate protective efficacy in animals, or should "efficacy" be interpreted as immunogenicity?	Accepted.
281	Vaccines Europe	Comments: **Data requirements for authorization of "core dossier":** As it would not be feasible to provide efficacy data in the "core dossier" because the real pandemic strain will not yet be circulating, Vaccines Europe would like EMA to clarify that the "efficacy" data to be included in the "core dossier" is nonclinical efficacy data and/or "clinical immunogenicity data".	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change : the sentence should be reworded accordingly: e.g. "This "core dossier" should provide data on the safety and **immunogenicity** of the vaccine construct …."	
285-286, 288-293	Vaccines Europe	Comments: Pandemic core dossier approach: Can EMA clarify if the following requirement is similar to multi-strain dossier approach (cf Vaccine Europe proposal/reflection paper previously sent to EMA – see Annex) and whether manufacturers are expected to update their core dossier accordingly?: 'Safety and immune data for the same vaccine construct but containing other potential pandemic strains and seasonal strains should be included in the core dossier as supportive evidence' 'Applicants are strongly encouraged to investigate two or more versions of the same construct that contain poorly immunogenic strains to which most humans are naive in order to gain a better understanding of the likely performance of the vaccine construct in case of an actual pandemic. Any efficacy data generated previously with the same or similar vaccine construct(s) authorised or used in the EU (e.g. seasonal or zoonotic vaccines) should be included in the "core dossier" as supportive evidence. '	Not accepted. A pandemic core dossier does not constitute a formal multistrain approach.
286	Vaccines Europe	Proposed change:	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Suggest that the words “if available” be added to the end of the sentence	
295	IFAPP	Comment: it is unusual to select the age group > 60 years Proposed change: change into > 65 years	Not accepted. It is noted that different practices exist in defining the lower age limit for elderly and that such cut off may be arbitrary. In line with previous practice with other pandemic influenza vaccines, the guideline was not modified.
298	PPD Inc	Comment: "particularly healthy children" means children who are especially healthy. Presumably what is meant here is "in particular, in healthy children". Proposed change: "in particular, in healthy children".	Accepted
299-303	Vaccines Europe	Comments: collection of safety and effectiveness data during the actual pandemic in populations such as pregnant women: The example of using registries to evaluate safety and effectiveness of a pandemic vaccine in pregnant women may not be very helpful. It’s true that pregnancy registries have been employed for a variety of drugs and for live virus vaccines, but they generally acquire cases from spontaneous reports or unsolicited inquiries from the public. Thus, they would be expected to capture a small fraction of actual pregnancy exposures, although of some value to rule out a very high rate of teratogenicity. But numbers	Not accepted. The list of examples given in the guideline is not intended to be exhaustive.

