EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 October 2018
EMA/746314/2018
Vaccine Working Party

Overview of comments received on 'Draft guideline on the clinical evaluation of medicinal products indicated for the prophylaxis or treatment of respiratory syncytial virus (RSV) disease' (EMA/CHMP/257022/2017)

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

Stakeholder no.	Name of organisation or individual
1	EFPIA and Vaccines Europe (including comments from Novavax)
2	CureVac AG, Tübingen, Germany
3	European Association of Hospital Pharmacists (EAHP)
4	Immunovaccine

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1. General comments

Stakeholder number	General comment (if any)	Outcome (if applicable)
3	EAHP overall agrees with the content of the Guideline on the clinical evaluation of medicinal products indicated for the prophylaxis or treatment of respiratory syncytial virus (RSV) disease. The guideline covers all important aspects, wherefore EAHP does not have any specific comments on the text.	**Noted**
4	The document as presented rightly states that the immune correlate of protection for RSV disease has not been established. Yet despite this, the remaining assessment into guidance of novel vaccines and therapies is focused solely on the measurement of neutralizing antibody responses. This makes for a unidimensional and limited view of the potential protective immune responses to this disease. It is likely that other components of the immune system (such a non-neutralizing but disease targeting antibodies, and T cell responses) may be desirable and necessary for full protection, particularly in virus experienced populations such as the elderly and should be addressed. The document states that it does not include guidance on the development of assays to measure virus neutralization titres. However, a standardized neutralizing antibody assay would be helpful in clinical trial development, particularly with the expectation to compare results to other technologies and vaccine candidates.	**This is not correct. The document does not focussed on neutralising antibody in the vaccine sections but discusses the immunological parameters. It is only in the section on MAbs that the focus is on their NA activity.** **It is agreed that a standardised method would be nice, but we are not there yet. However, in the updated draft reference is made to WHO IS, which are now available.**
1	RSV is the single most important cause of LRTI in infants and young children worldwide and can cause LRTI in elderly and immunocompromised patients; it is associated with significant	

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	morbidity and mortality in these target populations. Prophylactic antibodies were successfully developed against RSV. However, their use is restricted to a small group of infants considered at high risk of severe RSV disease. There is still no specific therapeutics or vaccine to treat or prevent RSV. As such, it remains a major unmet medical need. EFPIA and Vaccines Europe welcome the publication of this guideline that will guide the manufacturers in the development of medicinal products indicated for the prophylaxis or treatment of RSV disease. However, EFPIA and Vaccines Europe have some important comments as described below. <u>General comments on vaccine sections</u> Vaccine developments are long and complex. It is therefore important that the recommendations provided in the guideline represent an appropriate balance between de-risking of the clinical development in terms of safety of study participants and avoiding unnecessary delays in vaccine availability. Hence, suggestions are made thorough the document to adapt some of the requirements to the target population of the candidate vaccine (e.g. duration of follow up between studies, measures to address ERD, etc.). It should also be acknowledged that exceptions to the recommendations provided in the guideline may exist depending on the type of candidate vaccine and should be discussed on a case-by-case basis with regulatory authorities. The recommendations provided in the guideline should be	**No GL covers everything. It is always implicit that sponsors who find the GL not entirely applicable to their situation or who wish to deviate from the GL with justification will consult with EU Regulators.** **Furthermore, it says that:** Sponsors are encouraged to discuss their programmes with EU Competent Authorities even

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	sufficiently flexible to allow 1) the conduct of global developments addressing the needs of regulators and recommending bodies from different regions and 2) the development of vaccines that may have very different immunogenicity profiles. Therefore, it is important that the guideline is not restrictive in terms of age ranges of the target populations or contains recommendations that only address the development of vaccines with specific profiles (e.g. envisage only seasonal vaccines). Section 4 appears to be written with maternal immunization and infant vaccination in mind. Clarification of which comments relate to maternal immunization and which comments relate to infant immunization is needed. It is recommended to structure this section with appropriate delineating headings. Throughout the document, emphasis is placed on the importance of evaluating anti-RSV neutralising antibody titres in vaccine studies. As there is currently no established immune correlate of protection for RSV, in addition to neutralising antibody, any other relevant immune markers established from clinical or non-clinical studies also should be considered. In Section 7.1.2 Efficacy trials – Primary Endpoint, reference is made to Section 5.3 for considerations for defining cases of RSV disease and their severity. Clarification is needed on exactly what text in section 5.3 is applicable to vaccines.	if their plans are generally in line with this guidance. Sponsors may wish to evaluate candidate products in target groups that are not addressed in detail in this guidance, in which case consultation with EU Competent Authorities is strongly recommended. **With regard to flexibility, several comments show that commentators are reading the text as requirements even in places where it has been carefully worded to make it clear that something is desirable or to be considered.** **The GL does not in any way restrict how sponsors may wish to develop vaccines but it does focus on the populations that have been the subject of all programmes that have been discussed with regulators thus far.** **See responses to specific comments on this section below.** **This is incorrect. Reference to neutralising antibody is**

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	Consideration should be given to adding text applicable to vaccines to the corresponding vaccine-specific sections. Considering the importance of this guideline and the complexity of the topic, Vaccines Europe respectfully requests that the Vaccine Working Party organizes a meeting with manufacturers before the finalization of the guideline in case of disagreement with the specific comments provided below.	**confined to sections on monoclonal antibodies and maternal immunisation with aim to protect the infant, in which cases RSV neutralisation is thus far the only preventive strategy that has been discussed with regulators. There is nowhere in this document that necessarily expects that vaccines for other uses will elicit neutralising antibody or confer protection via NA.**
	<u>General comments on antiviral agents sections</u> It is mentioned that efficacy trials for DAAs may be confined to hospital to ensure comprehensive data collection. It is however recommended that clarification is provided regarding whether there is a need to study RSV treatment in the community setting (at risk of hospitalisation) as this is currently requested by PDCO. If so, it is suggested that considerations for a relevant endpoint in this setting be addressed.	**See responses to specific comments on this section below.**
	It is recommended that the guideline also addresses treatment within the context of an outpatient setting.	**Not possible before finalisation of the guideline due to prioritisation of the Agency's activities.**
	It is recommended that more guidance be provided for treatment of immunosuppressed patients, particularly post hematopoietic stem cell transplantation (HSCT) or solid organ transplantation (SOT), as this group is most likely to benefit from antiviral agents for RSV, and only limited guidance is provided (Section 6.3, Antiviral Agents).	**For the purposes of licensing it is not required that RSV treatments are studied in the community setting and the GL does not require this. It is for the sponsor to select the type of setting(s) in which the pre-licensure pivotal efficacy trial(s) will be conducted.**

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		The only difference would be the case definition to fit disease that can be treated in the community and the method of case ascertainment. There is no case definition requirement for the very reason that it needs to be flexible. See also changes made in response to comments below. **These are specialised populations and programmes that go straight to these populations without first demonstrating efficacy in a broader and more typical population would always have to be discussed on a case by case basis.**

2. Specific comments on text

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
Lines 69-70; 110; 170	1	**Comment**: The paediatric sub-group definitions should reflect those defined in ICH E11, Clinical Investigation of Medicinal Products in the Paediatric Population. **Proposed change (if any):** **Lines 69-70:** (…) may include newborn infants (aged 0-27 days), infants *and toddlers* (aged 28 days to ~~*11*~~ *23* months), ~~*toddlers (aged 12-23 months)*~~, (…) **Lines 110:** (aged 0-27 days), infants *and toddlers* (aged 28 days to ~~*11*~~ *23* months))~~, *toddlers (aged 12-23 months)*~~ **Line 170:** • Infants *and toddlers* (aged 28 days to ~~*11*~~ *23* months) ~~*and toddlers (aged 12-23 months)*~~, including those who (…)	**Accepted**
Lines 70-71; 121-124; 176	1	**Comment**: It seems premature to include an age limit for the adult population as vaccine developers are conducting global developments that should address the needs of regulators and recommending bodies in different regions. The development should cover the medical need which is	**Partly accepted; the intent was not to dictate to sponsors the lower age range for study but to reflect what is typically happening. The text has been amended but has been kept in line with the scope.**

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		impacted by the disease epidemiology and the subject health status. It is suggested to say “older adults” instead of “elderly”, the latter being defined by chronological age and not considered as a marker of someone’s health status. **Proposed change (if any):** **Lines 70-71:** (…) older paediatric *and adult* subjects predisposed to develop severe RSV disease~~, and elderly subjects (aged ≥ 65 years)~~. **Lines 121-124:** ~~Elderly subjects (aged ≥ 65 years)~~ *Older adults* with or without comorbid conditions, such as congestive heart failure, emphysema or asthma, are more likely than younger adults to develop LRTI requiring medical intervention. **Line 176:** • *Older adults* ~~Elderly subjects~~ ~~(aged ≥ 65 years~~).	
Lines 74-76	1	**Comment:** Clarification is requested regarding whether this sentence refers to extrapolation of efficacy to populations not studied in the clinical trials. **Proposed change (if any):**	**Accepted**

