12 December 2024
EMA/CHMP/429695/2019
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Information for the package leaflet regarding dextrans used as excipients in medicinal products for human use' (EMA/CHMP/187129/2016)

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

Stakeholder no.	Name of organisation or individual
1	Medicines for Europe
2	F. Hoffmann–La Roche Ltd
3	EFPIA
4	Pharmacosmos *[received post-consultation on 27-Apr-21]*

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	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* *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**	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	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	Not accepted. See above.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	corresponding information also in SmPC will help HCPs to better understand the risk and to advise patients appropriately.	
3	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.	Not accepted A warning or information statement should be data driven and is product specific. It also depends on the nature of the allergic reaction (e.g. type 1 versus type 3). If necessary, cross-reference may be made to other section of the PL to avoid repetition of the same information.
3	It would be very helpful if the guideline also outlined the type of wording the agency wants to see in the SmPC. This is particularly relevant for those excipients where they have added safety-related PIL texts. 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.	Not accepted See above.
4	Pharmacosmos wishes to express its serious concerns in relation to several aspects of the EMA draft document entitled Information for the package leaflet regarding dextrans used as excipients in medicinal products for human use (EMNCHMP/187129/2016). By way of background, Pharmacosmos has specialised knowledge relevant to dextrans, and it is to our knowledge the only FDA and EMA approved manufacturer of dextran 40 and dextran 70 APIs and excipients. Pharmacosmos does not market its own pharmaceuticals containing dextran polysaccharide excipients, but supplies dextran API such as Dextran 40 and Dextran 70 products to a wide range of pharmaceutical and medtech customers, who incorporate these excipients into a broad	This comment is addressed in the specific comments.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	range of pharmaceuticals including cancer therapies, wound care products, eye drops, cell therapies, and vaccines. Unfortunately, we missed the notice of this consultation and therefore we failed to respond before the stated public consultation period ended on 31 May 2019. We only very recently became aware of the draft document and, therefore, apologise for the lateness of our comments. Nevertheless, we trust that you will be able to take them into account as the draft goes through its remaining internal discussions and related regulatory procedures. In addition to it being in our interests to do what we can to ensure an accurate and balanced review of the subject, we believe that it is strongly in the public interest that our observations are taken into account. This is in line with Section 12 of the European Medicines Agency Code of Good Administrative Behaviour, EMA/264257/2013 ("EMA Code"). As it stands, we respectfully suggest that the text suffers from a number of important deficiencies, potentially misleading statements, and unbalanced conclusions. This includes apparent reliance upon animal data while ignoring important available data on human exposure and presenting data on, and seeming atatching significance to, the safety profile of an intentionally toxic compound, dextran sodium sulfate. Deficiencies of this kind create a real risk that readers will be confused and will reach conclusions on the state of scientific knowledge that are at best unbalanced and at worst completely invalid. Such approach is clearly in contradiction with Section 7 of the EMA Code which requires the EMA to "take into consideration the relevant factors and give each of them its proper weight in the decision, whilst excluding any irrelevant element from consideration".	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
4	Overall context is lackinq: In our view, the document does not present the use of dextrans in pharmaceuticals in its proper historical and current context. It does not take into account the history of dextran products or the wide variety of ways in which dextran products are used today for medical applications. Dextran 40 and Dextran 70 have been part JP, EP and USP for decades. The pharmacopoeias clearly define pharmaceutical dextrans as dextrans manufactured by Leuconostoc mesenteroides 10817 or B512F or substrains hereof. However, in this context, to refer to other types of dextran i.e. class 2 and class 3 dextran that are not applied in clinical use without explanation or qualification will simply confuse the reader. Furthermore, it has not been taken into account that clinical dextrans (Dextran 40 and Dextran 70) as large volume infusion solutions have been designated by the WHO as "Essential drugs" since 1950, and Dextran 70 still is (1). This fact underlines the relative safety of dextrans compared with gelatine, HES and other colloids. Infusion solutions applying Dextran 40 and Dextran 70 as the API, are established as safe and efficacious and remain in common use in many markets and entail intravenous infusions in doses that typically contain 50 grams to 100 grams of dextran for an adult human (2). In contrast, both Dextran 40 and Dextran 70, when applied as excipients in parenteral products, are typically applied in very low doses. The typical use of Dextran 40 and 70 as excipients, including in vaccines and lyophilized infusion drugs, involves in the order of 10 — 100 milligram i.e. typically a factor -1000 below the infusion drug application. This important dose context is entirely absent from the draft document.	