4 December 2023
EMA/544822/2023
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Information for the package leaflet regarding polysorbates used as excipients in medicinal products for human use' (EMA/CHMP/190743/2016)

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

Stakeholder no.	Name of organisation or individual
1	Croda International plc
2	Medicines for Europe
3	F. Hoffmann–La Roche Ltd
4	AESGP
5	EFPIA

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	"Tween" is a registered trademark of Croda International plc and should not be used to describe Polysorbate grades in general terms. It is noted that many references to Tween in the text are taken from the cited literature, and so long as that literature mentions "Tween" then there is no problem with the quote. But where Tween is used in the EMA text (as opposed to the quoted literature) then the fact it is a trademark should be indicated, i.e. shown as "Tween™". There are other supplies of polysorbates for pharmaceutical use.	Accepted. TM designation was applied in the report text (except literature).
1	Apply the "™" designation at lines: 47, 48 Where the quotes from the literature should have referenced Polysorbate then use that term rather than "Tween".	Accepted. TM sign was applied as requested.
2	The Annex provides a mandatory wording only for the PIL, but no wording is given for the SmPC. The problem is that all MAHs decide on their own about the wording in the SmPC which gives avoidable room for discussion with authorities. The consequence will be that texts are not harmonized in this respect. This aspect was also discussed in the CMDh meeting with representatives of Interested Parties (Minutes for the meeting on 29 May 2018): "Question 7: Implementation of Annex to the EC guideline	Not accepted. Guidance on the specific wording in the SmPC is not within the scope of the revision of the excipients guideline. As per the Notice to Applicants, consistent information should be stated in both the SmPC and the PL for all excipients listed in the Annex. It is up to the MAH to define the appropriate wording in the SmPC based on their data.

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	An update of the SmPC will be needed, but the guideline is specific to the PL and labeling and will therefore not contain wording for the SmPC. The expressed need to have a common wording for the SmPC will be also shared with the EMA for further consideration." -> Therefore we suggest to add a common wording for the SmPC.	
3	Information included in the Package Leaflet is required to be derived from SmPC (Article 59(3) of Directive 2001/83/EC), particularly those information relating to safe and effective use of the medicinal product. We have noticed that the required new additions in PL for the purpose of mitigating the risks associated with these excipients have not been requested to be reflected in SmPC. In addition, providing the corresponding information also in SmPC will help HCPs to better understand the risk and to advise patients appropriately.	Not accepted. Guidance on the specific wording in the SmPC is not within the scope of the revision of the excipients guideline. As per the Notice to Applicants, consistent information should be stated in both the SmPC and the PL for all excipients listed in the Annex. It is up to the MAH to define the appropriate wording in the SmPC based on their data.
4	In the draft, the following statement is proposed to be included in the package leaflet for orally administered medicinal products: "This medicine contains x mg of polysorbate* in each <dosage unit> <unit volume> <which is equivalent to x mg/ <weight> <volume> >. Polysorbates in this medicine may alter the effects of other medicines. Talk to your doctor or pharmacist if you are taking other medicines." As a rationale it is stated that "polysorbate 80 is known to increase the gastrointestinal absorption of other drugs".	Accepted. It is agreed that literature evidence for interactions between *oral* polysorbate containing medicinal products and the PK of concomitant oral medicinal products is currently too low to justify a general warning in SmPC/PIL for all oral medicinal products with polysorbates. The proposed threshold of 5 µg/day by EFPIA (Appendix 1) is not considered justified by any data. Therefore, the warning was deleted, and the report text has been revised accordingly.

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	In our view, the general requirement of a warning in the SPC/PIL of all oral medicinal products with polysorbate as excipient is inadequate for the following reasons: 1. The evidence of a significant and clinically relevant effect of polysorbate in oral medicinal products on the pharmacokinetics of simultaneously applied other medicinal product is insufficient based on the literature discussed in the draft document. This applies even more for products where polysorbate is contained in very small amounts (typically <3 mg/unit used in the coating of film-coated tablets). Please refer below for a detailed assessment. 2. The statement "Talk to your doctor or pharmacist if you are taking other medicines." is not helpful for the professionals at all as they have limited tools on hand to find out which medicines could be affected by a potential influence of simultaneously applied polysorbate-containing medicinal products on their pharmacokinetics. This would leave patients with inadequate advice und uncertainty of appropriate use of medicines. The warning is therefore impracticable. 3. Polysorbates are widely used in the food industry, for example in ice cream or desserts. The amounts in these products are much higher compared to the small amounts as excipients in medicinal products. For example, cake or desserts may contain up to 3g/kg polysorbate which amounts to 300mg assuming a single portion of 100 g. A warning only for medicinal products with minute amounts of polysorbate in comparison with the amounts contained in food products appears to be disproportionate.	Future use of excipients as absorption enhancers may warrant reconsidering this type of warning.

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	The proposed general warning concerning for all oral medicinal products is inadequate and impracticable for the professionals who are to be asked for advice by the patient. **Assessment on the evidence for the influence of polysorbate containing oral medicinal products on the influence on the pharmacokinetics of other medicinal products** The chapter in the draft document that deals with the influence on other medicinal products is "3.3 Interactions". As far as the oral administration is concerned, only the lines 651-658 are relevant. The rest of the chapter deals with parenteral application. Three references are quoted with regard to oral administration: Azmin et al., 1985 [3], Kreuter et al., 2013 [4] and CIR, 1984 [5]. A review of these publications shows that only Azmin et al. 1985 [3], published data on the influence of orally administrated polysorbates on the pharmacokinetics of other medicinal products and is thus relevant in this context. This publication deals with the absorption, distribution, and elimination of methotrexate (MTX) after oral and intravenous administration. After oral application the plasma level of MTX is higher with 6, 12 and 24 % polysorbate 80 compared to application without polysorbate 80. This effect was only seen in the 1st hour after administration. After 2 hours the control MTX without polysorbate 80 showed higher plasma levels in comparison with the polysorbate 80 containing solutions. The effect on the pharmacokinetics can be rated as moderate. The amount of polysorbate applied in this investigation is much higher than the amount typically used in medicinal products.	

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	The interaction or the absorption of other drugs was not tested according to this publication. The second mentioned publication in this section is Kreuter et al. (2013). But in this publication polysorbate containing particles were injected intravenously into rats, which makes no relevance to the oral use of polysorbate-containing drugs and therefore should not play a role for the proposed warning regarding orally administrated medicinal products. The third investigation quoted in the draft on page 22 under 3.3, 659-660: "At 0.01% in human serum, PS 80 decreased the binding of atropine sulfate to serum albumin (CIR 659 report 1984 [18])" goes back to the publication of Hammouda et al. (1978) which is not available anymore. Therefore, it is not possible to have a detailed view on the data. In summary, the proposed warning statement for oral medicinal products is based on just one publication (Azmin et al. 1985) on the interaction of polysorbate in relatively high concentrations with one active ingredient (methotrexate). The effect is moderate even with high concentrations of polysorbate and compared to the small amounts of polysorbate used in medicinal products no conclusions can be drawn for other active ingredients. Data regarding the influence of small amounts of polysorbate which are typically contained in the film of film-coated tablets (e.g. less than 3 mg per unit) on the pharmacokinetics of other, concomitantly applied medicinal products are not presented. Therefore, the data available is in our opinion not sufficient to justify a general warning in SmPC/PIL for all oral medicinal products with polysorbates and the widespread use of polysorbates in food contradicts the effect of such a warning for medicinal products.	