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
Lines 83-85	1	**Comment:** To assess the level of risk for vaccine-associated disease enhancement, the number of subjects exposed to RSV is more important than the duration of the follow-up. If a known number of subjects has evidence of exposure, the level of risk for vaccine-associated disease enhancement can be ascertained. It is recommended to reflect this in the guideline. It should also be clarified that this sentence pertains to vaccines. **Proposed change (if any):** To assess the risk, it is recommended that the duration of follow-up in each *vaccine* trial is sufficient to ensure that ~~*the majority*~~ *a known number* of subjects have experienced natural exposure to RSV, with or without a clinically apparent illness*, so that the level of risk can be ascertained.*	**This text is now removed; see further below**
Lines 85-87	1	**Comment:** With regard to infants born to vaccinated mothers, the goal should be for studies to provide adequate power and duration to detect adverse outcomes; it is not clear that continuing observations until anti-RSV levels are similar between infants born to vaccinated and un-vaccinated women is necessary to achieve this level of statistical certainty. With regard to vaccines for older adults, it is not clear why	**This text is now removed; see further below regarding changes in other places.**

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		information on the need and frequency of revaccination needs to be available at the time of licensure rather than post-licensure; this requirement would significantly delay approval and introduction of vaccines to address the unmet medical need (see also comments on lines 590 and 688). **Proposed change (if any):** ~~*For vaccines intended for pregnant women, case ascertainment in infants should continue until anti-RSV antibody levels are similar between infants born to vaccinated and unvaccinated women.*~~ In the elderly, it is desirable that some data are available on the duration of protection~~*, need for re-vaccination and the safety and immunogenicity of sequential doses*~~ at the time of licensure.	
Lines 101-102	1	**Comment:** Clarification of wording is recommended as it is not anticipated that all antibodies elicited by G and F are neutralising. **Proposed change (if any):** The glycosylated F and G surface proteins in the RSV envelope are essential for pathogenesis and *are able to induce* ~~*elicit*~~ neutralising antibodies in the host.	**Not accepted; the proposed revised text means the same as the current text.** **Instead, the word "can" has been added.**
Lines 116-117	1	**Comment:** Suggest adding asthma as an important long-term morbidity following RSV LRTI in early life, as well as specifying	**Accepted**

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		recurrent wheezing. **Proposed change (if any):** Long-term morbidity following RSV LRTI in early life may include *asthma and recurrent* wheezing.	
Line 118	1	**Comment:** RSV infection does not induce sterilising protection or protection from all RSV disease related clinical symptoms. It is proposed that the wording be amended accordingly. **Proposed change (if any):** RSV infection in early life does not provide ~~*solid*~~ *fully protective* immunity so that individuals may be infected and may develop clinical manifestations of RSV multiple times ~~*during their life span*~~.	**Not accepted; the current wording is correct and clear.**
Lines 121-124	1	**Comment:** It is suggest adding chronic obstructive pulmonary disease (COPD) as an important comorbid condition in older adults. **Proposed change (if any):** ~~Elderly subjects (aged ≥ 65 years)~~ *Older adults* with or without comorbid conditions, such as congestive heart failure, emphysema, ~~*or*~~ asthma *or chronic obstructive pulmonary disease (COPD)*, are more likely than younger adults to develop LRTI requiring medical intervention.	**Not accepted; these are just some examples in the background information; this GL is not meant to be a definitive text of RSV disease.**

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
Lines 121-123	1	**Comment:** Given the reference to dosing of immunodeficient patients in line 424, this section of the guideline should clearly state that this patient group is also at risk of severe RSV disease. **Proposed change (if any):** ~~Elderly subjects (aged ≥ 65 years)~~ *Older adults* with or without comorbid conditions, such as congestive heart failure, emphysema or asthma*, as well as immunodeficient persons,* are more likely than younger adults to develop LRTI requiring medical intervention.	**Not accepted; see above** **Also see relevant responses in specific parts of the text that follow.**
Lines 125-127	1	**Comment:** Propose to add subunit vaccines (e.g. protein vaccines) which are also under development. **Proposed change (if any):** There is a very large range of RSV vaccines currently under development, including inactivated, live attenuated, chimeric, live viral vectored (some in a prime-boost regimen with two different constructs), and nucleic acid vaccines *and subunit vaccines (e.g. protein vaccines)*.	**Partially accepted; subunit has been added, which suffices.**
Lines 128-135	1	**Comment:** It is suggested adding the below proposed sentence at the end of this paragraph to indicate that other types of vaccines producing neutralizing titres may also be considered for development in seronegative subjects. **Proposed change (if any):** In the 1960s an alum-adjuvanted, formalin-inactivated,	**Not accepted. Again, this is background and this section is not expressing any opinions on the preferred product characteristics.**

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		whole virion RSV vaccine was developed. When administered to RSV-naïve infants it was not protective and it was associated with a higher rate of severe RSV disease and some fatalities following subsequent natural infection compared to the unvaccinated control group. Whilst the exact mechanism of this vaccine-associated disease enhancement is not known, investigations indicated that the vaccine elicited mainly RSV binding antibody rather than virus neutralising antibody. Consequently, vaccine development for primary immunisation of RSV-naïve subjects has focussed on live attenuated or live viral vectored vaccines with the aim of eliciting high titres of RSV neutralising antibody and a Th-1 directed immune response. *However, there is no theoretical reason to a priori discard a vaccine candidate of any class provided that the candidate can be shown to induce a robust neutralizing antibody response following primary vaccination or as a boost immunization once an appropriate immune response has been primed.*	
Lines 172-173	1	**Comment:** In order to protect an infant at 28 days with a vaccine it may be necessary to immunise at birth since it requires some time to develop immunity. **Proposed change (if any):** Vaccination of newborn infants (aged 0-27 days) ~~*is a less likely strategy and it*~~ is not addressed, although the guidance provided would be broadly applicable.	**Not accepted; but the text has been amended in response to other comments.**

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
174	2	**Comment:** Pregnant women are not a group in which clinical benefit of vaccination is most likely to be demonstrated. The benefit is to their infants after birth. Proposed change (if any): ….for groups where vaccination is most likely to lead to clinical benefit…	**Not accepted; that is precisely what the text in line 174 says.**
Line 176	1	**Comment:** In addition to the age-based groups listed, please consider addition of high risk groups to list as described in the previous section (e.g. cystic fibrosis, neuromuscular diseases, COPD, congenital or acquired heart disease, etc.). Just as adults ≥50 years of age are considered to be at elevated risk for adverse outcomes of influenza infection in some regions (e.g. U.S.), consider whether older adults should be considered to be ≥50 years of age rather than elderly ≥ 65 for RSV vaccine indications. **Proposed change (if any):**	**Partially accepted;** **See amended text.**
Lines 185-186	1	**Comment:** The population referenced in lines 114-116 is omitted from this section of the guidance. Clarification is therefore requested regarding whether it is within the scope of the guidance. **Proposed change (if any):**	**Not accepted; there is no population "omitted" from the sections on DAAs but the text has been amended in several respects.**

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
Lines 185-186	1	**Comment:** Given the reference to dosing of immunodeficient patients in line 424, this section of the guideline should clearly state that this patient group is also at risk of severe RSV disease. **Proposed change (if any):** The focus of the guidance is on evaluating DAA agents for the treatment of RSV disease in newborn infants, infants, toddlers*, as well as immunodeficient persons* and the elderly.	**Accepted; see amended text**
Line 188	1	**Comment:** Guidance on the use of DAAs would be welcomed as the only analogous approach in the guidance is the preventive use of monoclonal antibodies, but the different mechanism makes that information irrelevant for a DAA to prevent RSV. The use of DAAs to prevent RSV should be part of the guidance (i.e. which endpoints should be used, which population could be targeted). **Proposed change (if any):**	**Not accepted; but see amended text in scope and in relevant places.**
Line 193	1	**Comment:** It is suggested adding the following guidelines in the list of relevant guidelines: • Guideline on strategies to identify and mitigate risks for first-in-humans and early clinical trials with investigational medicinal products	**Partially accepted. The first and last have been added. The second is now replaced by the draft revised clinical vaccine GL and the third is not currently of relevance to the clinical development of RSV preventive or therapeutic strategies.**