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		would likely be insufficient to assist with assessing vaccine effectiveness. Therefore, Vaccines Europe proposes to not only mention registries as the unique example, and provide also another example (electronic medical records), as proposed below. Proposed change : (new and revised text underlined) “During the actual pandemic safety and effectiveness data should be collected in populations that were and were not included in safety and immunogenicity studies in the MAA (e.g., pregnant women for whom data may be collected by means of registries or through electronic medical records within large healthcare organizations)”.	
313-315	Vaccines Europe	Comments: Please clarify that as the clinical studies during the inter-pandemic period are to be conducted in isolation that generation of pediatric safety and immunogenicity data will occur during the post-authorization phase.	Accepted.
316-319	Vaccines Europe	Comments: It may be helpful to indicate that seasonal efficacy data gathered in young seronaive subjects may be of particular value.	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
352-353	Vaccines Europe	Comments: Vaccines Europe understand that these two lines should be interpreted to mean that no studies are required in the paediatric population if no indication is being sought in that age group. This would seem appropriate, as zoonotic vaccines are intended for use in the context of outbreaks of zoonotic strains with pandemic potential in first responders (i.e. specific groups – e.g. lab workers -) and not children. Vaccines Europe consider that the need for a PIP for such vaccines should be waived accordingly.	Not accepted. This proposal is beyond the remit of the guideline and may be discussed with PDCO.
374	Vaccines Europe	Comments: The title “5.1. Non-Clinical aspects” should specify it is for pandemic and new seasonal influenza vaccines. It is Vaccines Europe understanding that non-clinical studies are not required for classical seasonal influenza vaccines (the lines 134 to 136 indicate indeed that non-clinical studies are not required as requirements for applications to change vaccine composition for seasonal influenza vaccines). Proposed change: Reword the title of line 374 as follows: “5.1. Non-Clinical aspects for pandemic and new influenza vaccines”	Accepted.
376	ECDC	Comment: ‘per vaccine type’ is unclear Proposed change: per influenza vaccine product	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		authorised?	
390-395	Vaccines Europe	Comments: Primary Pharmacodynamic studies • Immunogenicity studies The relevance of immune persistence in an animal model for seasonal influenza vaccines is unclear. Can EMA please clarify the rationale and specific time interval (including frequency) to evaluate "persistence of immunity" following immunization? Since non-clinical immunogenicity studies are classically performed in mice (see line 393) which of course have limited life-spans, persistence of immunity is difficult to practically evaluate beyond a relatively short time interval (e.g., 9-12 months after completion of immunization series) and therefore this parameter may have questionable relevance to humans. Comment: The cellular immune response can currently only be explored in the mouse model. The tools necessary to study this part of the immune response in other species are not yet available. Could you please acknowledge this in this guideline? Comment: The guideline should clarify what is expected regarding the study of "persistence of immunity" in animals. In man and in the context of the influenza vaccination, this usually corresponds to durations of 6 to 12 months. In the mouse model, such a time period would	Accepted.

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		represent old animals, especially for the 12 month time-point. Such a comparison would probably lose its significance.	
397	Vaccines Europe	Comments: The guideline should clarify what is expected by the following sentence: “Immune responses should ideally be assessed after single and multiple doses.”	Accepted.
392-399 5.1.1. Immunogenicity studies	MEB Netherlands	Comment: In this section five animal species have been mentioned as well-responding to human influenza vaccine (line 393). Immunogenicity of vaccines is irrelevant if this is not associated with protection against the disease. It is, therefore not clear what the purpose of the immunogenicity data is in the lines 392-399 (including cross-reactivity). Immunogenicity data in most of these species might be useful to demonstrate the reproducibility of the manufacturing process. Proposed change: Change the paragraph in line 392-399 reflecting the connection with protective activity. E.g. Cotton rats might be better than rats. Cross-neutralizing antibody response should be related to protection against heterologous influenza.	Accepted.
405-438	Vaccines Europe	Comments: Protection studies: animal model: Vaccines Europe questions the relevance of ferret as the preferred animal model for protection (or challenge) studies with new seasonal influenza	Accepted.

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		vaccines (while the ferret model is adequate for pandemic influenza vaccines), for the following reason: • Manufacturers have hence to verify that the wild influenza strains to be tested can replicate and induce clinical symptoms allowing to demonstrate efficacy of vaccination, in ferrets, and to define the relevant challenge dose to make the test meaningful (experience has indeed shown that some strains such as B strains, H3N2 strains and H1N1 seasonal strains do not replicate well in ferrets). Therefore, use of ferret for protection studies with seasonal influenza vaccines might yield marginal results. Proposed change: reword the sentence on line 408/409 as follows: "Ferrets might represent an adequate animal model for influenza challenge studies (provided that the concerned influenza strain replicates well and induce clinical symptoms in ferrets), as ……." Also, to conduct challenge studies in ferrets, usually represents a very significant project which may last for over 6 months.	
406 406 and 414	Vaccines Europe	Comments: **Protection studies: "new influenza vaccines":** Vaccines Europe is asking EMA to clarify the sense of "new influenza vaccines" for which protection studies	Accepted.

