July 7, 2021

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Director
Public Citizen's Health Research Group

Re: Docket No. FDA-2017-P-0867

Dear Petitioners:[1]

This letter responds to your citizen petition (the Petition) dated February 8, 2017, in which you request that the Food and Drug Administration (FDA, the Agency, we) "immediately require the removal from the market of hydroxyethyl starch (HES) intravenous (IV) solutions" because you believe that "the solutions' risks outweigh their limited benefits" and "there are a number of other, safer alternative IV solutions for the uses for which HES solutions are approved." Petition at 1. FDA sent you an interim response to the Petition on July 25, 2017. This letter responds to the Petition in full.

In this letter, we first review HES products and their recent regulatory history. We then present the applicable legal and regulatory framework, including the authorities under which FDA may require safety labeling changes for approved prescription drug products. We next discuss FDA's approach to assessing the clinical studies and other data and information relevant to the Petition. We describe our determination that, to reflect new safety information, changes to the labeling of all HES products are warranted. We consider the grounds presented in the Petition for the action you are requesting in light of these safety labeling changes and the legal standards for FDA action. We provide our conclusions based on the facts, the science, and the law.

We have carefully reviewed and considered the information submitted in the Petition and other relevant information relating to HES products, including our decision to require a safety labeling change for this class of products.[2] Based on our analysis of this information, and for the reasons described below, we deny the Petition.

[1] The citizen petition was submitted on behalf of Public Citizen by the following individuals (the Petitioners, you): Yolanda Giraldo, M.D., M.P.H., Resident, General Preventive Medicine, Johns Hopkins School of Public Health; Sammy Almashat, M.D., M.P.H., Researcher, Public Citizen's Health Research Group; Sidney Wolfe, M.D., Founder and Senior Adviser, Public Citizen's Health Research Group; Michael Carome, M.D., Director, Public Citizen's Health Research Group; Charles Natanson, M.D., Critical Care Physician; and Ian Roberts, M.B., B.Ch., F.R.C.P., F.P.H., Coordinating Editor, Cochrane Injuries Group, Co-Director, Clinical Trials Unit, London School of Hygiene & Tropical Medicine.

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Here is an outline of our response:

I. Background

A. HES Products

HES products are synthetic colloid solutions administered intravenously to maintain or expand plasma volume. They are indicated for the treatment or prophylaxis of hypovolemia (low blood volume) that may result from surgery, trauma, sepsis, burns, or anaphylaxis.

Three innovator HES products are currently approved in the United States (U.S.): HESPAN®,[3] HEXTEND®, and Voluven®.[4] HESPAN and HEXTEND are indicated for "treatment of hypovolemia when plasma volume expansion is desired," and Voluven is indicated for "treatment and prophylaxis of hypovolemia in adults and children."[5]

[2] We received approximately six comments to the docket for the Petition, most of which disagreed with Petitioner's request. We reviewed and considered the comments as well as the scientific publications that were identified by commenters. The studies that were specifically identified related to the use of HES products in apheresis, a use that was not addressed by the Petitioner.

[3] Two generic versions of HESPAN (6% hetastarch in 0.9% sodium chloride injection) are also currently approved (manufactured by Teva Parenteral Medicines, Inc. and Hospira, Inc.). Teva Parenteral Medicines, Inc., has not manufactured or distributed its HES product in the U.S. since 2013.

[4] A generic version of Voluven, Expanza, is also currently approved (B. Braun Medical Inc.); that product has never been marketed in the U.S.

[5] HESPAN is also indicated for adjunctive use in leukapheresis to improve the harvesting, and increase the yield, of granulocytes by centrifugal means.

Prior to 1972, crystalloids (such as Ringer's lactate or normal saline) and colloids (such as albumin) were standard of care for fluid resuscitation. After HESPAN was approved in 1972, its clinical use steadily increased over the next 30 years, as did reports of coagulopathy and excess bleeding. Once the mechanism underlying excess bleeding associated with HESPAN was understood,[6] next-generation products intended to avert these effects were developed, including HEXTEND and Voluven. Until recently, HES products were widely used for fluid resuscitation of hospitalized patients. Today, HES products are primarily used for treatment of hypovolemia in settings where adequate alternative treatment is unavailable.

HESPAN and HEXTEND are high-molecular-weight (HMW) hetastarches with molar substitution ratios of 0.75 in different vehicles: 0.9% sodium chloride injection for HESPAN and lactated electrolyte injection for HEXTEND. Voluven is a low molecular weight (LMW) tetrastarch with a molar substitution ratio of 0.40 in 0.9% sodium chloride injection. Table 1 presents information about these three HES products.

Table 1
FDA-Approved Non-Generic HES Products Marketed in the U.S.