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		(EMEA/CHMP/SWP/28367/07 Rev.1) • Guideline on adjuvants in vaccines for human use (EMEA/CHMP/VEG/134716/2004) • Guideline on Immunogenicity assessment of therapeutic proteins (EMEA/CHMP/BMWP/14327/2006 Rev 1). • Guideline on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use (EMA/CHMP/BMWP/86289/2010) **Proposed change (if any):**	
Lines 215-231	1	**Comment:** It is recommended that in the section on nonclinical efficacy data to support clinical trials for vaccines, a distinction is made between maternal immunisation and infant immunisation. **Proposed change (if any):**	**Partially accepted; see amended text.**
Lines 219-221	1	**Comment:** Due to species difference in antibody transfer from dams to offspring, it is proposed that the wording be amended to also allow measurement of efficacy in the offspring after passive antibody transfer. **Proposed change (if any):** Where relevant, studies may include vaccination of RSV non-	**Partially accepted. See amended text.**

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		naïve dams followed by measurement of ~~*neutralising antibody*~~ *immune response and/or efficacy* in the offspring at birth. *It is acknowledged that there are differences between species in the transfer of maternal antibodies from dams to offspring due to differences in placental biology. Therefore, passive antibody transfer can also be a valid evaluation model.*	
Lines 222-226	1	**Comment:** It should be clarified that challenge/efficacy nonclinical studies are recommended to be performed before moving to target population, but not necessarily prior to FTIH. The FTIH studies will be conducted in primed subjects, whereas challenge studies are more relevant to later studies conducted in the target population. The proposed nonclinical studies to demonstrate that the vaccine protects against development of RSV disease post challenge are relevant for evaluation of vaccine candidates intended to be used in RSV-naïve infants or for maternal immunization. However, the relevance of these models to evaluate the efficacy of vaccines targeting older adults (i.e. a primed population) is questionable. Primed animal models include adult cows naturally infected with the bovine RSV or rodents intranasally infected with live human RSV to mimic RSV natural infection “priming”. However, both experimentally induced and natural RSV infections provide protection against subsequent RSV experimental challenges, preventing the evaluation of vaccine-induced efficacy.	**Not accepted. The section does not in any way imply that such studies have to be done at any specific time in development and leaving it open is preferable.** **Accepted; the text has been modified but not as proposed.**

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): *During development,* ~~N~~*n*onclinical studies may be used to demonstrate that the vaccine protects against development of RSV disease post-challenge*, more particularly in RSV-naïve settings for the development of vaccines for infants*. If appropriate, studies may include challenge of offspring born to vaccinated dams *in the context of maternal vaccination*. Readouts may include effects of the intervention vs. placebo on viral loads in lower and upper respiratory tract tissues. The data from these experiments should be explored for correlations between immune responses and efficacy parameters. *Nevertheless, it is acknowledged that there are some limitations regarding the ability of animal models to evaluate vaccine-induced efficacy in RSV-non naïve conditions (when the vaccine is aimed for primed human populations).*	
Lines 225-226	1	**Comment:** It is better to use “may be” instead of “should be”, as most animal models don’t develop disease symptoms after RSV infection and therefore may not faithfully predict the correlates of protection. **Proposed change (if any):**	**Accepted**
Lines 227-231	1	**Comment:** Some features of vaccine-induced enhanced respiratory	**Not accepted. Data available to EU regulators indicates that the risk of**

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		disease (ERD) can be reproduced in RSV naïve preclinical animal models (BALB/c mice, cotton rats or calves) after vaccination followed by experimental RSV challenge and can be relevant in the context of the development of an RSV vaccine for infants. To the best of our knowledge the risk of vaccine-induced ERD has not been observed in RSV-seropositive children, toddlers and older adults primed by prior natural infection and can therefore be considered to be minimal, if any. This is supported both by the basic science of antibody affinity maturation, by clinical data that consistently show decreases in severity of RSV infection among non-naïve populations with each subsequent exposure, and by the absence of ERD noted in seropositive children who participated in the FI-RSV studies. Moreover, priming mice or cotton rats with a live RSV results in full protection upon challenge, with no signs of ERD. It is unlikely that vaccinating after live RSV priming will reverse the protective effect of previous RSV infection. Hence evaluation of ERD in animal models should not be required for candidate vaccines that are not intended to be used in naïve infants. Therefore, it should be clarified that evidences such as the characterization of the vaccine-induced immune responses and the demonstration that the vaccine elicits the type of immune responses that are expected to contribute to the protection in a given population are sufficient for vaccine candidates not intended to be indicated for naïve infants.	**enhanced disease occurring in vaccinated (unexpected data from one vaccine type, which may not be applicable across vaccine types, but this is yet to be investigated) RSV non-naïve subjects cannot be ruled out.**

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		References: • *Blanco et al., Vaccine. 2017 Jul 13;35(32):3951-3958* • *Cayatte et al., PLoS One. 2017 Nov 28;12(11):e0188708.* • *Graham, B. S., Virology. 2016 Jul;494:215-24* • *Schneider-Ohrum et al., Adjuvant. J Virol. 2017 Mar 29;91(8). pii: e02180-16.* • *Taylor et al., Sci Transl Med. 2015 Aug 12;7(300):300ra127* • *Taylor G. Vaccine. 2017 Jan 11;35(3)* • *Zhang et al., Vaccines. 2017 Mar 8;2:7* **Proposed change (if any):** Nonclinical studies should provide a preliminary assessment of the risk that vaccine-associated enhanced RSV disease could occur. *The evidences may include either immunological-based or post-challenge protection-based read-outs, depending on the characteristics of the vaccine and the target human population.* There are several issues that may impact on the ability of various animal models to evaluate the risk. This field is evolving and it is expected that sponsors will consider the scientific literature when designing the nonclinical programme to assess the potential risk of vaccine-associated RSV disease enhancement.	**The proposed change does not add anything useful since precise guidance on the most informative readouts cannot be given.**
Lines 227-231	1	**Comment:**	**Accepted; also, although no change to the**

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		New or novel approaches to vaccination should evaluate the potential for enhanced disease following vaccination in RSV-naïve models and could include large and small animal models with positive controls for ERD. Given the state of the scientific knowledge around the F protein structure, this should be very carefully assessed. **Proposed change (if any):**	**text was proposed, the relevant statement has been added.**
Lines 237-239	1	**Comment:** Efficacy in a cell line may be misleading, particularly where the DAA targets a host cell protein. Should consider testing in human primary cells or tissue and to include testing for potential influence of protein binding which can reduce efficacy. **Proposed change (if any):** Before commencing clinical trials, the antiviral activity of a DAA should be documented using a range of recent RSV clinical isolates. *For DAAs that target a host cell protein, determining efficacy in vitro on human primary cells or human lung tissue could be explored with a single strain of virus to provide additional evidence of efficacy.* The DAA should also be investigated for activity against other viruses, including those known to cause respiratory disease.	**Not accepted. The current scope of this document relates to DAAs, which, by definition, do not act on host cell targets.** **Thus, DAAs that target a host cell protein are not within the scope of this GL.** **Assessment of human plasma protein binding would be a routine element of the PK workup and does not need to be stated.**
Lines 240-241	1	**Comment:**	

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Development of resistance is likely to be a significant challenge for a DAA and so discussion should be expanded. **Proposed change (if any):** The mechanism of action of the DAA should be investigated, *as well as the mechanism(s) of resistance in any RSV isolates that appear to have reduced susceptibility in vitro. Multiple passages of in vitro RSV infection in the presence of the DAA could be used to screen for such resistant strains.*	**Not accepted. It suffices to say that resistance should be investigated. The methods for doing this do not need to be prescribed and multiple passages is a very simplistic approach.**
Lines 242-246	1	**Comment:** The statement on utility of *in vivo* models is overly pessimistic. The mouse shows significant weight loss and pulmonary inflammation on RSV infection, and both ribavirin and palivizumab have been shown to reduce symptoms when used prophylactically in the mouse. *References:* • *Mejias et al Antimicrobial Agents and Chemotherapy, 2004, 48, 1811, and 2005, 49, 4700;* • *Bolger et al Can J Physiol Pharmacol. 2005 83, 198.* **Proposed change (if any):** Nonclinical data may provide preliminary evidence of efficacy, *particularly in terms of viral load in vivo, although impacts on body weight loss and pulmonary inflammation may also be informative.* ~~*In most of the in-vivo nonclinical models that have been used, RSV replication does not*~~	**Partially accepted in that "most" has been changed to "some" and effects on body weight and pulmonary inflammation have been added.**