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		should be performed, mentioning some examples. For candidate influenza vaccines with novel mechanisms of action (not based on immunity conferred by receptor-blocking antibodies to HA), when suitable human clinical data or reliable correlate of protection data are not available, protection (or challenge) studies should be performed with new influenza vaccines in adequate animal model. Also, Vaccines Europe wonders what would be the ideal animal model for supra-seasonal vaccines. Other comment and Proposed change: on line 414, replace the term “heterologous” by “hetero-subtypic” **Passive immune transfer studies** Passive immunisation ferret studies, which investigate the level of protection induced in naïve animals following passive transfer of antigen-specific sera from immunised animals or sera from vaccinated humans, would be considered supportive of protective immunity with respect to induced humoral immune responses. Such studies are especially relevant for non-replicating pandemic and zoonotic vaccines, where the objective is to determine the antigen-specific neutralizing antibody titre associated with the protection.	
419-421 5.1.1 Protection	MEB Netherlands	Comment: The draft Guideline states: High doses of challenge virus (105 ID50 or a lethal dose if known) are preferable; the use of lower doses to encompass animal welfare should be appropriately justified.	Partly accepted. High challenge doses are preferable for the results to be meaningful. The text was modified for improved clarity.

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studies		The MEB would emphasize that this argumentation should be turned around. The use of lower doses to encompass animal welfare should be preferable. Disease endpoints such as body weight loss, body temperature, and viral shedding can be used to show protective activity, as mentioned in line 422-427. Companies should specifically justify when there is a reason to use a lethal dose. The guideline does not justify this appropriately. Proposed change: Change the requirement for justification of the lower dose into a requirement for justification of a lethal dose.	
432 Protection studies	MEB Netherlands	Comment: The draft reads: Cross-protection following challenge with heterologous viruses should be assessed for … seasonal adjuvanted formulations However: Line 136 indicates for seasonal vaccines that nonclinical studies are not required. Proposed change: The two sections should be brought to consistency. We propose to add in line 136: In case of change to heterologous viral strains protection studies might be of added value to support the protective potency of the new vaccine.	Partly accepted. The guideline has been modified to better differentiate the requirements for initial marketing authorisation (line 432) from the requirements for seasonal strain change (line 136). Line 432 was clarified to indicate why cross-protection data may be needed.
501	Vaccines Europe	Comments: Fever should be replaced by “changes in body temperature” because mice usually don’t respond with fever but do exhibit decreased body temperatures with challenge, and ferrets can experience fever followed by	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		a lowering of body temperature later in the course of infection. Proposed change: Change accordingly.	
502	Vaccines Europe	Comments: As highlighted in the general comments, no animal models exist which are predictive of autoimmunity. Proposed change: Remove requirement.	Accepted.
503	Vaccines Europe	Comments: If an adjuvanted vaccine has been shown to be efficacious at a particular dose of antigen/adjuvant for a particular set of strains, additional testing to find the optimal ratio may prove very difficult. This optimal ratio may be specific for the antigen used in a particular season, or an individual's history. Thus, it may actually be preferred to use doses in the plateau region to assure a consistent response regardless of strain or individual immune experience. Proposed change: Change '… should also be performed.' To '… is preferred, and may provide additional insight.'	Accepted.