This comment is addressed in the specific comments.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	Dextrans and dextran derived products have been widely used in pharmaceuticals and medical devices since the 1950s and they have been widely researched, resulting in more than 50 000 hits on PubMed. However, the draft document does not reflect this wealth of knowledge and it is unclear why specific references are cited while other plainly relevant publications are not referenced at all. 1. WHO Model List of Essential Medicines 21st edition, 2019. WHO/MVP/EMP/IAU/2019.06: Plasma substitutes. p 35. World Health Oraanization model list of essential medicines: 21st list 2019 (who.int) 2. Pfizer labeling: Dextran 40 injection, solution. labeling.pfizer.com/ShowLabelina.aspx?id=5407	
4	In the opinion of Pharmacosmos, this draft document is poorly referenced and fails to reflect adequately or at all relevant data in humans and, therefore, potentially misleads as to the state of scientific and technical knowledge. As it stands, we believe that the draft requires substantial revision if it is not to lead to misunderstandings and confusion. We believe that in view of the deficiencies described above the document does not provide an appropriate basis for assessment of the proposed packaged leaflet text for products containing dextran excipients. The basis for the zero threshold described is unexplained, and in our view, cannot be substantiated by available data. The potential for allergic reactions that is described is based on very rare reactions seen in response to dextran infusion products where the typical dose is in the order of 50-100 grams. There is no sound basis for extrapolating that observation to products containing 100 to 10,000 times less dextran per administration.	This comment is addressed in the specific comments.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	Pharmacosmos believes that the draft requires considerable amendment and amplification and, therefore, after a new version is prepared, it would probably be appropriate to undertake a new public consultation.	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Executive summary (31-48) Clinical safety data (202-220)	3	**Comment:** Low-molecular dextrans (LMD) have also a risk for osmotic nephrosis and acute kidney injury in animals and humans (Dickenmann M, Oettl T, and Mihatsch MJ. Osmotic Nephrosis: Acute Kidney Injury With Accumulation of Proximal Tubular Lysosomes Due to Administration of Exogenous Solutes. American Journal of Kidney Diseases; 51(3): 491-503, 2008 and references therein). **Proposed change:** The above risk should be discussed and summarized in the indicated sections.	Accepted. This proposal has been developed in the clinical safety section, although it has not been included in the labelling.
Line 50 New information to be included in PIL Table, Row 1 Parenteral and Inhalation Threshold Zero	2	**Comment:** Since dextrans can cause severe allergic reason, a clear mention of dextrans in SmPC 4.3 is necessary, where patient having hypersensitivity to the API and excipients is contraindicated. A warning in SmPC should be considered. **Proposed change:** Propose change to comments column: Dextrans can cause anaphylactoid reactions in some patients.	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. Additionally, as per QRD template on the SmPC, hypersensitivity to the API or excipients is to be applied in section 4.3 (Contra-indication):

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		A mention of Dextrans in SmPC 4.3 should be included, example text: [Tradename] contains dextran 70 or dextrans 40). ***A warning on the excipient in section 4.4 in the SmPC should be considered.*** ** The type of dextran(s) (e.g. dextran 70, dextran 40) in the medicinal product should be mentioned here.*	*Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1*
Line 50 (Table)	3	**Comments:** The draft guideline does not convey in which section the new information in the package leaflet should be added. It would be helpful if the table in the guidelines in addition to providing the new text, also convey to which section this information should be included in the package leaflet. Within package leaflets, it appears this new information should be included in section 2 'What you need to know before you use 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.	No accepted. See above.