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		~~*produce quantifiable symptoms so that the effect of a DAA is based on demonstrating effects on viral titres compared to untreated controls. One*~~ Another approach to consider is the naïve bovine model, which could be used to estimate the effect of the DAA on symptomatic illness caused by bovine RSV, which appears to have a similar pathogenesis to RSV in naïve humans.	
Lines 244-246	1	**Comment:** Both calf (bovine RSV-based) and lamb (RSV-based) models mimic the pathology of a severe RSV lower respiratory tract infection and display a robust virus replication. In addition, calf and lamb lung architecture are similar to human lung architecture. Assessment of lung injuries via macroscopic inspection and histopathology might offer a more reliable and objective method than evaluating the occurrence of symptoms such as abnormal lung sounds, nasal discharge and loss of activity (not always clearly expressed by the animal even if a severe disease is present and potentially heavily influenced by RSV-unrelated factors such as bacteraemia and anti-inflammatory treatment). **Proposed change (if any):** One approach to consider is the naïve *ovine and/or* bovine model, which could be respectively used to estimate the effects of the DAA on *the pathology caused by human* ~~*or symptomatic illness caused by*~~ bovine RSV, which appears to have a similar pathogenesis to RSV in naïve humans.	**Accepted; see amended text**

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
Lines 250-252	1	**Comment:** Immunogenicity data collected in RSV non-naïve adults may not be representative of the immune response induced in an RSV-naïve population. This should be acknowledged in the guidance. **Proposed change (if any):** Regardless of the target population(s) for a candidate vaccine, the first trials are expected to be conducted in healthy adults (e.g. aged 18 to <45 years) to provide data on safety and immunogenicity in RSV non-naïve male ~~and~~ *or* non-pregnant female subjects*, acknowledging that the observed immunogenicity response may differ from that induced in an RSV-naïve population.*	**Not accepted; this is not an issue specific to RSV vaccines.**
Lines 250-252	1	**Comment:** The upper age limit of <45 years for first in human testing of RSV vaccines is not justified. We are not aware of any increased risk from immunization inherent to individuals 45 years of age and older that would make this age group unsuitable for participation in first-in-human studies. Given the very low risk of an RSV immunization study in an RSV-experienced adult, a much higher upper age limit, or no upper age limit, should be recommended. **Proposed change (if any):** Regardless of the target population(s) for a candidate vaccine, the first trials are expected to be conducted in	**Accepted.**

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		healthy adults ~~*(e.g. aged 18 to <45 years)*~~	
Line 254	1	**Comment:** The recommendation of a two-step evaluation in non-naïve children before moving to naïve infants does not seem required. As toddlers have larger airways and are less vulnerable to severe RSV disease compared to infants, it seems indeed appropriate to perform a first study in RSV non-naïve toddlers to collect reactogenicity and safety data (excluding ERD risk) before moving to naïve infants. However, safety and immunogenicity results in an RSV non-naïve population are not predictive of the risk of ERD in a naïve population. Therefore performing a study in non-naïve infants before moving to naïve infants would delay the development without de-risking the use of the vaccine in naïve infants and without offering a potential benefit to non-naïve infants. **Proposed change (if any):** It is recommended that safety and immunogenicity data are obtained from RSV non-naive toddlers before moving to RSV ~~non-naïve and~~ naive infants.	**Partially accepted.** **EU regulators have reason to believe that caution is necessary. Furthermore the guidance is in keeping with the approach taken by sponsors who have sought scientific advice on programmes aimed ultimately at naïve infants.** **However, this position may change in future as data are accumulated with a range of vaccine constructs. The text has been amended to at least allow the possibility of moving straight to naïve infants depending on accumulated evidence.**
Lines 263 – 266	1	**Comment:** Quantification of neutralising antibody may not, in all cases, be the primary assay used for baseline serostatus determination. It is proposed that allowance be made for the use of other assays through clinical or epidemiological studies	**Partially accepted; see revised text.**

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		shown to discriminate between naïve and non-naïve subjects. **Proposed change (if any):** For older infants with no remaining maternal anti-RSV neutralising antibody and for toddlers the protocol should provide criteria for defining RSV-naïve or non-naïve status at baseline that take into account the ~~*lower*~~ limit~~s~~ of detection and *lower limit of* quantification of neutralising antibody for the assay used, *or any other assay shown to discriminate between naïve and non-naïve subjects through clinical or epidemiological studies.*	
Lines 266 – 269	1	**Comment:** Relationship between baseline serostatus and previous RSV exposure is likely to be confounded by the presence of passively transferred maternal antibodies or waning of the immune response over time below detectable levels. It is proposed that allowance be made for evaluation of an anamnestic response which may also be helpful in differentiating RSV-naïve and non-naïve subjects. **Proposed change (if any):**	**Not accepted; this section is about patient selection and the proposal does not help identify serostatus *at baseline*, to achieve a population initially that is totally non-naïve followed by a mixed population and/or wholly naïve, which is the crux of the matter. However, comparing immune responses between subjects thought to be naïve vs. non-naïve should be assessed during the trial and this is covered in the general vaccine GL.**
Lines 272-273; 292-293; 546-547 570-571; 588-	1 (Pfizer)	**Comment:** The guideline recommends stratification at randomization by age sub-group for older infants/toddlers (lines 272-273) and for elderly subjects (lines 292-293). Similarly, stratification	**Advising stratification at randomization does not imply that trials would be powered for analyses within strata. However, it is acknowledged that it may**

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
589		at randomization by seasonal/non-seasonal region is suggested for infants/toddlers (lines 546-547), by geographic region for pregnant women (lines 570-571), and by region for elderly (lines 588-589). If the guideline is recommending a separate, stand-alone analysis for each stratum, it will not be practical to design studies with adequate power to achieve this. In particular, the EMA recommendation that "Trials should be conducted to support selection of the dose regimen(s) for age sub-groups 65-74 years, 75-84 years and 85 years and older" would be problematic if they are implying separate studies within each age sub-group to make an age-specific dose selection. Similarly, we do not feel that studies can be effectively powered for comparisons at the geographical level, particularly if these become granular (e.g. at the country level). It should therefore be clarified what is intended by stratification recommendations. Is stratifying by all of these factors simultaneously recommended? Should stratification factors be included in the primary analysis (as suggested by other guidelines)? This guideline also refers to the general guideline on the Clinical Evaluation of New Vaccines. The earlier guideline does not explicitly recommend stratification at randomization, but does note that "it may be very important to plan for	**not be necessary to recommend stratification in all places and amendments have been made.** **Similarly, the point is that adequate numbers should be enrolled in each age stratum to be able to make some assessment of any differences there may be in immune responses to the same dose. The sentences in two places clearly differentiate between adequate representation in safety and immunogenicity trials vs. stratification in efficacy trials.**

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		analyses in subsets according to factors such as age, ethnicity, and pre-existing antibody status." **Proposed change (if any):**	
Line 273	1	**Comment:** As this section is related to vaccine trials in infants and toddlers, in most of the trials healthy children will be planned to be enrolled. Therefore, "subject" is considered a more appropriate term than "patient". **Proposed change (if any):** The ~~*patient*~~ *subject* selection criteria should include the minimum gestational age at birth and the minimum and maximum ages required for enrolment.	**Accepted**
Line 276	1	**Comment:** Baseline serostatus in infants under 6 months of age will be difficult to interpret due to the presence of passively transferred maternal antibodies independently of the clinical stage of development. **Proposed change (if any):** It is not expected to be feasible to determine baseline serostatus prior to enrolment into *development and* efficacy trials *in infants less than 6 months of age*.	**Not accepted. It is not expected that baseline serostatus is determined in any vaccine *efficacy* trial due to the numbers involved.**
280-284	2	**Comment:** The statement that "It is expected that women will usually be vaccinated in the third trimester to maximize	**Accepted; the statement is unnecessary and has been removed.**

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		the amount of maternal antibody that is transferred to the foetus" should be revised for the following reasons: (1). Tdap is given in the second trimester with good effect (Gall et al., 2011, J Obs Gyn). (2) If more than one injection is needed, restricting the window to the third trimester will limit the vaccine's use. (3) Given the goal of protecting neonates born <35 weeks of gestation, vaccination before 28 weeks is important (4) Onset and duration of response: total IgG and IgG1 RSV-PreF levels increased substantially from baseline to day 30 after vaccination, and neutralizing antibody levels persisted well above baseline to day 90 in a Phase 2 clinical trial of non-pregnant women (Beran et al., 2018, JID), (5) although placental transfer increases with gestational age, there are data that very high concentrations of vaccine-specific Ab may result in saturation of the FcRn receptor and also that cumulative immunogetal transfer beginning earlier may make up for low transfer efficiency. **Proposed change (if any):** "…will usually be vaccinated in the second or third trimester…"	
285-289	2	**Comment:** Given the effect of HIV and malaria on placental transfer, studies in pregnant women with placental insufficiency should be studies separately. **Proposed change (if any):**	**Not accepted; the text leaves open both options.**
Line 291	1	**Comment:**	**Not accepted; the text follows CHMP age**