FDA Approval	Proprietary Name	Application Holder	Molecular Weight (kDA)	Molar Substitution Ratio	Vehicle
1972[7]	HESPAN	B. Braun Medical Inc.	600	0.75	0.9% Sodium chloride
1999	HEXTEND	Hospira, Inc.	670	0.75	Lactated electrolyte
2007	Voluven	Fresenius Kabi	130	0.40	0.9% Sodium chloride

B. Recent Regulatory History of HES Products

Post-June 2002 Blood Products Advisory Committee meeting: The following warning statement was added to the label of HESPAN: "HESPAN® is not recommended for use as a cardiac bypass pump prime, while the patient is on cardiopulmonary bypass, or in the immediate period after the pump has been discontinued because of the risk of increasing coagulation abnormalities and bleeding in patients whose coagulation status is already impaired."

[6] Excess bleeding is due to decreased activity of factor VIII moieties (i.e. procoagulant factor VIII, factor VIII-related ristocetin cofactor and von Willebrand factor antigen concentrate) and decreased platelet adhesion.
[7] HESPAN BN160889 (6% Hetastarch in 0.9% NaCl in glass bottle) was approved in 1972. HESPAN BN890105 (6% Hetastarch in 0.9% NaCl, 250, 500, 1000 ml EXCEL containers) was approved in 1991.

September 6-7, 2012: FDA convened a public workshop to discuss new information about the potential effects of HES products on hemostasis and on the renal system. Presentations and panel discussions were held on the risks and benefits of HES products in different clinical settings.[8]

June 24, 2013: FDA issued a Safety Communication to announce that it had analyzed recent data that "indicate[d] an increased risk of (i) mortality and renal injury requiring renal replacement therapy [RRT] in critically ill adult patients, including patients with sepsis and those admitted to the ICU [intensive care unit]; and (ii) excess bleeding particularly in patients undergoing open heart surgery in association with cardiopulmonary bypass."[9] FDA concluded that HES products should not be used in critically ill adult patient populations, including patients with sepsis and those admitted to the ICU, and that a Boxed Warning to include the risk of mortality and severe renal injury in these patients was warranted. FDA also determined that an additional warning about excessive bleeding in patients undergoing open heart surgery in association with cardiopulmonary bypass was needed in the Warnings and Precautions section of the package insert. On the same date, FDA sent safety labeling change notifications to HES application holders.

November 25, 2013: FDA issued a revised Safety Communication announcing that FDA had approved safety labeling changes to the prescribing information for the class of HES products to add the new Boxed Warning about the risk of mortality and renal injury requiring RRT and to update the Contraindications, Warnings and Precautions, Adverse Reactions, and Clinical Studies sections.[10] The labeling of HES products therefore included a Boxed Warning containing the statements "WARNING: MORTALITY[;] RENAL REPLACEMENT THERAPY"; "In critically ill adult patients, including patients with sepsis, use of hydroxyethyl starch (HES) products, including [product name], increases risk of…[m]ortality [and] [r]enal replacement therapy"; and "Do not use HES products, including [product name], in critically ill adult patients including patients with sepsis." The Contraindications section included the statement, "Do not use hydroxyethyl starch (HES) products, including [product name], in critically ill adult patients, including patients with sepsis, due to increased risk of mortality and renal replacement therapy (RRT)." The Warnings and Precautions section included statements relating to renal dysfunction and coagulopathy.

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[8] Food and Drug Administration Notice of Public Workshop: Risks and Benefits of Hydroxyethyl Starch Solutions; 77 FR 43601, 43601 (Jul. 25, 2012); available at: https://www.federalregister.gov/documents/2012/07/25/2012-18110/risks-and-benefits-of-hydroxyethyl-starch-solutions-public-workshop; accessed 4/14/2021.

[9] The June 2013 Safety Communication is no longer available on the FDA website. A description of its content can be found in this MedWatch Safety Alert: Hydroxyethyl Starch Solutions: FDA Safety Communication – Boxed Warning of Increased Mortality and Severe Renal Injury and Risk of Bleeding, June 11, 2013; available at https://wayback.archive-it.org/7993/20170112164508/http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm358349.htm; accessed 4/14/2021.

[10] FDA Safety Communication: Boxed Warning on increased mortality and severe renal injury, and additional warning on risk of bleeding, for use of hydroxyethyl starch solutions in some settings, November 25, 2013. https://wayback.archive-it.org/7993/20170112095648/http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ucm358271.htm; accessed 4/14/2021.

July 2014: The Voluven application holder added the following text to the Voluven Package Insert: "Studies conducted in children have not been of sufficient size or follow-up duration to assess the risks of renal injury and mortality in this patient population."