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5.1.6 Additional considerations. Adjuvanted vaccines	MEB Netherlands	Comment: Line 495: the number of the WHO Guideline could be added. Line 496: “For adjuvants” should be read as “for adjuvanted vaccines”, as “addressing the level of antibodies induced”, is only relevant if there is an antigen present in addition to an adjuvant. Proposed change: Change accordingly.	Accepted.
507-511 5.1.6 Additional considerations	MEB Netherlands	Comment: The draft emphasized that for new adjuvanting systems, specific safety data are required. In line 510-511 this is more in depth specified for genotoxicity and reproductive toxicity. The MEB advises to delete these statements as they belong to a general guideline on adjuvants, where more nuances can be given, e.g. only in case an adjuvanting system contains a synthetic small molecule. Proposed change: Delete line 510-511, and refer to the WHO-Guideline on Adjuvanted vaccines.	Accepted.
519	Vaccines Europe	Comments: In studies where lung replication is prevented in nearly all animals low level replication in an occasional animal may be seen. Proposed change: Suggest that “prevent” be replaced with “significantly suppress”.	Accepted.
525-529	Vaccines Europe	Comments:	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Deposition studies for LAIV have been conducted with control vehicle and the results have been difficult to interpret due to spread of signal from one region to another.	
551	Vaccines Europe	Comments: Include RNA vaccines as well as DNA vaccines	Accepted.
555-556 Page 15 5.2.1	University of Siena	Comment: The definition of Single Radial Haemolysis (SRH) technique as an assay able to detect antibody against the haemagglutinin (HA) antigen may be quite controversial because the assay measures antibodies against whole influenza viruses and not specifically HA antibodies. Proposed change : Single Radial Haemolysis instead of Serial Radial Haemolysis. The assessment of the immunogenicity of influenza vaccines is based mainly on two tests, the Haemagglutination Inhibition (HI) and Single Radial Haemolysis (SRH) assays. The HI assay detects antibody directed against the HA antigen while the SRH assay antibody directed against the whole influenza virus.	Partially accepted. The text was amended to include the right definition for SRH.
556-558 Page 15	University of Siena	Comment: Despite the wide use of the assays (SRH and HI), they have not been yet standardized and different protocols	Noted. However it was considered that no changes in the text of the guideline would be necessary at this stage.

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5.2.1		are available. It would be advantageous whether an unique validated protocol for SRH and HI assays can be reached in order to have standardized assays and to reduce inter laboratory variability. It would be ideal to have a validated protocol officially recognized and accepted by the regulatory agency. If it is not feasible to reach a unique validated protocol for SRH and HI assays, we suggest to perform the assays in qualified laboratories (e.g. GCLP certificated) with wide and recognised experience in this field.	Accepted.
558-559 Page 15 5.2.1	University of Siena	Comment: The recommendation to perform HI and SRH assays in a single laboratory needs to be clarified. Although the designed laboratory is qualified, we suggest to perform the assays in different qualified laboratories in order to guarantee unbiased results. If a single designed laboratory is preferred, please add clarification to the main requirements to become a “single designed laboratory”. Proposed change : In any one clinical development programme it is recommended that HI and SRH assays are conducted in qualified (e.g. GCLP certificated) designated laboratories.	Partially accepted. The guideline was modified to improve clarity.
562-563 Page 15	University of Siena	Comment: Validated assays are a crucial point in the clinical	Noted. It was considered that the text of the guideline does not

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
5.2.1		development programme. We think that every assay must be preceded by a validation of the assay recognized by regulatory agency and according to ICH guidelines. Initially, international standards must be used for assays. Subsequently, bridge study will be performed in order to compare the results of international standards and in-house controls. If results are acceptable, in-house controls can be used with or in place of the international standards. International standards should be approved by regulatory agency. We suggest to add few information concerning the international standards such as the lower titer limit, below which the standard is not acceptable or at least a range of values. Proposed change : Sponsors should employ validated assays and international standards, unified laboratory protocols and standard reagents.	diverge in essence from the comment received, no change is proposed.
564-576 Page 15 5.2.1.	University of Siena	Comment: The Virus Neutralisation (VN) assay is a particularly useful technique able to detect functional antibodies but, as for HI and SRH assays, different protocols are available such as neutralisation based on the inhibition of cytopathic effect or assay with microtitre plates in	Partially accepted. it was felt neither feasible nor appropriate to define a priori the assay parameters in the guideline. The guideline identifies which ones are the most critical aspects that should be subject of careful consideration by the manufacturers.