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5	The EMA draft information for the package leaflet provides a good overview of polysorbates used excipients in medicinal products. Based on the clinical evidence, the Agency proposes thresholds for disclosing polysorbate content in the package leaflets based on the significant toxicities for the oral, parenteral and inhalation products.	
5	This guidance appears to apply stringent risk mitigation language for all potential applications of polysorbates without considering the potential harm to the public of unnecessarily conservative warnings and precautions. Polysorbates are widely used as low-concentration stabilizers in SC and IV -administered biologic products which represent a large and growing class of therapeutics with important benefits to public health. There is currently no evidence that use of polysorbates as a stabilizer in protein therapeutics poses severe risks to public health, yet the guideline appears to take sporadic evidence of risks from much less common applications of polysorbates, and apply this evidence, in the most conservative interpretation, as applicable to the more common and less risky applications such as low-dose stabilizers for protein therapeutics and vaccines.	Accepted. Exposure from Biologicals and vaccines was corrected in the report to both reflect amount per dose and exposure per kg body weight in a 60 kg adult. The report appropriately reflects the difference in exposure between small molecules (55 mg/kg) and Biologicals (< 1.2 mg/kg) and vaccines (< 0.1 mg/kg).
5	EMA should consider adapting the language of this guideline to account for the lower risks in common applications for biologics and vaccines so that the benefits of targeted modifications to safety labelling, for higher risk products, are not outweighed by the risks of creating unnecessary alarm among health care providers and patients considering use of biologic products and vaccines. It is recommended to create a more appropriate threshold than zero.	Not accepted. Parenterally given protein therapeutics and vaccines (exposure < 1.2 mg/kg), are affected by the currently proposed zero threshold for the warning about allergic/hypersensitivity reactions. In recent years there have been several additional case reports of hypersensitivity reactions (including severe

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		anaphylactoid reactions) also after subcutaneous or intramuscular administrations of therapeutic proteins (e.g. mAbs and epoietins) and vaccines (Gardasil; Covid-19 vaccines) showing positive Prick tests to PS 20 or 80 which are present at very low concentrations in these medicinal products. At least in some cases, esp. those with occurrence after the third (or later) administration of the same product, an IgE-mediated genesis cannot be excluded (e.g. Badiu et al. 2012; Palacios Castano et al. 2016); see addition in chapter 4.1 of the report). Due to the very rare possibility of IgE-mediated anaphylaxis and the inability to define a threshold above zero for pseudoallergy, the threshold zero appears to be reasonable and justified. The report has been supplemented by the most recent literature data.
5	In the safety assessment "free forms" of polysorbate are combined. The safety profile of particles is significantly different to warrant a specific limit. EFPIA companies strongly suggest to address these differences and not carry over the risks related to particulate materials in to the "free form" polysorbates .	Not accepted. No risks related to particulate materials have been carried over to "free forms" of polysorbate. All current threshold proposals and warnings relate to "free polysorbate".

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5	For allergic reactions, the Agency proposes that leaflets must disclose polysorbates at any level for all products regardless of route of administration (i.e. threshold of zero). This zero threshold contradicts the evidence reviewed in the document, which shows allergic reactions to be rare, reversible and non-immunologic in nature. Specifically, the Agency acknowledges the safe history of biologics and vaccines containing much lower levels of polysorbates compared to those used in oral and inhalation products and yet zero threshold is proposed. For polysorbates, there is some evidence that the underlying MoA is related to oleic acid content and auto-oxidation and cleavage at the ethylene oxide subunits, as well as hydrolysis of the fatty acid ester bond and hydroperoxide formation. This is quantifiable to some extent with the peroxidation-value as defined in the EuPh. Based on the available evidence, we respectfully request that the Agency considers another threshold for allergic reactions considering the polysorbates levels that have been shown to be safe use of in the biologics and vaccines. * see slides below this table. EFPIA companies welcome requests for further clarification of the data shown in the slides.	Not accepted. In recent years there have been several additional case reports of hypersensitivity reactions (including severe anaphylactoid reactions) also after subcutaneous or intramuscular administrations of therapeutic proteins (e.g. mAbs and epoietins) and vaccines (Gardasil; Covid-19 vaccines) showing positive Prick tests to PS 20 or 80 which are present at very low concentrations in these medicinal products. At least in some cases, esp. those with occurrence after the third (or later) administration of the same product, an IgE-mediated genesis cannot be excluded (e.g. Badiu et al. 2012; Palacios Castano et al. 2016); see addition in chapter 4.1 of the report). Due to the very rare possibility of IgE-mediated anaphylaxis and the inability to define a threshold above zero for pseudoallergy, the threshold zero appears to be reasonable and justified. The report has been supplemented by the most recent literature data.
5	It would be helpful to have further guidance on the location in the package leaflet (PL) for the required text. Currently it is up to the MAH to decide, and then in turn at the assessor's discretion. This may lead to inconsistency in the PL between MAH of products with the same excipient. • Within package leaflets, it appears this new information should be included in section 2 'What you need to know before you use	Guidance on the positioning of the excipient warning in the package leaflet can be found in the QRD guidance documents: Product-information templates - Human | European Medicines Agency (europa.eu) There is a specific subheading in section 2. [Excipients warnings]

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	TRADENAME', but the table should also be specific under which sub-header in section 2 this new information should be included depending on what the new text is conveying, e.g., under 'Warnings and precautions' for severe allergic reactions, under 'Other medicines and TRADENAME' for polysorbate in oral products altering the effects of other medicines.	<X contains {name the excipient(s)}>
5	Alignment between PIL and SmPC will require that the SmPC will also need to contain language on PS. • There is an expectation in the Guidelines to have equivalent information in the SmPC and PIL, so adding extra texts in PIL inevitably leads to an equivalent update to the SmPC. • It would be helpful if the guideline also outlined the type of wording the agency wants to see in the SmPC and where such wording need to be included in the document. This is particularly relevant for those excipients with safety-related wording.	Not accepted. Guidance on the specific wording in the SmPC is not within the scope of the revision of the excipients guideline. As per the Notice to Applicants, consistent information should be stated in both the SmPC and the PL for all excipients listed in the Annex. It is up to the MAH to define the appropriate wording in the SmPC based on their data.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
60, 61 117 Oral route 745-749 881-884	4	**Comments:** The estimated maximum oral dose of polysorbates (PS) 80 or PS 20 in authorized medicinal products is estimated to be about 1 mg/kg/day, which is far below the ADI of 25 mg/kg bw/day. Therefore it is concluded in the draft, that a threshold for oral administration of polysorbates as excipients is not considered meaningful. We agree with this, but the consequence of this statement should not be to set the threshold for additional information to zero, but rather to refrain entirely from adding any information in the PIL regarding PS at oral routes. The amount of PS in authorized medicines for oral use has to be looked in the light of the overall intake of this substance, summarized from medicines and food. For example Regulation (EU) No 1129/2011 provides a maximum level of 1 000 mg PS/ kg of ice cream as food additive. In comparison, an orally applied drug with 0.3 mg PS 80 per dose (example of the commenting company) does not significantly increase the burden, as already mentioned in the draft (lines 60-61, 881-884). The high background level from food suggests that polysorbates in drugs are negligible. Besides, polysorbates do not switch drug carrier proteins on or off, but may marginally influence the effectivity of the flux	Accepted. The proposed information and warning for oral administration has been deleted. (See also response to comment from stakeholder 4 on page 3).