Line 50 (Table)	3	**Comments:** Since dextrans can cause severe allergic reaction, a clear mention of dextrans in SmPC 4.3 is necessary, where patient having hypersensitivity to the API and excipients is contraindicated. A warning in SmPC should be considered.	No accepted. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: To add to comments column: "Dextrans can cause anaphylactoid reactions in some patients. *A mention of Dextrans in SmPC 4.3 should be included, example text: [Tradename] contains dextran 70 or dextran 40).* *A warning on the excipient in section 4.4 in the SmPC should be considered.*	
p. 52 Section "1. Characteristics"	4	**Comment:** Section "1. Characteristics" mischaracterizes the chemistry of dextrans in pharmaceutical use The definition of dextrans including "alternan" and "mutans" as so-called class 2 and class 3 dextrans. This definition is inconsistent with the majority of literature over the recent decades. Medical applications of dextran polysaccharides are limited to predominantly a-I ,6 glucose polysaccharides as defined in the pharmacopoeias (see generally dextran 40 EP, USP, JP, dextran 70 EP, usp, JP. See also (3). Section 1.2, Following a debate in the 1950s about which production organisms to use, all clinical dextrans in recent decades have been produced by fermentation of sugar (sucrose) by Leuconostoc mesenteroides only, as clearly	Partly accepted. The section has been reviewed and adjusted, including adding an update to the publications.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		specified in the USP, EP, JP & ChP. The reference to other production methods is no longer relevant and will mislead. Section 1.3, Contrary to the assertion in the draft document, dextran for pharmaceutical use is not derived from starches (which are characterized by a-I ,4 glycosidic bonds as opposed to a-I ,6 glycosidic bonds in dextran). The discussion on other non-dextran dex-ingredients is confusing and irrelevant to the discussion. 3. De Belder, A.N, Dextran. Handbook from Amersham Biosciences. 18-1166-12. Edition AA. https://tdblabs.se/content/u ploads/2020/03/18116612-aa-pl 3. pdf	
p. 98 Section "2. Pharmaco-toxicoloqical data"	4	**Comment:** Section "2. Pharmaco-toxicoloqical data" is flawed and scientifically invalid. not least in its reliance on the toxicoloqv of dextran sulphate. which is quite unrelated to that of dextran itself. The toxicology section starts with, and therefore gives prominence to, references to dextran sodium sulfate (DSS). The toxicology of DSS is quite unrelated to that of dextran itself. The main application of DSS is (as noted briefly in the text) to induce colitis in animal disease models — i.e. it is a chemical derivative of dextran developed specifically for its toxic properties. It surelv has no relevance to. and should not be referenced in. a document about the use of unmodified clinical dextran fractions. which can safely be administered parenterally.	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Examining the properties of DSS to characterize clinical dextran fractions and to guide labelling is scientifically invalid. We respectfully suggest that there is a good case for removing the various references to DSS and focusing the document on data that are relevant to clinical use.	