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		combination with an ELISA assay. In order to achieve a standardized protocol, we suggest to define principal and critical assay parameters such as the type of readout, the duration of incubation that should be included in the validation process. We suggest to better define the initial dilution of 1:10 (is the initial dilution referred only to the serum, to the virus-serum mix or to the virus-serum-cell mix? This is a critical point since every laboratory has its own interpretation) and for which reason the use of the non-permissive cell lines is accepted.	The initial dilution of 1:10 is referred to the serum only (text modified). The reference to non-permissive cell lines has been deleted.
579	Vaccines Europe	Comments: In addition to what was stated in the general comment it should be noted that it is very challenging and logistically difficult to enrol subjects of such age, and to make these stratification. Inevitably, the numbers provided will be very low. This, added to the not clear understanding of CMI data, will end up with non-interpretable results	Partially accepted. It is acknowledged that there are difficulties in recruiting older elderly and to stratify them by age with meaningful numbers. The text was modified accordingly, however it is expected that every effort is made to generate data on elderly above 75 years of age.
587	Vaccines Europe	Comments: In addition to what was stated in the general comment it should be noted that there are no standardized NA tests; quantity of NA in the single vaccines is not measured, nor standardized. There are no criteria to interpret anti NA antibodies. The value of this evaluation is questionable.	Partially accepted. There is some value in evaluating anti-NA antibodies and it is recommended that this is considered by manufactures based on the type of product under investigation and based on future developments in the field of anti-NA antibody testing.

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587-588 Page 16 5.2.1.	University of Siena	Comment: Neuraminidase (NA), in addition to HA, is the other major surface glycoprotein of the influenza viruses. The studies conducted on NA exhibit an ample scenario from the point of view of the techniques used. We suggest to give indication on which assay could be used. The assay needs to be validated and performed in qualified laboratories (e.g. GCLP certificated) with wide and recognised experience in this field. Proposed change : Sponsors are encouraged to evaluate anti-neuraminidase NA antibodies at least in randomly selected subsets. The assay should be validated and performed in qualified (e.g. GCLP certificated) laboratories.	Accepted
589	Vaccines Europe	Comments: antibody kinetics as indicator of past priming and of maturation of the immune responses VE questions the relevance of these requirements specifically in the case of seasonal vaccines. The need and usefulness of this data is questionable, as population should be vaccinated every year given it is an annual seasonal vaccine.	Partially accepted. The guideline has been modified to improve clarity.
589-590 Page 16 5.2.1.	University of Siena	Comment: Since studies of antibody kinetics are an useful tool for the evaluation of vaccines, guideline should better explain the criteria for the evaluation of the data.	Not accepted. There are no established criteria and the kinetics of antibodies measured by non-functional and functional assays are different. It is preferable to keep the recommendation open at

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			this stage.
595-597	Vaccines Europe	Comments: cross-priming for zoonotic and pandemic vaccines: Vaccines Europe would like EMA to clarify the exact intent of the cross-priming study, as the following wording in the draft guidance is not clear: “i.e. evidence of an anamnestic response to challenge with a related but drifted strain following initial vaccination with the selected vaccine strain based on comparison with a first dose of the drifted strain vaccine in an unvaccinated control group.” Proposed change: EMA should reword the sentence for more clarity. One proposal could be e.g.: “i.e. evidence of an anamnestic response after boosting with a related but drifted strain vaccine following initial vaccination with the selected vaccine strain based on comparison with a first dose of the drifted strain vaccine in an unvaccinated control group.”	Accepted.
611-612 Page 16 5.2.1.	University of Siena	Comment: The immunological data are related to HI and VN assays. We suggest to add SRH assay or explain why it is excluded. The SRH assay is a serological method widely used for measuring antibodies against influenza viruses. The	Accepted.