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		pumps. Therefore, the proposed information seems to be disproportionate. In fact, there are some case reports about adverse events after parenteral administration of PS containing drugs. But similar cases after oral intake are not known. Moreover, as documented in the draft (lines 745-749), oral administration instead of intravenous keep from severe adverse effects. Therefore, the oral route must be considered independent from the parenteral in regard to safety labelling. Although toxicological studies are available, they lack the clinical relevance of a possible interaction with other drugs by the oral route. The information that led to this proposal is based on in vitro studies only, which are not relevant to the safety and the life situation of the patient. The reference to a doctor's consultation in case of multiple therapy is general and should always be included in a PIL. There is no special reason to implement this demand only with polysorbates. **Proposed change:** Delete proposed information for oral administration.	

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66-71	5	**Comments:** In this paragraph IV route is discussed, and again in line 888. However, the corresponding warning is on parenteral route, with threshold zero. This paragraph proposes zero threshold to address hypersensitivity reactions including anaphylactoid shock following intravenous (IV) administration. Based on the literature reviewed, it would be more appropriate to clarify the thresholds for intravenous (IV) infusion versus subcutaneous (SC) injection. This warning in its current version will include the vaccines administered by IM, SC or ID route. If the vaccines are not meant for inclusion in this warning, further precision on threshold or route of administration would be helpful. <see other comments on the zero threshold> **Proposed change:** (1) Please propose separate threshold for IV versus SC routes, if supported by the clinical evidence (2) amending the EMA proposed route of administration from "parenteral" to "intravenous"	Not accepted. In recent years there have been several additional case reports of hypersensitivity reactions (including severe anaphylactoid reactions) also after subcutaneous or intramuscular administrations of therapeutic proteins (e.g. mAbs and epoietins) and vaccines (Gardasil; Covid-19 vaccines) showing positive Prick tests to PS 20 or 80 which are present at very low concentrations in these medicinal products. At least in some cases, esp. those with occurrence after the third (or later) administration of the same product, an IgE-mediated genesis cannot be excluded (e.g. Badiu et al. 2012; Palacios Castano et al. 2016); see addition in chapter 4.1 of the report). Due to the very rare possibility of IgE-mediated anaphylaxis and the inability to define a threshold above zero for pseudoallergy, the threshold zero appears to be reasonable and justified. The report has been supplemented by the most recent literature data.

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69-71	5	**Comments:** There is insufficient data to say that there is not a threshold for anaphylaxis and the wealth of clinical data with biologics formulated with PS80 would suggest there is a safe threshold for this toxicity. Also, this allergic reaction has been seen with high levels of PS80 and not PS20, so PS20 should not have the same threshold concern. This is also supported in line 393 where PS80 has more of an effect in activating complement than PS20. A zero threshold is not operational. With increasingly better analytical methods, one can expect to be able to find PS in a majority of drug products. EFPIA companies, strongly suggest to put a threshold in place which is not zero. **Proposed change:** "As hypersensitivity reactions including anaphylactoid shock have been observed after IV administration of the drug product, a warning of allergic reactions at threshold zero is proposed. **A threshold of 1 mg/kg is proposed for anaphylaxis based on the totality of clinical data with parental administered mAbs formulated with PS80.**" See appendix 1	Not accepted. There is no hint for a difference between PS 80 and 20 as inducers of anaphylactic reactions (Bergmann et al. 2020). Anaphylactic reactions have indeed been reported after IM or SC injections of therapeutic proteins and vaccines: mepolizumab (PS 80; Bergmann et al. 2020), omalizumab (PS20; e.g. Perino et al. 2018), epoetins (PS 80; Steele et al. 2005), a HPV vaccine (PS80; Badiu et al. 2012), and, most recently, after Covid-19 vaccination in patients tested positive for PS 80 in skin tests (Paoletti et al. 2021; Ieven et al. 2021; Burlando et al. 2021). These reports, although very rare and possibly non-IgE-mediated in many cases, do not allow to draw a threshold above zero. Therefore, a warning of allergic/hypersensitivity reactions at threshold zero after parenteral exposure (all routes, not just IV) is considered justified. The report has been supplemented by the most recent literature data.

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76	5	**Comments:** Suggest that 10 mg/kg (i.v. bolus) trigger more than a warning and instead that 10 mg/kg (i.v. bolus) is considered unacceptably high as vasoplegia has been observed at this dose. **Proposed change:** Thus from the totality of preclinical and clinical data ~~**a threshold of**~~ 10 mg/kg (given as bolus dose) is considered ***unacceptably high*** ~~**justified to trigger a warning**~~ regarding cardiovascular effects (e.g. hypotension).	Accepted. The hemodynamic (and perhaps also the potential cardiotoxic) effects appear to be rather related to the infusion rate (peak exposure) than to the total dose (cumulative exposure). Bolus doses of 10 mg/kg PS80 (as given by the amiodarone commercial formulation) lead to hypotension and cardiac depression in dogs (Torres-Arraut et al. 1984). The reported lowest adverse effect level leading to hypotension in dogs is **0.43 mg/kg/min (10 min infusion at this rate) or 4.3 mg/kg bolus dose**; Cushing et al. 2009). This is supported by Varma et al. 1985 who demonstrated a blood pressure lowering effect in dogs after their lowest dose of 5 mg/kg PS 80 IV bolus. Cushing et al. (2009) reviewed that polysorbate 80 alone (at doses between 2 and 20 mg/kg) produced profound reductions in arterial blood pressure in dogs and other animal models. A proof of the alleged effect at 2 mg/kg could not be found in the literature cited. Therefore, it is agreed that a threshold of 10 mg/kg IV bolus dose is too high for the warning. A human equivalent dose of about 3 mg/kg is estimated from the lowest effective dose of 4.3 mg/kg in the dog (allometric factor for dogs: 1.4), which caused a drop in blood pressure. Therefore, a threshold of a cumulative dose of 3 mg/kg/day is derived, which in the worst case could be administered as a bolus injection.