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		The need to have adequate representation of age sub-groups is acknowledged, however slight modifications to the upper/lower age of these subgroups should be acceptable. It is therefore suggested that the guideline is not specific regarding the age range of the sub-groups. **Proposed change (if any):** It is important that there is adequate representation of age sub-groups ~~*65-74, 75-84 and ≥ 85 years*~~ across the safety and immunogenicity trials.	**categorisations for the elderly.**
Lines 319-322	1	**Comment:** Clarification is requested regarding whether this means that one could proceed directly from adult Phase 1 PK/safety trial to paediatric Phase 2 trials with only modelling and simulation, i.e. adult human challenge study. **Proposed change (if any):**	**Not accepted; that is precisely what the text says.**
Lines 322-323	1	**Comment:** Trials in adult subjects should include elderly and non-elderly subjects. Elderly subjects are considered to be a risk of severe RSV infection. Non-elderly subjects with comorbidities (e.g., COPD, CHF, etc.) are also considered to be at risk of severe RSV infection, and thus should be included as target population for clinical trials. **Proposed change (if any):**	**Not accepted; as explained in the scope the focus is on "older adults" as define there for the stated reasons. The text recognises that some sponsors may wish to investigate other populations.**

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Trials that evaluate safety, pharmacokinetics and/or efficacy in ~~*elderly*~~ *adult* patients should include representation from all age groups.	
Lines 323-324	1	**Comment:** Regarding the proposed stratification by age for elderly patients in efficacy trials, it is considered that given the different capacity of the immune system with age, one can expect that the natural defence mechanisms are less effective with increasing age, which in turn might affect disease course. However, there are several categories for which to stratify thus there is a risk of obtaining very small subgroups with inconclusive results. If needed, a two-way stratification may be sufficient since it is unlikely that the differences are significant enough to require stratification groups. In line with the comment made on line 291, it is suggested that the guideline is not specific regarding the age range of the sub-groups. **Proposed change (if any):** Stratification by age ~~*(e.g. <65 and ≥65 65-74, 75-84 and ≥ 85 years)*~~ should be considered in efficacy trials.	**Partially accepted; see revised text.**
Line 325	1	**Comment:** It is recommended that this text be clarified. **Proposed change (if any):**	**Accepted.**

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Patient selection in efficacy trials should be based on a case definition that combines clinical signs and symptoms *of respiratory tract infection* with laboratory evidence of RSV.	
Lines 328-329	1	**Comment:** It is recommended that reference to very severe disease be omitted as it is unclear how this differs from severe disease. **Proposed change (if any):** The demonstration of a clinically important benefit of treatment is most likely to be possible in those with severe ~~*or very severe*~~ RSV disease.	**Partly accepted; the WHO publication that came out of a consultation meeting proposes criteria for differentiating severe and very severe disease at least in children. Although the criteria may be subject to revision, the text in a few places reflects the possibility that sponsors may derive criteria to demarcate severe and very severe cases.**
Lines 328-335	1	**Comment:** In many acute viral infections, like RSV or influenza infections, viral replication occurs primarily early in the illness, when symptoms are mild. The severe symptoms occur after an immune response has been elicited, curtailing viral replication. Therefore, antivirals are unlikely to demonstrate benefit when introduced after subjects begin to show severe symptoms. New antivirals need to be tested first when the disease is mild and viral replication is most active, preventing severe disease from occurring after an immune response has occurred. **Proposed change (if any):**	**Partially accepted; see revised text. If the first approval is based on trials only in subjects with mild disease it is very likely that there will be a marginal effect on duration of illness and that the product will immediately be used off label such that sequential placebo-controlled trials in the severely ill will not be possible. It is also not necessarily true that viral replication has already started to subside in those who first present with severe disease or progress to severe disease.**
Line 332	1	**Comment:**	**Partially accepted; the stated focus is on**

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		The guidance should consider that other populations may need to be studied as well. There are patients in the younger age group (<65 years) which also are predisposed to severe RSV e.g. subjects with respiratory or cardiovascular disease, immunocompromised subjects. **Proposed change (if any):** …recommended that *initial* efficacy trials with new….	**the populations defined in the scope, where it also says that sponsors may wish to study other populations.**
Lines 334-335	1	**Comment:** Stratification will ensure the balance between different groups within each stratum, but not necessary guarantee sufficient number of subjects enrolled in certain strata. **Proposed change (if any):** …efficacy trials with a new treatment for RSV should be confined to patients considered to be at the more severe end of the disease spectrum or should be stratified *by severity of RSV disease.* ~~to ensure that a sufficient proportion of patients with severe disease are enrolled to be able to assess efficacy in this sub-group~~	**The sentence has been removed to address points above and to clarify the situation.**
Lines 337-339	1	**Comment:** There is limited information or guidance available in the public domain regarding classification of RSV disease severity from either well recognized public health or professional bodies. Guidance from EMA in this regard would be useful to include in the document.	**Not accepted; it is not possible to provide such guidance at this stage. Furthermore, it may be detrimental to attempt to state preferred case definitions at this stage since it is not yet known what can be achieved by the types of interventions**

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change (if any):	**discussed.**
Lines 339-340	1	**Comment:** Assuming this is intended to suggest that 'severity' is largely determined by oxygen saturation, a lower limit should be included and clarification is required as to whether this limit would depend on absence or presence of respiratory or CV disease. In addition, regarding the measurement of oxygen saturation on room air, this may be also problematic to do clinically, as it will require removing supplemental oxygen in a subject who is requiring. **Proposed change (if any):** The inclusion of at least one eligibility criterion that is an objective measure, such as oxygen saturation on room air corrected for altitude *(when clinically feasible)* and measured under standardised conditions, is encouraged.	**Not accepted; see above.** **However, "on room air" has been removed since "under standardised conditions" will suffice.**
Lines 339-341	1	**Comment:** It is suggested adding tachypnea as another example of an objective measure that may be used to assess RSV disease severity. **Proposed change (if any):** The inclusion of at least one eligibility criterion that is an	**Accepted**

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		objective measure, such as oxygen saturation on room air corrected for altitude *or tachypnea* and measured under standardised conditions, is encouraged.	
Lines 341-343	1	**Comment:** It is unclear whether the patient categorisation refers to inclusion/exclusion criteria or to stratification factor or to analysis of outcomes by these categories. **Proposed change (if any):**	**Partially accepted; this section falls under DAAs and therefore the discussion is about patient selection criteria but the text has anyway been amended to address other comments.**
Line 342	1	**Comment:** It is recommend to include a reference for each of the published clinical scores provided as examples (RDAI and RACS) **Proposed change (if any):**	**Accepted**
Lines 344-345	1	**Comment:** Hospitalized subjects infected with RSV may be expected to be discharged from the hospital into the outpatient setting at different timepoints. It is therefore not feasible to expect that the collection of data will be confined to the inpatient setting. **Proposed change (if any):** Efficacy trials may be confined to hospitalised patients so that comprehensive data can be collected and/or if the treatment is administered each day by a healthcare professional, *while the subject remains*	**Partially accepted; see amended text to recognise that the patient location may change.**

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		hospitalised. It is anticipated that a proportion of subjects will be discharged from the hospital, in which case, collection of data and/or administration of treatment may be continued.	
Lines 348-351	1	**Comment:** Stratification by time from start of treatment versus symptom onset using 12 hour intervals may create too many categories to be feasible. **Proposed change (if any):** Consideration may be given to stratification at randomisation by time intervals elapsed since onset of *symptoms ~~(e.g. using 12hours intervals).~~ Duration of intervals depends on the specific characteristics of the compound and the mechanism of action.*	**Partially accepted; 12-24 h intervals has been added.**
Line 356	1	**Comment:** Proposal to add the alternative for central confirmatory testing if RDT that is not similar is used across sites. **Proposed change (if any):** … to minimize the possibility that there is an imbalance across trial sites in baseline viral loads. *Alternatively, central confirmatory testing may be considered.*	**Not accepted; for the purposes of enrolment into treatment trials the RDT will have to be conducted locally since there will not be time to obtain a central lab result. It is only when the text in this section is being used to derive case definitions in preventive trials that the central lab result would be appropriate.**
Line 370	1	**Comment:** It is suggested to add the potential for subgroup analysis due to their possible impact on the severity and course of the	**Not accepted. This section is about patient selection and not how to analyse subgroups.**