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		greatest advantage of SRH is its safety because is performed with inactivated virus. This aspect is particularly advantageous in the case of avian influenza strains considering also the relatively poor sensitivity of the HI assay for detection of antibodies against avian influenza viruses. SRH is rapid, reliable, reproducible and provides unbiased results. The assay allows the simultaneously and rapidly analysis of a large number of samples without pre-treatment (excluding complement inactivation) and requires only a small volume of sera. Basically, it is an established technique considering the wide use in serological field. Proposed change : GMTs (with 95% confidence intervals) and pre-/post-vaccination ratios (GMRs) should be calculated for HI, SRH and VN data.	
611-612	Vaccines Europe	Comments: Clinical immunogenicity: Analysis and presentation of immunological data (GMR): Pre and post vaccination ratios (GMRs): Can EMA clarify whether this is the same as SCF (Seroconversion Factor)?	The geometric mean ratio is the ratio between the geometric mean titres pre and post-vaccination. In this regard GMR and seroconversion factor could be considered analogous terms.
613-615 Page 17 5.2.1.	University of Siena	Comment: Standard calculation for VN assay should be suggested and included in the guideline. An explanation of which mean to use between arithmetic and geometric would be useful.	Not accepted This level of granularity is not considered needed in the guideline.

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613	PPD Inc	Comment: Can SRH be used in place of HI assays? Comment applies throughout this section where HI is mentioned and SRH is not. Parameters for evaluating SRH results should be specified.	Accepted.
633-635 17 5.2.1.	University of Siena	Comment: We suggest to add SRH assay. Proposed change : The VN data should be analysed in a similar fashion with appropriate cut-offs applied to titres and data trends should be compared with the HI or SRH results or both.	Accepted.
640-641	Vaccines Europe	Comments: Clinical immunogenicity: Essential immunogenicity studies (dose finding studies) Dose-finding studies for “different target groups for which an indication is sought” - Can EMA clarify the level of granularity of the target groups referred to (i.e. age, medical conditions, etc.)? -Is this applicable for all vaccines (seasonal, pandemic/zoonotic, adjuvanted, non-adjuvanted, …)?	Accepted.
653-656	Vaccines Europe	Comments: The term "suitably immunogenic" needs further clarification	Accepted.
668-674	Vaccines Europe	Comments:	Partly accepted.

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		Revaccination studies with a non-adjuvanted vaccine should not be required pre-licensure	The guideline was modified to clarify the cases for which the provision of persistence/revaccination data is considered of particular interest, and when this data should be obtained.
675-679	Vaccines Europe	Comments: The requirement of 6 month immunogenicity follow up for a pandemic vaccine should not be a pre-licensure requirement. Recommend making explicit that this requirement would be a post-licensure commitment in a pandemic situation.	Partially accepted. See above
680 689	Vaccines Europe	Comments: This section is obscure to Vaccines Europe members. As stated in the Guideline, there are no serological markers for priming, and it is not clear how to discover them. But even if a serological marker is found, the value of this information is questionable for seasonal vaccines, which should be administered each year. If the serologic markers that reflect effective priming (e.g., HI > 1:40) are in question, what is the acceptable sign of an "anamnestic response" vs unvaccinated control and why at 6 to 12 months rather than 3 to 4 weeks post vaccination? The clinical rationale for this switch is unclear and, to the best of our knowledge, has not been validated in efficacy trials.	Accepted.
704 5.2.1.	MEB Netherlands	Comment: It is recommended to add a reference to the Prentice criteria	Not applicable.