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			Up to 7.7 mg/kg/day has been shown to be safe in **neonates if given at a rate of max. 0.13 mg/kg/min** (Cohen-Wolkowiez et al. 2011). Outcome: Change into Threshold of 3 mg/kg/d for the warning, and a consideration for risk minimization by lowering the rate of infusion has been added to the comments section in the Annex. PS exposure from therapeutic proteins and vaccines (max 1.2 mg/kg bolus dose) will not be affected by this threshold. Values equal to or above should trigger a warning regarding cardiovascular effects (hypotension/cardiac depression, also comprising infusion related hypersensitivity reactions). (The Guideline states "The threshold is a value equal to or above, which it is necessary to provide the information stated, it is not a safety limit.")
84-87	5	**Comments:** Suggest clarifying exactly (preferably in a table), which max bolus dose is acceptable and which max infusion dose/rate is acceptable to infants/neonates and adults respectively. **Proposed change:** to add: A small PK and safety study with anidulafungin infusions in infants and neonates with maximum PS 80 exposure of 7.7 mg/kg/day (max infusion rate over 60 min: 0.13	Partially accepted. The information on the anidulafungin study is included in the report. The comments section has been updated.

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		mg/kg/min) gives support that short term exposure at low infusion rates of PS 80 < 10 mg/kg per day is safe even in infants and neonates.	
88-89	5	**Comments:** Suggest setting exact limits for bolus and infusion doses/rates. **Proposed change:** Thus, a general recommendation for risk minimisation by lowering the rate of injection/infusion is given as a comment for consideration in the SmPC of parenteral products.	Accepted. The comments column has been updated accordingly.
111-116	5	**Comments:** The guidance acknowledges that polysorbate exposure via administration of therapeutic proteins and vaccine is very low (<0.25 mg/kg) being below all thresholds apart from zero. The zero threshold for anaphylaxis is not supported by the data in this document. **Proposed change:** "This is considered appropriate as it is in line with the absence of any signal of cardiotoxicity or hepatatoxicity after vaccine exposure from epidemiology or pharmacovigilance**. A threshold of 1 mg/kg is proposed for anaphylaxis based on the totality of clinical data with parental administered mAbs formulated with PS80."**	Not accepted. In recent years there have been several additional case reports of hypersensitivity reactions (including severe anaphylactoid reactions) also after subcutaneous or intramuscular administrations of therapeutic proteins (e.g. mAbs and epoietins) and vaccines (Gardasil; Covid-19 vaccines) showing positive Prick tests to PS 20 or 80 which are present at very low concentrations in these medicinal products. At least in some cases, esp. those with occurrence after the third (or later) administration of the same product, an IgE-mediated genesis cannot be excluded (e.g. Badiu et al. 2012; Palacios Castano et al. 2016); see addition in chapter 4.1 of the report). Due to the very rare possibility of IgE-mediated anaphylaxis and the inability to define a

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			threshold above zero for pseudoallergy, the threshold zero appears to be reasonable and justified. Outcome: The report has been supplemented by the most recent literature data.
117	2	**Comments:** "For risk minimisation, a SmPC warning on the risk of concomitant use of medications that prolong the QT/QTc interval should be considered." **Proposed change:** A concrete proposal for SmPC wording would be very helpful at this point to avoid discussions with authorities.	Not accepted. Guidance on the specific wording in the SmPC is not within the scope of the revision of the excipients guideline. As per the Notice to Applicants, consistent information should be stated in both the SmPC and the PL for all excipients listed in the Annex. It is up to the MAH to define the appropriate wording in the SmPC based on their data.
?	2	**Comments:** "In neonates doses > 80 mg/kg/day of polysorbate caused severe (fatal) hepatotoxicity." Is this comment an additional proposal to be implemented in the SmPC or just a rationale for the PIL wording?	This comment explains the rationale for the threshold and is not a proposal to be implemented in the SmPC. It has been updated with further information. "Case reports in adults at exposures below 80 mg/kg/d may indicate an earlier onset of signs of hepatotoxicity already at a cumulative daily dose of 35-40 mg/kg."
117	5	**Comments:** Companies have indicated that the content of this table is not aligned with the practice and experience in pharmaceutical industry. It is considered incorrect that the effects from nanoparticles have not been separated from "free" polysorbate.	Not accepted. The report clearly separates between effects from nanoparticles (see chapter 2.1.2 Blood brain barrier) and "free" polysorbate. The Annex does not specify any restrictions relating to particle effects. The comment simply highlighted potential

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		Differences in parenteral products exists which require a more fine-tuned limit setting to avoid restrictions/ warnings for certain groups of products which contain amounts of PS which has been shown to be safe in clinical use. (e.g. biopharmaceuticals).	pharmacokinetic interactions should be considered, either for free polysorbate or direct effects of particles. However, the comment was removed, as potential pharmacokinetic interactions are product specific and need to be evaluated during development. Any warnings for interactions need to be added to the product information, where relevant.
117	5	< see also under general comments> **Comments:** Zero threshold is proposed for allergic reactions for all medicinal products regardless of polysorbate levels and regardless of the route of administration. This contradicts the clinical safety data reviewed in 4.1. Safety in Adults – Hypersensitivity, Pseudoallergy. The zero threshold in the table says that PS80 may influence the pharmacokinetics (PK) of concomitant drugs (e.g. brain uptake, inhibition of intramuscular absorption). However, there is significant data with biopharmaceuticals showing no increase in brain uptake. This is different from coated nanoparticles so it's not appropriate to have a zero threshold. The literature cited in lines 282-300 had high doses of PS or they were loaded on coated nanoparticles which is quite different than the low concentration used to prevent aggregation in biopharmaceutical formulations.	Partly accepted. 1) Not accepted with regards to allergic reactions. In recent years there have been several additional case reports of hypersensitivity reactions (including severe anaphylactoid reactions) also after subcutaneous or intramuscular administrations of therapeutic proteins (e.g. mAbs and epoietins) and vaccines (Gardasil; Covid-19 vaccines) showing positive Prick tests to PS 20 or 80 which are present at very low concentrations in these medicinal products. At least in some cases, esp. those with occurrence after the third (or later) administration of the same product, an IgE-mediated genesis cannot be excluded (e.g. Badiu et al. 2012; Palacios Castano et al. 2016); see addition in chapter 4.1 of the report). Due to the very rare possibility of IgE-mediated anaphylaxis and the inability to define a threshold above zero for pseudoallergy, the threshold zero appears to be reasonable and justified.