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		disease. **Proposed change (if any):** Patients with RDT results indicating the presence of additional viruses that may be contributing to the clinical presentation should still be enrolled *but considered for potential subgroup analysis.*	
Lines 393-398	1	**Comment:** As currently worded, this section does not leave open the possibility for maternal vaccine licensure based on functional antibody levels comparable to those provided by passive administration of monoclonal or polyclonal antibodies (Synagis, Respigam) in quantities known to protect young infants. The effectiveness of neutralizing antibodies in preventing RSV disease indicates that there is a knowable protective level of antibody, although agreement on this level has not yet been achieved. Regulators should be open to the possibility of granting licensure of new vaccines based on their ability to elicit neutralizing antibody titres comparable to those conferred by doses of Synagis or Respigam known to protect infants from severe disease. **Proposed change (if any):** If there is no established immune correlate of protection that can be applied to immune responses against a candidate vaccine, the possibility of inferring efficacy using an immunobridging approach, whereby the candidate vaccine is	**Not accepted; currently it is not considered that this approach would suffice for licensure.**

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		shown to elicit a comparable immune response to a licensed vaccine for which efficacy has been demonstrated, *or to elicit neutralizing antibody levels comparable to those given by therapeutic doses of monoclonal or polyclonal antibodies (Synagis, Respigam)*, would have to be discussed with EU Competent Authorities on a case by case basis.	
Line 379	1	**Comment:** Clarification is required regarding the meaning of "infants ± toddlers". **Proposed change (if any):**	**Accepted**
Lines 390-392	1	**Comment:** Propose adding a sentence to indicate the importance of also standardizing assay methods in the case where an immune correlate of protection is established. **Proposed change (if any):** Nevertheless, even if an immune correlate of protection has been identified from an efficacy trial with one vaccine it may not be widely applicable across candidate vaccine constructs and in different populations. *In addition, the assay methodologies must be standardized before an immune correlate can be adopted.*	**Accepted but the amended text is not that proposed. Also, it is in a different place.**
Lines 411-415	1	**Comment:** Feedback from key opinion leaders (KOLs) in the EU is that	**Not accepted; the GL is not asking for placebo-controlled efficacy data in the**

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		for immunodeficient persons, very often ribavirin is used, either inhaled or oral, for RSV treatment. In addition, several publications show the benefit of use of ribavirin. As such, KOLs also advise that it would not be feasible to recruit subjects for a placebo controlled study if use of ribavirin is not permitted. **Proposed change (if any):** **Line 413** Therefore, *except in immunodeficient persons*, a candidate DAA should be shown to be superior to a control group that receives placebo in the all treated population based on a clinically relevant primary endpoint. **Line 424** *Immunodeficient persons represent a special case given their higher viral loads and longer duration of replicating virus and their greater morbidity and mortality associated with RSV infection. While there are no approved DAA for RSV in immunodeficient persons, there are some agents, such as inhaled, intravenous, or oral ribavirin or intravenous immunoglobulin G which are used in common practice and for which there is supportive literature of clinical benefit. The use of these agents may need to be accounted for in study design and a design allowing the use of these standards of care treatments may be needed (e.g. a placebo controlled trial of a DAA added to a stratified background standard of care regimen). In addition,* immunodeficient persons may require a	**immunocompromised – however, some changes have been made to the text to clarify the point.**

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		different……	
Lines 428-431	1	**Comment:** Clarification is required regarding whether exploratory data alone might suffice to support a recommended posology within the SmPC. **Proposed change (if any):**	**The text already says this, however "uncontrolled" has been added in response to the comments above.**
Lines 428-431	1	**Comment:** In the setting of an exploratory trial in immunocompromised patients, guidance would be welcomed regarding the anatomical level of infection (URTI, LRTI) to be studied and also the trial design (placebo controlled, all subjects receiving standard of care [SoC]). Ribavirin, IVIG and/or palivizumab are used in clinical practice for the treatment of RSV infection in immunocompromised subjects, despite the lack of an indication. Given the anticipated differences regarding the use of these agents in the treatment of RSV infection in this population, it should be considered that in clinical trials antivirals are used as a component of SoC treatment chosen by the investigator where the investigational agent is an add on to SoC treatment. **Proposed change (if any):**	**Not accepted; see clarification above. A comparison with SOC is not required if evidence to support a dose regimen can be obtained in other ways.**
Lines 443-447	1	**Comment:** It is proposed that the population for the next trial be	**Accepted.**

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		clarified. **Proposed change (if any):** It is recommended that trials that include RSV-naïve subjects should require follow-up for RSV disease for at least one season before moving to the next trial in ~~*this population*~~ *RSV-naïve subjects.*	
Lines 448-449	1	**Comment:** In order to assess whether maternal antibody could potentially interfere with the immune response to active immunisation of infants there is a need to compare infants with no maternal antibody with infants that have maternal antibody. In some age groups, almost all infants will have some maternal antibody, and this may not be feasible. **Proposed change (if any):** The potential for maternal antibody to interfere with the immune response to active immunisation of infants should be assessed*, if feasible.*	**Not accepted. It is not necessary that some infants have no maternal antibody, only that the range is sufficiently wide to explore whether those with the highest levels have the lowest immune responses to vaccination and *vice versa.* See the amended text to explain this.**
Lines 454-457	1	**Comment:** Cord blood may not always be available, propose to add the option of using blood from the mother around the time of birth if cord blood is not available. **Proposed change (if any):** Dose regimen selection for pregnant women may be based	**Not accepted; this is possible in a small clinical trial setting and it is the only way to attempt to maximise the benefit that may be achieved and fully understand the relationship between NA reaching the infant and protection.**

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		on maximizing the difference in neutralising antibody titres in cord blood between infants born to vaccinated and unvaccinated mothers whilst maintaining an acceptable safety profile. *Every effort should be made to obtain cord blood for evaluation of maternal antibody transfer. When cord blood is not available, maternal blood can be collected at time of delivery, and data obtained with maternal blood reported separately.*	
Line 454	1	**Comment:** While there may not be a generally agreed immune correlate of protection for RSV disease, there is extensive evidence regarding the protective RSV neutralizing antibody titre in infants from large controlled clinical trials and many years of experience protecting human infants from RSV disease through the use of both monoclonal (palivizumab) and polyclonal (Respigam) neutralizing antibody preparations. The guidance should acknowledge the availability of these data and leave open the possibility of maternal vaccine licensure based on eliciting and passively transferring neutralizing antibody titres already known to be associated with protection of infants through passive antibody administration. **Proposed change (if any):**	**Not accepted.**
Lines 459-461	1	**Comment:** The rationale for this guidance is not clear. Unlike the infants	**Partially accepted; see the revised text.**

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		of some non-human mammals, human infants do not absorb antibody from breast milk into the serum. Therefore, the recommended studies have a low probability of providing useful information. Indeed, given human physiology, if differences in the decay of transplacentally transferred antibodies are observed as a function of breast feeding, the differences would most likely be due to uncontrolled confounding factors, not due to breast feeding itself. The measurements suggested here may therefore be of academic interest but will provide little useful information for evaluation of products for licensure. Literature references • Kemola et al., 1986. *Acta Paediatr Scand* 75:230-232 • Van de Perre, 2003. *Vaccine* 21 :3374-3376 **Proposed change (if any):** **Lines 459-461** ~~*The RSV neutralising antibody decay curves in infants should be documented. If trials are conducted in areas with variable rates and durations of breastfeeding sponsors may consider exploring the antibody decay curves accordingly.*~~	
Lines 462-463	1	**Comment:** Due to natural infection and re-exposure, the immune response of vaccinated mothers might never return to baseline. In addition, the objective of maternal immunization is to ensure that high levels of neutralizing antibodies are	**Partially accepted; see revised text.**

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		present during the last trimester of pregnancy to maximize placental transfer, the return to baseline is therefore less relevant in this population (as the intent is not to protect the mothers). The follow up of antibody persistence in vaccinated mothers is important to provide guidance on the need for revaccination in case of subsequent pregnancy shortly after the first one and should be evaluated in a subset of pregnant women. However, the return of post-vaccination antibody titres to baseline levels should not be the determinant of whether dosing during a subsequent pregnancy is needed. It should be driven by whether the infant would benefit from the boost from the pre-immunization titre during the subsequent pregnancy, even if that pre-immunization titre is higher than it was during the preceding pregnancy. Because of the increased exposure of women to young children and, therefore, to RSV after the birth of a child, especially a first child, it is likely that, on a population basis, RSV titres of new mothers will not return to baseline, pre-pregnancy levels until their newborns reach adolescence. Additionally, if revaccination data are required at the time of licensure, it will likely delay the availability of potentially effective vaccines in order to collect these data. It should be acceptable to evaluate repeat vaccination post-licensure. **Proposed change (if any):** The RSV neutralising antibody decay curve should be documented in vaccinated women during and *for a period of*	