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Clinical Immunogenicity			The reference to Prentice criteria was deleted.
704-707 Page 19 5.2.1.	University of Siena	Comment: Explanation of which model is used should be added to the report.	Not applicable. This paragraph was deleted.
718-721	Vaccines Europe	Comments: Efficacy studies for LAIV would not require injections. Proposed change: To achieve a double blind design and to avoid (or at least minimise) the use of placebo injections it is necessary....	Accepted.
739	Vaccines Europe	Comments: **Clinical efficacy in the elderly:** Vaccines Europe questions the feasibility of including a very old population in efficacy study in the elderly. Enrolling sufficient elderly (particularly in the >85 years of age) in order to statistically show clinical efficacy can be a challenge based on limited numbers of individuals in this age-range and limited numbers of individuals potentially willing to be part of such a trial. Proposed change: Replace the wording (on line 739) "it is important to include …." by it may be useful, if feasible, to include …..”	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
742-745	Vaccines Europe	Comments: Clinical efficacy: Vaccines Europe refers to the paragraph stating that "The protocols for protective efficacy studies should pre-define when and in which subsets samples will be obtained for immunological evaluation and should state the assays to be used." However, to allow for exploratory translational medicine studies, allowances should be made for consenting patients for, and conducting additional exploratory analyses with, patient samples that are not specified in the protocol. Therefore, Vaccines Europe proposes to add a sentence in this paragraph accordingly, as highlighted below: Proposed change: The protocols for protective efficacy studies should pre-define when and in which subsets samples will be obtained for immunological evaluation and should state the assays to be used. However, it is recognized that to advance new techniques that evaluate efficacy and quality of immune responses, allowances should be made for exploratory endpoints. Patients should be consented to allow the use of samples for uses not specified in the protocol to enable use of techniques that are still early in development but ultimately would prove useful for understanding the immune response for improved vaccine generation.	Not accepted The guideline should not enter into such details of clinical trial design and planning.
808	Vaccines Europe	Comment: vaccine effectiveness Clarify on what basis data from other regions can be	Not applicable. The mentioned text has been deleted. Please make reference

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		extrapolated to EU population (population structure: age, race, co-morbidities, etc; industrialized world populations?)	to GEP and ENCePP guidelines.
819	Vaccines Europe	Comment: Screening method may be efficient but is more subject to bias/confounding	Noted
823-824	Vaccines Europe	Comment: Provided data can be obtained, how will investigation of the impact of possible virus drift on effectiveness be used?	Not applicable. The text mentioned has been deleted.
825-827	Vaccines Europe	Comment: "To characterize the potential wane of vaccine protection after vaccination, data should be collected throughout the season and in sequential seasons." Re-vaccination would abrogate the ability to observe waning of vaccine protection in a subsequent season. It should therefore be made explicit that studies need not be powered to assess waning over subsequent seasons in those who happen to not be re-immunized in subsequent years. Indeed, this factor may make it un-feasible to study multi-year waning of vaccine protection. Moreover, across seasons, it is very unlikely that subjects will receive the same brand of vaccine every season and thus the effect of repeated vaccination season after season is unlikely to be evaluated on a brand level. Alternatively for new participants, data may be collected retrospectively on previous seasonal	Accepted.

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		vaccination(s), but the quality of such data may be limited and product (i.e. brand) specific information is likely to be missing. Proposed changed: the guidance should not request for data about duration of protection	
828-844	Vaccines Europe	Comments: Non-lab confirmed endpoints should not be included as they are not specific. State whether effectiveness against mild vs. moderate to severe disease matters more from the viewpoint of the guidance/regulators since this will impact the choice of endpoints, settings, sample size, and feasibility	Accepted.
850-852	Vaccines Europe	Comments: Many elderly patients with flu do not have fever. Will ILI definition be sufficient or will it bias results? “Laboratory confirmation of influenza by reverse transcription polymerase chain reaction (RT-PCR) or culture using an established method…” Given the continued advancements in diagnostic technology, particularly nucleic acid-based testing, the guidance should allow for the future use of alternatives to RT-PCR and culture, provided that the acceptable performance of alternative virus detection techniques can be demonstrated. What level of external quality assessment is sufficient?	Not accepted. Premature to broaden the recommendations
858	PPD Inc	Comment: Any specific age range for children and adolescents	Not accepted. The guideline is sufficiently prescriptive on this aspect.