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		Proposed change: Please review the clinical data and take into consideration the nature of the allergic reactions reported for the different routes of administration and the vastly different levels of polysorbate used for each route.	The report has been supplemented by the most recent literature data. 2) Accepted: General comment on PK interaction (e.g. brain uptake etc.) has been removed. However, of note, it had never been intended to be part of the warning. The interaction potential of a medicinal product needs to be addressed during development, and warnings added in the product information, where relevant.
117	5	**Comment regarding the SmPC:** The addition of QT prolongation represents a completion of the sequence from in vitro and non-clinical findings to the worst case clinical outcome of potentially life-threatening Torsades de Pointes. QT prolongation furthermore represents an easily measurable ECG finding and predictor of patient risk. **Proposed change:** The risk of severe hypotension could be minimised by slowing down the infusion (by more than 5 minutes). Electrophysiological studies show cardiac depression in dogs and inhibition of hERG currents by polysorbates in vitro. The potential for **QT prolongation and** torsades de pointes in humans is unknown.	Accepted. The comments have been reworded.
117	5	**Comments:** A risk similar to the use of concomitant medications that prolong the QT/QTc interval (acquired long QT syndrome)	Accepted. The proposed addition has been included.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		exists for patients who have one of the rare forms of congenital QT syndrome. For patients with a known diagnosis of the latter BI considers such statement a meaningful addition that completes the warning with respect to preexisting QT/QTc prolongation, regardless of its aetiology. **Proposed change:** For risk minimisation, a SmPC warning on the risk of concomitant use of medications that prolong the QT/QTc interval **or congenital QT syndrome** should be considered.	
117 Table, Row 1 Oral, Threshold Zero	3	**Comments:** The information about interaction with concomitant drug use should be also reflected in SmPC. **Proposed change:** Change to the Comments column: … May influence the pharmacokinetics of concomitant drugs (e.g. brain uptake, inhibition of intramuscular absorption). **This potential need to be assessed, if relevant, the information should be included in SmPC as well** ** The type of polysorbate(s) (e.g. polysorbate 80 or 20) in the medicinal product should be mentioned here.*	Not accepted. Guidance on the specific wording in the SmPC is not within the scope of the revision of the excipients guideline. As per the Notice to Applicants, consistent information should be stated in both the SmPC and the PL for all excipients listed in the Annex. It is up to the MAH to define the appropriate wording in the SmPC based on their data. Investigation of potential interactions and (in)compatibilities is part of the product development and relevant results need to be expressed in the product information as instructed in the SmPC guidance. https://health.ec.europa.eu/system/files/2016-11/smpc_guideline_rev2_en_0.pdf

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Table, Row 2 Parenteral, Threshold Zero	3	**Comments:** Information about when administered parenterally, severe allergic reaction may occur, about interaction with concomitant drug use and about compatibility, is necessary to include in SmPC as well. **Proposed change:** Change to the Comments column: May influence the pharmacokinetics of concomitant drugs (e.g. brain uptake, inhibition of intramuscular absorption). ***This potential need to be assessed, if relevant, the information should be included in SmPC as well*** Information on compatibility of the medical device type (if any) with the polysorbate in the product should be indicated ***in SmPC as well***. To add: ***A warning on the potential risk of severe allergic reaction should be included in SmPC.*** ***A mention of polysorbate in SmPC 4.3 should be included, example text: [Tradename] contains polysorbate.***	Not accepted. Guidance on the specific wording in the SmPC is not within the scope of the revision of the excipients guideline. As per the Notice to Applicants, consistent information should be stated in both the SmPC and the PL for all excipients listed in the Annex. It is up to the MAH to define the appropriate wording in the SmPC based on their data. Investigation of potential interactions and (in)compatibilities is part of the product development and relevant results need to be expressed in the product information as instructed in the SmPC guidance. https://health.ec.europa.eu/system/files/2016-11/smpc_guideline_rev2_en_0.pdf

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Table, Row 2 Parenteral, Threshold Zero	5	**Comment:** Information about when administered parenterally, severe allergic reaction may occur, about interaction with concomitant drug use and about compatibility, is necessary to include in SmPC as well. **Proposed change:** To add to comments column: "A warning on the potential risk of severe allergic reaction should be included in SmPC. A mention of polysorbate in SmPC 4.4 should be included, example text: [Tradename] contains polysorbate."	Not accepted. Guidance on the specific wording in the SmPC is not within the scope of the revision of the excipients guideline. As per the Notice to Applicants, consistent information should be stated in both the SmPC and the PL for all excipients listed in the Annex. It is up to the MAH to define the appropriate wording in the SmPC based on their data.
Table, Row 3 Parenteral, Threshold 10 mg/kg/dose	3	**Comments:** For parenteral medicinal products a precaution regarding rate of infusion to prevent cardiovascular effects should be considered. **Proposed change:** To add the following in Comments column: … For risk minimization, a SmPC warning on the risk of concomitant use of medications that prolong the QT/QTc interval should be considered.	Accepted. The wording on risk minimisation has been revised.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		A precaution regarding rate of infusion to prevent cardiovascular effects in SmPC section 4.4 should be given as well.	
Table, Row 3 Parenteral, Threshold 10 mg/kg/dose	5	**Comment:** For parenteral medicinal products a precaution regarding rate of infusion to prevent cardiovascular effects should be considered **Proposed change:** To add the following in Comments column: "[…] For risk minimization, a SmPC warning on the risk of concomitant use of medications that prolong the QT/QTc interval should be considered. A precaution regarding rate of infusion to prevent cardiovascular effects in SmPC section 4.4 should be given as well."	Accepted. See above.
Table, Row 4 Parenteral, Threshold 35 mg/kg/day	3	**Comments:** The potential risk of serious hepatotoxicity adverse events should be included in SmPC as well. **Proposed change:** Proposed changes to Comments column: In neonates doses > 80 mg/kg/day of polysorbate caused severe (fatal) hepatotoxicity.	Not accepted. Guidance on the specific wording in the SmPC is not within the scope of the revision of the excipients guideline. As per the Notice to Applicants, consistent information should be stated in both the SmPC and the PL for all excipients listed in the Annex. It is up to the MAH to define the appropriate wording in the SmPC based on their data.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		A warning on the potential risk of serious hepatotoxicity adverse events should be included in SmPC.	
Table, Row 4 Parenteral, Threshold 35 mg/kg/day	5	**Comment:** The potential risk of serious hepatotoxicity adverse events should be included in SmPC as well **Proposed change:** Proposed changes to Comments column: "In neonates doses > 80 mg/kg/day of polysorbate caused severe (fatal) hepatotoxicity. A warning on the potential risk of serious hepatotoxicity adverse events should be included in SmPC."	Not accepted. Guidance on the specific wording in the SmPC is not within the scope of the revision of the excipients guideline. As per the Notice to Applicants, consistent information should be stated in both the SmPC and the PL for all excipients listed in the Annex. It is up to the MAH to define the appropriate wording in the SmPC based on their data.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Table, Row 5 Topical use, Threshold Zero	3	**Comments:** Since adverse events of skin disorders may occur, it should be reflected in SmPC section 4.8, if it is an identified risk for a given product. For both cases of identified or a potential risk, include a warning on the excipients in SmPC **Proposed change:** To add in Comments column the following: ***Include a waring on the potential skin disorder risk of this excipient in SmPC.*** ***If skin allergy is an identified ADR caused by polysorbates 80 or 20 for a given product, this should be included also in SmPC section 4.8***	Not accepted. Guidance on the specific wording in the SmPC is not within the scope of the revision of the excipients guideline. As per the Notice to Applicants, consistent information should be stated in both the SmPC and the PL for all excipients listed in the Annex. It is up to the MAH to define the appropriate wording in the SmPC based on their data.
117	5	**Comment:** In the header or at another appropriate place of the table a statement should be included (e. g. as a footnote) that for products which have already a hypersensitivity warning in the SPC and leaflet (e.g. FVII products – see Core SPC EMA/CHMP/BPWP/1619/1999 rev. 3) it is possible to adjust the wording of the already existing hypersensitivity warning by including the information on Polysorbate. **Proposed change:** To add in the package leaflet: *)	Not accepted. This is not specific to polysorbate. By default statements should be added to the product information where considered the most relevant. The appropriateness of combining information/warnings would be decided on a case-by-case basis.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		*) for products which have already a hypersensitivity warning in the SPC and leaflet, the wording of the already existing hypersensitivity warning can be adjusted to include the information on Polysorbate.	
200-201 1059-1061 1065 and 171	5	**Comment:** It seems that there is a mistake/inconsistency in the expression of exposure to polysorbate: in the first part of the document it is expressed in mg/kg bw (e.g. 0.75 mg/kg bw and 1.175-4.85 mg/kg bw) while in other part of the document (lines 1059-1061) it is expressed in mg/dose (e.g. 0.75 mg/dose and 1.175 mg/vaccine dose). **Proposed change:** Harmonize the document with the following units: 0.75 mg/dose and 1.175 mg/dose	Not accepted. Harmonisation is not necessary, because the units are correct and, in all cases, translated to the corresponding amounts per kg BW.
Line 281	5	**Comment:** This section implies that PS80 increases the Blood brain barrier (BBB) transit of large molecules. In fact, polysorbates have been used for years as excipients in antibody formulations, and no evidence exists to suggest that these molecules are able to transit the BBB regardless of the formulation. We suggest that this section be tightened up and that the details regarding increased BBB transit are clarified regarding molecule type.	Partly accepted. Section 2.1.2 describes data from literature about enhancement of brain uptake either at high intravenous doses of PS 80 (> 3 mg/kg) or as a coat on drug nanoparticle formulations. Both are not considered relevant for SC administered antibody formulations containing PS80 < 1.2 mg/kg/dose, therefore it is agreed that a warning in the PI leaflet is not appropriate for monoclonal antibody formulations. The report has not been changed. Potential PK interactions need to be taken into account during the assessment of