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		time following the pregnancy. *However, it is acknowledged that* ~~and the time taken to~~ *it may not be feasible to establish a* return to pre-vaccination levels *due to ongoing re-exposure to RSV.* ~~should be determined~~	
Line 468	1	**Comment:** The requirement to follow up infants for more than one season between each trial in a maternal vaccination program does not seem justified. Administration of an RSV vaccine to adults (pregnant women in this case), all of whom can be assumed to have been naturally infected with RSV before, is expected to boost the immunological memory induced by previous natural infections (Anderson et al, 2013). Previous research has shown that the children of mothers who had high titres of RSV neutralizing antibodies had a decreased risk of disease (Anderson, 2013; Stensballe, 2009, Glezen, 1981, Lamprecht, 1976). With the transfer of these antibodies from the mother to the infant, the risk of ERD in the infants is considered negligible. In support of this hypothesis, enhanced respiratory disease has not been observed with the use of *Synagis* or with the transfer of serum of the FI-RSV vaccinated animals to recipient animals (Kwon, 2014). Therefore, a requirement to wait for observation through a season before starting a subsequent trial would have the consequence of delaying the introduction of potentially effective products without contributing significantly to safety.	**Not accepted; however, the text has been amended to be less definitive.**

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		The recommendation to follow for a full season between each trial should be subject to whether ERD has been sufficiently de-risked (including via nonclinical or other published reports, proven efficacy of other similar vaccines, or high neutralizing titres achieved in non-pregnant women). **Proposed change (if any):** It is recommended that trials should require follow-up of infants for RSV disease for at least one season before moving to the next trial. This cautious approach allows for very preliminary assessments of any risk of enhanced disease to be made in infants born to vaccinated vs. unvaccinated mothers before exposing additional subjects, and likely larger numbers, in the next trial. *However, the need to follow infants for a full season between each trial could be re-evaluated based on available nonclinical studies, proven efficacy of other similar vaccines, or high neutralizing titres achieved in non-pregnant women.*	
Lines 473-474	1	**Comment:** The guidance suggests that an assessment of optimal dose regimens is required in different age subgroups (65-74 473 years, 75-84 years and 85 years and older). If this is the guidance, it seems unprecedented compared to existing vaccines recommended for the elderly (such as influenza, pneumococcal, and herpes zoster vaccines). Such determinations would require very large studies for sufficient power and would be unlikely to lead to any change in clinical	**Partially accepted; see amended text.**

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		practice. Recommendations for such differential dosing are very unlikely because the operational confusion resulting from such a complicated scheme would counteract any immunological benefit. It would be more practical to select a single dose regimen that maximizes the benefit-risk ratio across the older adult population. Sub-analyses to determine protective efficacy or immunogenicity based on age subgroupings could be performed and reported in the SmPC. Please clarify the intent of this guidance. **Proposed change (if any):**	
477	2	**Comment:** "…neutralising antibody response to vaccination is analysed by pre-vaccination serostatus" is not entirely clear. **Proposed change:** ….suggest it is analysed with reference to or in the context of pre-vaccination serotstatus.	**Accepted; the text was already amended in response to other comments.**
Lines 490-494	1	**Comment:** The levels of non-neutralizing antibody alone are not sufficient to predict a potential interference with protection from neutralising antibodies. The level of non-neutralizing antibody needs to be evaluated in context with the levels of neutralising antibody to make this assessment. **Proposed change**: If a candidate vaccine elicits a large increment in non-neutralising antibody *in the absence of a robust neutralising response* in one or more subsets of subjects in safety and immunogenicity trials, there is concern	**Partially agreed; the text has been amended but not exactly as proposed.**

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		that this could potentially interfere with the protection afforded by neutralising antibody.	
Lines 503-508	1	**Comment:** There is a lack of flexibility in expected primary endpoint in the current text. Primary endpoint focuses on incidence of cases, but severity, duration or infant mortality could also be considered. **Proposed change (if any):**	**Not accepted; currently this is the recommended primary endpoint. Primarily we need to know if vaccines can prevent disease. The other issues mentioned are important secondary endpoints.**
Lines 503-531	1	**Comment:** This section seems to use the terms 'primary analysis' and 'primary endpoint', 'secondary analysis' and 'secondary endpoint' interchangeably. These terms do not necessary mean the same thing. Several places when the term 'primary (or secondary) analysis' is used, it means 'primary (or secondary) endpoint'. For a given endpoint, there could be several analyses done, primary analysis, secondary analysis, sensitivity analysis, etc. It is recommended to be more precise in the description and be consistent with the most recent ICH E9 (R1) addendum on estimands and sensitivity analysis in the guideline on statistical principles for clinical trials. **Proposed change (if any):**	**Accepted; the text has been amended.**
523-524	2	**Comment:** it is not entirely clear that these lines refer to a	**Not accepted; it is not agreed that the**

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		perceived need for healthcare interaction related to RSV illness instead of the normal healthcare interaction associated with delivery of an infant -- clarify	**text could be misconstrued in this way.**
Lines 544-546	1	**Comment:** It is specified that the completion of the vaccine course should be no more than a few weeks prior to the transmission season. Such a recommendation can be justified to de-risk ERD in early studies, but the design of the efficacy studies should be more flexible in defining the interval between the vaccination and the season. Vaccine developers are conducting global developments that should address the needs of regulators and recommending bodies in different regions. In order to estimate the true benefit/risk ratio, efficacy studies should also explore the vaccine being administered in a non-season dependent way especially if the vaccine is intended to be included in the routine vaccination schedule and administered year-round. Therefore, timing the recruitment period in regions where RSV is seasonal such that the last assigned dose is given no more than a specified number of weeks before the usual season start month may not generate the appropriate data. The concern if the vaccine is given earlier is that the period of maximal efficacy through the season would not be captured, which could lead to an underestimation of the potential vaccine efficacy, but would not pose a safety risk to study participants.	**Partially accepted; this is not a requirement for approval, just an approach to usefully shorten the development time. The text has been amended.**

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		We suggest to remove requirement for seasonal vaccination from section 7.1.2 Efficacy Trials. Adding some recommendations on seasonality in sections addressing early development studies can be considered. **Proposed change (if any):** ~~*At trial sites in regions where RSV is seasonal the recruitment period should be timed such that the last assigned dose is given no more than a specified number of weeks before the usual season start month. If the trial includes sites in seasonal and non-seasonal regions it may be useful to stratify enrolment accordingly.*~~ ~~*If the total (i.e. blinded to treatment assignment) number of cases of RSV accrued that meet the case definition fulfils the requirements of the statistical analysis plan, the primary analysis may be conducted after the end of the first season or after an equivalent time period post-vaccination if sites in non-seasonal regions are included.*~~	
Lines 552-559	1	**Comment:** This section speaks to advisability of evaluating efficacy in directly immunized infants and toddlers for 2-3 seasons to assure complete exposure. However, to assess the risk of ERD, infection rate is more important than the duration of follow-up in terms of the number of seasons. Also in the first season, the infection rate may have been high enough to observe ERD in the vaccine recipients if it were to occur. In addition, if the vast majority is infected during the first	**Partially accepted; the reference to seasons is removed because it is evidence of background exposure rates that matters. Further amendments have been made to the section describing follow-up durations.**

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		season, these subjects are not at risk any more during the 2nd season and therefore adding an additional year of follow-up does not bring much additional value. The guidance that the duration of follow-up to rule out disease enhancement for infants and toddlers should extend for 2-3 RSV seasons does not have a sound statistical justification. The recommendation should be for follow up with a sufficient number of subjects exposed to RSV (as judged by infections in the control group, not in the subject group, which might be protected) to detect a moderate to high risk of enhancement. This number of exposed subjects will be obtained simply by having enough subjects with a single season of observation to detect vaccine-mediated protection. **Proposed change (if any):**	
Lines 562-565	1	**Comment:** The guidance should specify that studies should not be powered to allow analyses of the level of protective efficacy in individual settings but that descriptive analyses can be performed. **Proposed change (if any):** The level of protective efficacy of a candidate vaccine may reflect maternal and placental health as well as the rate of decline in neutralising antibody in infants, which may not be	**Accepted; the wording has been amended but not exactly as proposed.**