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		may be helpful, as this definition is different across countries/cultures	
858-862	Vaccines Europe	Comments: While effectiveness can be assessed by age groups, fully powering studies for this purpose is not feasible. it is deemed unlikely that results will be conclusive based on data collected in one season due to several factors: - The influenza attack rate will vary from season-to-season - Product availability in countries and sites is variable from season to season (tender markets) - Even a broad network of sites in various countries cannot guarantee sufficient exposure to a product, - The exposure for some age groups may be limited due to low overall immunization rates (lack of recommendations, e.g. young children) Proposed change : Though any effectiveness study should include subjects of any age or risk group, the requirement should not be to power the studies to generate meaningful data within any age stratum or risk group (or brand). It should be clear which prerequisites need to be fulfilled before results can be reliably interpreted (e.g. how will low exposure [overall or per sub-group], low influenza attack rate, strain changes from one season to	Partly accepted. The text was modified to include some flexibility around age stratification or subgroup analysis but the requirement to generate product-specific data remains (see general comments).

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		another, level of match etc be dealt with?)	
859 740	Vaccines Europe	Comments: The older age subgroups proposed to be included in effectiveness studies (≥65 years and > 80 years of age) are not the same than in efficacy studies (75 – 84 years and >85 years of age) while the aim is the same : to study the protection in elderly ; we suggest to harmonize the cut-off	Accepted.
861-862	Vaccines Europe	Comments: "…sub analyses should be performed concerning underlying medical conditions including frailty." In the generic protocols, one of the exclusion criteria is "to be institutionalised" as these subjects do not have similar exposure to influenza viruses than subjects in the community. As previously mentioned, the study will not be powered for this purpose. Proposed change : " …sub analyses could be performed concerning underlying medical conditions'	Accepted.
866	Vaccines Europe	Comments: As vaccine registries don't exist in most countries, what forms of vaccine exposure validation are valid from this guidance's perspective?	Noted, it is agreed that vaccine exposure has to be validated but to define this is outside the scope of the guideline.
875	Vaccines Europe	Comments: What is the best way to address confounding by indication which is likely to be one of the most	Not applicable. The mentioned text was deleted from the guideline.

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		important confounding factors?	
881-882	Vaccines Europe	Comments: Interim analysis of influenza vaccine effectiveness are not always feasible, a minimum sample size is needed and as PCR analysis are done in reference laboratory, the laboratory results are not usually available in real time. Also vaccine effectiveness early in the season may not be indicative of vaccine effectiveness over the full season Proposed change : to delete “Therefore, IVE for different outcomes might be calculated at different time periods.”	Partly accepted. The difficulties are acknowledged and the guideline has been modified.
882-886	Vaccines Europe	Comments: Final results will not be obtained/presented at the time of the submission of the strain update for the next season; only interim results will be obtained and could be presented (with known limits) in an updated RMP in order to allow for timely adjustments of the study protocol for the evaluation of vaccine effectiveness for the next season or additional training of participating centres Proposed change : Line 883: “Final results should be submitted when available. The submission of these results is disconnected from the submission of the annual variation”	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Other option: Line 883: “Final results should be submitted at the time of the November PSUR. The submission of these results is disconnected from the submission of the annual variation”	
899	PPD Inc	Comment: Again, please define age ranges for the different age groups	Not accepted. The guideline is considered sufficiently clear.
869-871	Vaccines Europe	Comments: Frailty/functional status maybe one important confounders not accounted for in historical studies; this should probably be collected and included as a confounder	Noted, however the list in the guideline is not intended to be exhaustive.
938-940	Vaccines Europe	Comments: Except paediatric and for the age groups (PIP and paediatric regulation), it is up the pharmaceutical companies to decide the indication and to include or not data on immunocompromised individuals (position of the European commission).	Noted. The guideline has been modified for improved clarity.
1010	PPD Inc	Comment: “foAnnex” typo?	Accepted