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			specific medicinal products, and warnings introduced in the product information, when relevant. The information on the influence on PK of concomitant drugs has been removed from the PL.
281-313	5	**Comment:** a) The paragraph cites several publications. They mainly evaluate nanoparticles containing polysorbate 80 (PS80). The paragraph cites several papers. Azmin et al. 1985 and Calvo et al. 2001 in detail: Calvo et al. (2001) showed that a polysorbate 80 intravenous dose of 20 mg/kg in rats increased BBB permeability to sucrose (which was a small part of the actual paper). In the Azim paper it is reported that Free PS80 in solution seems to increase brain concentration of MTX (Azmin graph below); while in another paper (Gulyaev et al. 1999; abstract reviewed) a solution of PS80 did not facilitate brain concentration of doxorubicin – only PS80 coated vesicles did. Therefore both papers are somewhat contradictory. Also most of the publications used high PS80 concentrations; for example the first Azim paper (1985) used 300 mg/kg PS80 IV (6% solution). b) The nanoparticle data should not be used when addressing oral or intravenous formulations with polysorbate excipient in solution, since distribution, uptake, and/or effects with polysorbate associated nanoparticles are not	Partly Accepted. *See response above*

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		predictable for "free polysorbate in solution". The effects are considerably different and seen at different doses. **Proposed change:** a) The first sentence of the paragraph should be replaced by a more careful statement: ~~"It has been known for a long time that polysorbate 80 increases the uptake of drugs into the brain 282 (Azmin et al., 1985 [3])~~ Some publications indicate that polysorbate 80 may change brain uptake of other drugs." b) In the document, effects with nanoparticles should be clearly separated from effects of "free" polysorbate.	
389-400	5	**Comment:** The Coors et al paper was a single patient that responded to PS80 in a skin prick allergen test after receiving an IV infusion of 0.5% PS80 in a multi-vitamin prep. This is a high dose of PS80 and does not support a zero threshold. This section on complement activation is the only data that talks about pseudoallergic responses. The studies described here attribute the allergic reactions to medicines containing polysorbate to "Complement activation-related pseudoallergy (CAPRA)" and that the anaphylactoid reaction to be of non-immunologic origin. This is strong evidence supporting a threshold, other than	Partly accepted. The pseudoallergic nature of many reactions to polysorbate is not doubted. However, in recent years there have been several additional case reports of hypersensitivity reactions (including severe anaphylactoid reactions) also after subcutaneous or intramuscular administrations of therapeutic proteins (e.g. mAbs and epoietins) and vaccines (Gardasil; Covid-19 vaccines) showing positive Prick tests to PS 20 or 80 which are present at very low concentrations in these medicinal products. At least in some cases, esp. those with occurrence after the third (or later) administration of the same product, an IgE-mediated genesis cannot be excluded (e.g. Badiu et al. 2012; Palacios Castano et al. 2016); see addition in chapter 4.1 of the report). Due to the very rare