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		constant in all settings; *analyses of the level of protective efficacy in individual settings can be conducted as a descriptive analysis, but it is not expected that studies would be powered to evaluate this.*	
Lines 566-567	1	**Comment:** A descriptive analysis based on breastfeeding "yes/no" can be conducted. However, it is not feasible to control for frequency, volume, antibody level, etc. for breastfeeding and perform an analysis. The guidance should specify that any analysis of the impact of breastfeeding would be descriptive, and not a prospective sample where breastfeeding parameters are controlled/assigned. **Proposed change (if any):** Furthermore, if immunogenicity trials suggested an effect of breastfeeding on infant neutralising antibody levels it is possible that regional differences in the rates and durations of breastfeeding could affect the efficacy observed. *Descriptive analyses of the impact of breastfeeding can be performed, but it is not expected that studies would be powered or specifically designed to control for and evaluate this.*	**Accepted; to reflect an earlier comment and change reference to breastfeeding has been removed from the section.**
Line 572	1	**Comment:** Requirement to vaccinate pregnant women ahead of season and follow for a season should be only until it can be	**Partially accepted; text has been amended in line with amendments made to infant section.**

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		concluded that the risk of ERD is minimal. It is expected that maternal immunization would be recommended regardless of RSV season, so efficacy study should be conducted with that population and approach. The requirement for seasonal enrolment of pregnant women in efficacy studies should be removed from the guideline. **Proposed change (if any):** ~~*Recruitment of pregnant women and completion of vaccination should be timed so that their infants are at risk of RSV exposure at least throughout the first 3-6 months of life.*~~	
Lines 573-575	1	**Comment:** Because the guideline recommends vaccinating pregnant women that will have newborns exposed to RSV season during the first 6 months of their life, what is proposed in this sentence does not seems feasible. Because by the time “geometric mean neutralising antibody titres are similar for infants born to vaccinated and unvaccinated mothers”, many will have been exposed to RSV. It might thus not be possible to identify this time. We agree that follow up of waning kinetics is important; however following up titres to until levels are similar to those of infants born to unvaccinated mothers is likely not feasible as we expect that roughly 50% of all infants will be exposed to RSV during the first RSV season.	**Partially accepted; essentially, we want the risk of enhanced disease to be followed until such time that residual maternal antibody will be none or negligible. The text has been amended accordingly.**

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): It is recommended that infants are followed up *to evaluate waning kinetics, but it is recognized that levels may vary due to continued re-exposure to RSV.* ~~the time at which prior data indicate that geometric mean neutralising antibody titres are similar for infants born to vaccinated and unvaccinated mothers~~	
Lines 586-595 and 688	1	**Comment:** In the absence of information on product characteristics and on potential correlate of protection, it is not appropriate to exclude the possibility to develop supraseasonal vaccines that could be administered year-round. The guideline should therefore not impose that the last doses are given no more than a specified number of weeks before the expected start of the RSV season. For the same reason, it is also premature to impose that data on revaccination is available pre-licensure. For example, some vaccines could allow maintaining high level of neutralising antibodies for several years. For such vaccines it seems more appropriate to follow waning of neutralizing antibodies to evaluate the need and timing for booster doses in the post-approval period. In addition, requesting that data on revaccination is available pre-licensure could result in longer times in getting effective vaccines available to patients. **Proposed change (if any):**	**Partially accepted; see related issues above; text has been amended.**

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Line 586-595 ~~*At trial sites in regions where RSV is seasonal the recruitment period should be timed such that the last doses are given no more than a specified number of weeks before the expected start of the RSV season.*~~ *Vaccines for older adults can provide seasonal or supraseasonal protection. If global efficacy studies include clinical sites in regions where RSV is seasonal and regions where it is not*, ~~*Depending on the site distribution and seasonality*~~ the sponsor should consider stratification by region. There may be sufficient cases accrued during the first RSV season to be able to conduct the primary analysis. In all cases, subjects should be followed through 2 or 3 seasons ~~*with re-randomisation*~~ *and it may be appropriate to re-randomise subjects* of the initial vaccinated group to be re-vaccinated or not in the sequential years so that advice on the need for re-vaccination to maintain protection can be given at the time of licensure. This advice *may not be applicable for vaccines for which persistence of the immune response has been demonstrated in early development studies and/or* can be modified in the post-approval period as additional data emerge (e.g. if data suggest that vaccination every 2-3 years is sufficient to maintain protection). **Line 688** It is expected that elderly subjects will likely require repeated dosing, perhaps annually, to maintain protection against RSV	

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		disease. The safety profile of repeated dosing over 2-3 seasons should be fully documented and compared with that of the first dose(s). *In case of a supraseasonal vaccine, and if re-vaccination is not needed, the safety profile of repeated dosing is not required.*	
Lines 596-603	1	**Comment:** Vaccine co-administration studies in pregnant women present specific challenges. It can be considered unethical to defer/delay administration of a recommended vaccine for the purpose of conducting a clinical study. The guideline could suggest that co-administration studies conducted in non-pregnant women can be acceptable in supporting co-administration in pregnant women. **Proposed change (if any):**	**Accepted.**
597-598	2	**Comment:** Co-administration trials are important since pregnant women in many geographies receive other vaccinations (TdaP, tetanus toxoid and influenza vaccines) in the second and third trimester. This would also be aligned with the 2017 WHO PPC for RSV.	**Accepted; the text was already amended in response to other comments.**
Lines 628-635	1	**Comment:** The value of challenge models is understated as a potential tool in the development of antiviral agents for treatment in adults. The visibility of this section could be enhanced to highlight the potential value of challenge models in early efficacy trials. This option could be highlighted as an	**Not accepted; human challenge models (HCM) are mentioned but it is not considered appropriate to stress them since it may be perceived that they are a requirement. Essentially it is for the sponsor to decide whether to conduct**

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		opportunity to generate key data to cover development needs (e.g. safety and PK), but in a potentially smaller sample size exposing fewer subjects to a novel untested therapeutic. Potentially a more efficient development approach to demonstrate proof of concept than a larger natural infection approach. **Proposed change (if any):**	**them.**
Line 629	1	**Comment:** Clarification is requested regarding the criteria for 'clinically apparent infection'. Challenge studies have demonstrated changes in signs/symptoms as evaluated by the subject; however these are usually limited in terms of lower respiratory tract signs. **Proposed change (if any):**	**Accepted; in that the reference has been removed and the text has been otherwise amended.**
Lines 649-650	1	**Comment:** Clarification is requested regarding the meaning of 'type of healthcare contact' e.g. hospitalisation, ICU, different departments/specialities, outpatient contacts. **Proposed change (if any):**	**Accepted; but need to avoid repeating rest of sentence about ventilation.**
Lines 651-653	1	**Comment:** Post treatment monitoring should be considered due to the risk of resistance developing for DAAs.	**Accepted; but it should be noted that this will be genotypic because RSV poorly survives shipping, which would limit any**

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		Proposed change (if any): It is recommended that efficacy trials should assess the effect of treatment on viral loads in appropriate respiratory samples collected at baseline and at intervals during treatment at least in a randomised subset of treated and untreated patients to permit analyses of response by baseline load. *Trials should include monitoring for the emergence of resistant strains with particular focus on patients failing to respond to treatment.*	**phenotypic testing.**
Lines 660-661	1	**Comment:** This section is a general introduction for safety aspects across all vaccine approaches and populations. It should be highlighted that the approach for evaluating ERD and how to appropriately de-risk ERD is not the same across all settings. **Proposed change (if any):** Currently, it is considered essential to assess the risk of vaccine-associated disease enhancement in the clinical programme for each candidate vaccine and regardless of the intended target population for use*; however, it is acknowledged that the approach to evaluating and ultimately de-risking vaccine-associated disease enhancement will not be the same across all settings*.	**Not accepted; the proposed additional wording does not assist the reader in any useful way.**
Lines 660-663	1	**Comment:** The first sentence in this paragraph should be qualified to	**Not accepted; such a statement does not belong in the body of the text.**

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		indicate that there has been no evidence of enhanced disease in any population other than seronegative infants. In addition, a sentence highlighting the difference with passive immunization should be included as proposed below. **Proposed change (if any):** Currently, it is considered essential to assess the risk of vaccine-associated disease enhancement in the clinical programme for each candidate vaccine and regardless of the intended target population for use. *However, it is acknowledged that there has been no evidence of enhanced disease in any population other than seronegative infants. The assessment of the risk of vaccine-associated disease enhancement should be adapted to the target population of the candidate vaccine. In addition, t*he requirements for such an assessment for a specific type of candidate vaccine may change in future if extensive experience indicates that similar vaccine constructs pose a negligible risk. *As passive immunization with both screened high-titer polyclonal antibodies and monoclonal antibodies has clearly been shown not to be associated with enhanced disease, vaccinating pregnant women for the purpose of passive transfer to infants does not pose the same level of risk as active immunization.*	**Furthermore, it is no longer entirely correct.**