p. 169 Section "3. Pharmacokinetics (in Humans)"	4	**Comment:** The Section "3. Pharmacokinetics (in Humans)" does not appear to have captured the relevant literature and. contrary to the headline. focuses on studies in rats. Section 3, The discussion on Pharmacokinetics is incomplete and is, therefore, unbalanced. Almost all the few studies mentioned are animal studies conducted in Japan, despite the heading that the text is to discuss data in humans and despite there being a wealth of published clinical material from Europe and USA from the 1950s and onwards. In fact, not a single study mentioned was performed in humans. Surprisingly, the author immediately dives into studies on rats. The author appears unaware that rats are highly sub-optimal surrogates for human pharmacokinetics in the case of dextrans (4, 5). Any discussion of the results of toxicological studies in these animals requires qualification or it will mislead since almost all rats (except for Whistar rats expressing the recessive Non-Reacting (NR) genetic trait, usually denoted as Whistar—NR or NELP rats.), react to dextrans with direct histamine release which induces pronounced oedema in all organs in which mast cells are	Partly accepted. The section has been reviewed and adjusted, including adding an update to the publications.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		found e.g. lungs, skin, etc. Such direct histamine release does not occur with other mammals, including humans. 4. Blazso G, Koitai M, Otlecz A, Minker E. Acta Physiol Acad sci Hung. Dextran anaphylactoid reaction in Sprague-Dawley CFY rats. https://pubmed.ncbi.nlm.nih.aov/95467/ 5. West GB, Int Arch Allergy Appl Immunol. 1977;55(1-6):542-5. Anaphylactoid responses in rats. https://pubmed.ncbi.nlm.nih.aov/591116/	
p. 202 Section "4. Clinical safety data"	4	Section "4. Clinical safety data" is based on a very small subset of the potentially available data in the literature and includes several incorrect statements. The draft states, without supporting references, that dextran can cause more severe anaphylactic reactions than gelatines and starches, but it does so in a sentence that implicitly references their use as plasma volume expanders (i.e. high doses of typically 50-100 grams per patient per infusion). This comment on relative risk is unbalanced unless reference is made to other data suggesting that the incidence of anaphylactoid reactions for dextran is lower than with gelatine (leading to the withdrawal of gelatine from the US market), and similar to HES (6) and it also fails to mention that large volume dextran infusion products are not associated with increased risk of kidney failure and death in certain populations, which recently led to strengthened warnings for HES in both the EU and US. The draft states that "Side-effects can be very serious (anaphylaxis, volume overload, pulmonary oedema, cerebral	Partly accepted. The section has been reviewed and adjusted, including adding an update to the publications.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		oedema, 206 or platelet dysfunction). This has been serious enough for some parenteral iron preparations to be 207 withdrawn by the FDA, e.g. Imferon@, withdrawn in 1990. " This statement is incorrect. First, although the assertion that Imferon was withdrawn due to safety reasons has erroneously made it into some publications (that the author may have relied upon), it is incorrect. Imferon was manufactured by the British company Fisons and the product, along with other Fisons products, was recalled from the market due to serious GMP issues discovered during FDA inspections around 1990 (7). Consistent with this, iron dextran from another manufacturer was introduced into the US market soon thereafter and remains in the market to this date (INFeD, NDA #017441). Furthermore, whereas an injection of iron dextran in the US, according to its approved label, would not exceed 400mg of dextran*, Dextran 40 large volume infusion solution is also on the US market and does not carry a boxed warning in spite of the fact that a typical infusion would provide 50-100 gram of dextran 40 (2). In any event, the adverse effects of dextran mentioned under this section (incl. volume overload, pulmonary or cerebral oedema, etc.). do not apply to the small doses of dextran used as excipients in vaccines, cryopreservation, etc. Overall, the clinical safety section appears insubstantial, and it ignores the wealth of publications supporting the safety profile of dextran infusion products used in clinical practice since the 1950s.	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		* This can be concluded based on the FDA approved label for iron dextran injection (INFeD) and USP entry for iron dextran injection 2. Pfizer labeling: Dextran 40 injection, solution. labeling.pfizer.com/ShowLabelina.aspx?id=5407 6. Arfors K-E, Buckley P B, Pharmacological characteristics of artificial colloids. In Bailliere's Clinical Anaesthesiology. 1997; 11(1):1547. https://www.researchqate.net/publication/259334855 Arfors KE Buckley P B Pharmacoloqical characteristics of artificial colloids in Baillieres Clinical Anaes thesiologv 11 1 1997 15 -47 7. FISONS OPTICROM IMF-ERON MAY BE OFF U.S. MARKET UNTIL LATE 1992 AS THE COMPANY UPGRADES U.K. MANUFACTURING PLANT TO MEET FDA QUALITY CONTROL CONCERNS Pink Sheet (informa.com)	