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		zero, for allergic reactions. (Supporting slides can be found below this table.) **Proposed change:** Please consider the non-immunologic nature of the pseudoallergic reactions of polysorbate and propose a threshold other than zero.	possibility of IgE-mediated anaphylaxis and the inability to define a threshold above zero for pseudoallergy, the threshold zero appears to be reasonable and justified. Research by Li et al. (2014) suggest that isosorbide components of polysorbate 80 (polyoxyethylene isosorbide oleate) and polyamine receptor-mediated endocytosis may be involved in causing pseudoallergy by polysorbate 80. The report has been supplemented by the most recent literature data.
434	5	**Comments:** Table 3 is under the tumor promotion/growth inhibition section, but the parameters are a compilation of everything discuss previously. This needs to be under a new heading. Also, no mention of anaphylaxis or pseudoallergy in this table, so there are no data to justify a zero threshold. **Proposed change:** Recommend this table be given its own section. In addition, anaphylaxis/hypersensitivity should be mentioned and the assigned threshold.	Not accepted. Table 1 and Table 2 (previous tables 2 and 3) are placed at the end of section 2.1 as a whole, just before section 2.2; they are not specifically related to section 2.1.5 (tumor growth).
478	5	**Comment:** Need to define total n from which only one mouse developed a benign skin tumor. **Proposed change:**	Not accepted. This number is not relevant for the outcome of the report, i.e. the warnings in the PIL.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Please define.	
486-488	5	**Comment:** Need to specify the species in which the oral effects of PS 80 on reprotox were evaluated. **Proposed change (if any):** Please specify.	Accepted. Species "rats" were added to section "Reproductive function toxicity", as well as the sentence: "The no observed adverse effect level (NOAEL) of polysorbate 80 for mother animals **(rats)** and the subsequent generation (F1) was considered to be 1.0 vol% (2,013 mg/kg body weight/day) as a level in drinking water.
530	5	**Comment:** How can an LD50/90 be a single number?	Accepted. Farkas et al. describe an LD50/90-day value, which means that the newborn rats were observed for 90 days. The wording in the report has been changed accordingly.
679-683	5	**Comment:** With respect to the inhibition of intramuscular absorption due to PS, the relevance of referenced publications is deemed questionable. Kobayashi 1977 states: "No significant difference in the uptake of drugs by the muscles either in the presence or absence of PS80 could be demonstrated", and " there was a marked inhibition in the distribution rate of isonicotinamide from blood to muscle, and the extracellular spaces were greatly decreased by pretreatment with polysorbate 80"	Accepted. The statement "May influence the pharmacokinetics of concomitant drugs (e.g. brain uptake, inhibition of intramuscular absorption" has been removed from the labelling text.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: The proposed statement for the package leaflet on inhibition of intramuscular absorption should be deleted: "May influence the pharmacokinetics of concomitant drugs (~~e.g~~. brain uptake~~inhibition of intramuscular absorption~~). "	
705-729	5	**Comment:** This paragraph discusses hypersensitivity and pseudoallergy toghether, but fails to come to a conclusion what type of reaction is the concern for polysorbates. Based on the above series of comments on this paragraph, it is suggested that the evidence for hypersensitivity is re-evaluated and a concise conclusion drawn. Additionally it is noted that the section does not discuss anaphylaxis which is the basis for using a zero limit for inclusion of warnings in the leaflet. **Proposed change:** Reevaluate and rewrite section 4.1 paragraph	Partly accepted. In recent years there have been several additional case reports of hypersensitivity reactions (including severe anaphylactoid reactions) also after subcutaneous or intramuscular administrations of therapeutic proteins (e.g. mAbs and epoietins) and vaccines (Gardasil; Covid-19 vaccines) showing positive Prick tests to PS 20 or 80 which are present at very low concentrations in these medicinal products. At least in some cases, esp. those with occurrence after the third (or later) administration of the same product, an IgE-mediated genesis cannot be excluded (e.g. Badiu et al. 2012; Palacios Castano et al. 2016); see addition in chapter 4.1 of the report). Due to the very rare possibility of IgE-mediated anaphylaxis and the inability to define a threshold above zero for pseudoallergy, the threshold zero appears to be reasonable and justified. Section 4.1 Hypersensitivity has been re-written and complemented with most recent literature data.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
708	5	**Comment:** The data with docetaxel is at much higher levels of PS80 than is seen with biopharmaceuticals. **Proposed change:** These side-effects have been attributed, in part, to the high levels of polysorbate 80 found in the docetaxel formulation.	Accepted. The paragraph on docetaxel in section 4.1 was amended accordingly.
718-721	5	**Comment:** The study described here is for an infusion product containing polysorbate and multivitamins. While polysorbate was identified as the causative agent for an immediate-type allergic shock reaction, no polysorbate-specific IgE antibodies were identified, thus confirming the non-immunologic nature of the anaphylactoid reaction. This study supports a threshold, other than zero, for anaphylactoid reaction of non-immunologic nature. **Proposed change:** Please consider the non-immunologic nature of the pseudoallergic reactions of polysorbate and propose a threshold other than zero.	Not accepted. In recent years there have been several additional case reports of hypersensitivity reactions (including severe anaphylactoid reactions) also after subcutaneous or intramuscular administrations of therapeutic proteins (e.g. mAbs and epoietins) and vaccines (Gardasil; Covid-19 vaccines) showing positive Prick tests to PS 20 or 80, which are present at very low concentrations in these medicinal products. At least in some cases, esp. those with occurrence after the third (or later) administration of the same product, an IgE-mediated genesis cannot be excluded (e.g. Badiu et al. 2012; Palacios Castano et al. 2016); see addition in chapter 4.1 of the report). Due to the very rare possibility of IgE-mediated anaphylaxis and the inability to define a threshold above zero for pseudoallergy, the threshold zero appears to be reasonable and justified. The report has been supplemented by the most recent literature data.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
722-725	5	**Comment:** Perez-Perez paper is also a single patient case study and was only seen following repeated injections, so this was a different response. **Proposed change :** We recommend deleting the sentence with the Perez-Perez reference since this is a very different response and not a pseudoallergic response. "~~A positive prick test performed with polysorbate 80 has indicated the role of this substance in the development of urticaria in a 28-year-old adult after injection of Humira® and Stelara® (Perez-Perez et al., 2011 [78]).~~"	Not accepted. In recent years there have been several additional case reports of hypersensitivity reactions (including severe anaphylactoid reactions) also after subcutaneous or intramuscular administrations of therapeutic proteins (e.g. mAbs and epoietins) and vaccines (Gardasil; Covid-19 vaccines) showing positive Prick tests to PS 20 or 80. The report has been supplemented by the most recent literature data.
726-729	5	**Comment:** The study describes the provocation of mast cells as the mechanism for pseudoallergy for polysorbate. This mechanism supports the fact that allergic reactions to polysorbate is mild, reversible and easily managed with use of anti-histamines. **Proposed change:** Please consider histamine release as mechanism for pseudoallergy for polysorbate and consider threshold other than zero.	Partly accepted. However, in recent years there have been several additional case reports of hypersensitivity reactions (including severe anaphylactoid reactions) also after subcutaneous or intramuscular administrations of therapeutic proteins (e.g. mAbs and epoietins) and vaccines (Gardasil; Covid-19 vaccines) showing positive Prick tests to PS 20 or 80, which are present at very low concentrations in these medicinal products. At least in some cases, esp. those with occurrence after the third (or later) administration of the same product, an IgE-mediated genesis cannot be excluded (e.g. Badiu et al. 2012; Palacios Castano et al. 2016); see addition in chapter 4.1 of the report). Due to the very rare possibility of

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			IgE-mediated anaphylaxis and the inability to define a threshold above zero for pseudoallergy, the threshold zero appears to be reasonable and justified. Research by Li et al. (2014) suggest that isosorbide components of polysorbate 80 (polyoxyethylene isosorbide oleate) and polyamine receptor-mediated endocytosis may be involved in causing pseudoallergy by polysorbate 80. The report has been supplemented by the most recent literature data.
854-855	5	**Comment:** This statement says the Total parenteral nutrition (TPN) is widely used and hypersensitivity skin reactions are rare. So these data should support that there is a threshold and this is not a common event for PS80 containing large molecules. **Proposed change:** "Total parenteral nutrition (TPN) is widely used. Although mechanical, septic, and metabolic complications are well known, hypersensitivity skin reactions are rare. **Therefore, a threshold of 1 mg/kg is further supported by these data.**"	Not accepted. Limited data on TPN (IV administration) do not prove that there is a threshold for hypersensitivity after IM or SC administration. It is agreed that currently marketed Biologicals contain PS levels < 1.2 mg/kg. In recent years there have been several additional case reports of hypersensitivity reactions (including severe anaphylactoid reactions) also after subcutaneous or intramuscular administrations of therapeutic proteins (e.g. mAbs and epoietins) and vaccines (Gardasil; Covid-19 vaccines) showing positive Prick tests to PS 20 or 80 which are present at very low concentrations in these medicinal products. At least in some cases, esp. those with occurrence after the third (or later) administration of the same product, an IgE-mediated genesis cannot be excluded (e.g. Badiu et

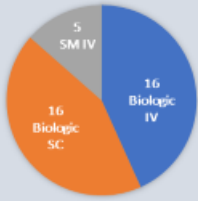
Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			al. 2012; Palacios Castano et al. 2016); see addition in chapter 4.1 of the report). Due to the very rare possibility of IgE-mediated anaphylaxis and the inability to define a threshold above zero for pseudoallergy, the threshold zero appears to be reasonable and justified. The report has been supplemented by the most recent literature data.
919-920		**Comment:** Agree that a margin to hERG IC50 should guide max exposure. Suggest increasing to more than the suggested 30-fold also to minimise risk of QTc prolongation. Potential protein binding of polysorbate (decreasing free fraction) may work in favour of this.	Partly accepted. An increase of the margin > 30fold IC50 for QT risk (considering protein binding) is theoretical and not suited to guide the threshold setting for warnings in the PIL. From the totality of preclinical and clinical data a threshold of 3 mg/kg/day was derived for a cumulative daily dose, in worst case administered as a bolus injection, which triggers a warning regarding cardiovascular effects (e.g., low blood pressure) in humans. See also response on page 15. It is further proposed (in the comments section of the Annex) that a warning on the risk of concomitant use of medications that prolong the QT/QTc interval is considered for the SmPC of all products containing polysorbates above the threshold of 3 mg/kg/day when given as bolus.

Information supporting the 1 mg/kg threshold proposed in the document- EFPIA companies welcome further discussion to explain these data.

Use history of PS80

BASIS: 37 commercial products containing PS80 ARE IDENTIFIED

Modality/RoA[1]	Mechanism for use	Commercial Product
Biological / IV	Interfacial stabilizer	Soliris, Wilate, Bivigam, Blincyto, Entyvio, Actemra[3], Trogarzo, Stelara, Benlysta, Remicade[3], Imfinzi, Ziplava, Anthim, Portrazza, Keytruda, Opdivo
Biological / SC	Interfacial stabilizer	Humira[3], Kineret, Dupixent, Cyltezo, Amjevita, Nucala, Cosentyx, Rituxin Hycela, Crysvita, Ilumya, Tremfya, Taltz, Zinbryta, Repatha[3], Aranesp, Aimovig
Small Mol / IV	Solubilizer	Ryanodex, Jevtana, Amiodarone[3], Vizamyl, Docetaxel[3]



[1]ROA: route of administration

PATIENT EXPORSURE NORMALIZED TO "PS 80 peak dose (mg/kg)"

PS80 PEAK DOSE = Maximal PS80 dose received on a given day when the drug product is administered, taking into account the different product presentations and dosing regimens (e.g. starting dose, recommended dose or maintenance dose)

$$\text{PS80 PEAK DOSE (mg/Kg)} = \frac{[10 * \text{PS80 concentration (w/v \%)}]\ (\text{mg/mL}) * \text{DP peak dose}\ (\text{mg})}{\text{DP concentration}\ (\text{mg/mL}) * 60\ (\text{kg})}$$

Summary of PS80 (%w/v) and peak dose (mg/kg) in the 37 Commercial Products

	PS80 (% w/v)		PS80 (mg/kg)	
	Min	Max	Min	Max
Biologics IV	0.01	0.2	0.00833	0.52
Biologics SC	0.005	0.2	0.000833	0.134
Small Mol IV	0.4	10	0.007	21.6

Appendix 1: suggested refinement of Table at Line 117 (based on the sum of Company comments)

Route of administration	Threshold	Information for the Package Leaflet	Comments
Oral	Low level (i.e. 5 µg/day)	This medicine contains x mg of polysorbate* in each <dosage unit><unit volume> <which is equivalent to x mg/<weight><volume>>. Polysorbates in this medicine may alter the effects of other medicines. Talk to your doctor or pharmacist if you are taking other medicines.	Although most available safety data is for PS 80 or 20, the package leaflet information should be used for all types of polysorbates unless omission is justified. May influence the pharmacokinetics of concomitant drugs (e.g. enhancement of gastrointestinal absorption). * The type of polysorbate(s) (e.g. polysorbate 80 or 20) in the medicinal product should be mentioned here.
Intravenous (IV)	Low level (i.e. 5 µg/day) or 1 mg/kg	This medicine contains polysorbate*. Polysorbates can cause severe allergic reactions.	May influence the pharmacokinetics of concomitant drugs (e.g. brain uptake for some drugs). Information on compatibility of the medical device type (if any) with the polysorbate in the product should be indicated. "As hypersensitivity reactions including anaphylactoid shock have been observed after IV administration of the drug product, a warning of allergic reactions at threshold 'low level" is proposed; otherwise the threshold of 1 mg/kg is applicable. A risk for severe hypersensitivity reactions needs to be mentioned in the SmPC in section 4.4 e.g "[Tradename] contains polysorbate." * *See above*
Parenteral mAbs and vaccins, Total parenteral nutrition	Low level (i.e. 5 µg/day) or 1 mg/kg	This medicine contains x mg of polysorbate* in each <dosage unit><unit volume> <which is equivalent to x mg/<weight><volume>>.	As hypersensitivity reactions including anaphylactoid shock have been observed after patenteral administration of the drug product, a warning of allergic reactions at threshold "low level" is proposed; otherwise the threshold of 1 mg/kg is applicable.
Parenteral	10 mg/kg per dose	This medicine contains x mg of polysorbate* in each <dosage unit><unit volume> <which is equivalent to x mg/<weight><volume>>. Polysorbates can have an effect on the circulation of your blood and on your heart (e.g. low blood pressure, heart beat changes).	The risk of severe hypotension could be minimised by slowing down the infusion (by more than 5 minutes). This risk is to be mentioned in SmPc Section 4.4. Electrophysiological studies show cardiac depression in dogs and inhibition of hERG currents by polysorbates in vitro. The potential for QT Prolongation and torsades de pointes in humans is unknown.

			For risk minimisation, a SmPC warning on the risk of concomitant use of medications that prolong the QT/QTc interval or congenital Long QT Syndrome should be considered.
Parenteral	35 mg/kg per day	This medicine contains x mg of polysorbate* in each <dosage unit><unit volume> <which is equivalent to x mg/<weight><volume>>. Ask your doctor or pharmacist for advice if you have a liver disease. This is because polysorbates can have an effect on the liver.	In neonates doses > 80 mg/kg/day of polysorbate caused severe (fatal) hepatotoxicity ; a warning needs to be added to the SMPC.
Parenteral Particulates	Please derive separate limit		The safety profile of particles is significantly different to warrant a specific limit.
Subcutaneous administration			There is need for a specific statement on this route e.g. for vaccines.
Topical	1 mg/kg	Polysorbates can cause skin allergy (e.g. rash, itching).	