September 23, 2014: FDA presented a safety review of Voluven to the Pediatric Advisory Committee (PAC). In light of the safety information presented in the label, the PAC discussed the limited use of this product and speculated that there should be little pediatric use. The PAC voted unanimously that the Voluven package label adequately conveyed safety information and agreed with FDA's recommendation to continue routine monitoring of the FDA Adverse Events Reporting System (FAERS) for new safety signals.[11]

II. Legal and Regulatory Framework

The HES products you address in the Petition are drugs with approved new drug applications (NDAs) or abbreviated new drug applications (ANDAs) regulated under the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 301 et seq.; FD&C Act). FDA's regulation of drug safety is governed by the FD&C Act and the Agency's implementing regulations (codified in Title 21 of the Code of Federal Regulations (CFR)). The FD&C Act makes it unlawful to market a new drug product without first obtaining approval of an NDA or ANDA. *See* section 505(a) of the FD&C Act; *see also* section 301(d) of the FD&C Act (prohibiting the marketing of any article in violation of section 505). Before approving an application, FDA must determine that the drug is both safe and effective for use under the conditions prescribed, recommended, or suggested in the product's labeling. Sections 505(b)(1) and 505(d) of the FD&C Act.

After approval of a drug, FDA continues to monitor adverse events associated with the drug and may take regulatory action as authorized and appropriate. One possible action is withdrawal of a drug product's approval. Section 505(e) of the FD&C Act (21 U.S.C. § 355(e)) establishes the circumstances under which the Agency will, after due notice and opportunity for a hearing, withdraw such approval. With respect to safety concerns, the Agency will withdraw approval of a drug product if it finds:

> (1) that clinical or other experience, tests, or other scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved; [or]
> (2) that new evidence of clinical experience, not contained in such application or not available to [FDA] until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to [FDA] when the application was approved, shows that such drug is not shown to

[11] Minutes of the Pediatric Advisory Committee, September 23, 2014, https://wayback.archive-it.org/7993/20170113201637/http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM425366.pdf; accessed 4/14/2021.

be safe for use under the conditions of use upon the basis of which the application was approved.

21 U.S.C. § 355(e)(1) and (2). FDA regulations in 21 CFR part 314 set forth the procedures for withdrawal of approval. *See, e.g.*, 21 CFR 314.150.

In addition, section 505(o)(4) of the FD&C Act authorizes FDA to require certain holders of approved applications for prescription drug products to make safety labeling changes if the Agency becomes aware of "new safety information" that FDA determines should be included in the drugs' labeling. 21 U.S.C. § 355(o)(4). "New safety information," with respect to a drug, is, in part, information derived from a clinical trial, an adverse event report, a postapproval study, or peer-reviewed biomedical literature, or other scientific data deemed appropriate by the Agency, about "a serious risk or an unexpected serious risk associated with use of the drug that [FDA] has become aware of (that may be based on a new analysis of existing information) since the drug was approved." 21 U.S.C. § 355-1(b)(3).

When FDA becomes aware of new safety information that FDA believes should be included in the labeling of a drug, FDA notifies the holder of the approved application for that drug. 21 U.S.C. § 355(o)(4)(A). In response, the application holder must either submit a supplement with proposed labeling changes to reflect the new safety information or notify FDA that it does not believe a labeling change is warranted and submit a statement detailing the reasons why such a change is not warranted. 21 U.S.C. § 355(o)(4)(B). If FDA does not accept an application holder's reasons why labeling changes are not warranted, the Agency will initiate a discussion period to reach agreement on whether and how the labeling for the drug should be modified to reflect the new safety information. 21 U.S.C. § 355(o)(4)(C)-(D). Within 15 days of the conclusion of the discussion period, FDA has the authority to issue an order requiring the safety labeling change to be made. 21 U.S.C. § 355(o)(4)(E).

III. Discussion

In the Petition, you request that FDA "immediately require the removal from the market" of HES products, and reference section 505(e) of the FD&C Act (21 U.S.C. § 355(e)).[12] We interpret this as a request that FDA withdraw the approvals of HES products. According to the Petition, the basis for this request is that "the solutions' risks outweigh their limited benefits" and "there are a number of other, safer alternative IV solutions for the uses for which HES solutions are approved." In support of your request, you make a number of assertions, and cite numerous studies to support these assertions.

Below, we describe FDA's review of the studies referenced in the Petition and other relevant information, describe FDA's determination that changes to the labeling of all HES products are warranted, and address the assertions that you make in support of your request.

[12] The Petition refers to "Section 355(e) of the Federal Food, Drug, and Cosmetic Act"; we assume you intend to reference Section 505(e) of the FD&C Act, codified at 21 U.S.C. § 355(e).

A. FDA's Review of Information and Data Regarding the Safety of HES Products

As a preliminary matter, we describe FDA's approach to reviewing the information and data relevant to the Petition and to FDA's action regarding HES products.

As stated above, in 2013, FDA required certain safety labeling changes for HES products, after considering all information and data available since the products' approvals. For purposes of the Agency's current review, FDA assembled a multidisciplinary team to likewise evaluate all information and data now available regarding the safety of HES products. In light of the Agency's extensive 2013 review, FDA's current analysis has focused on, but has not been limited to, the information and data about the products' safety that have become available since that time.

1. Clinical Study Data

FDA has reviewed information on the safety of HES products from clinical studies, including those referenced in the Petition, with particular attention paid to studies published in 2013 and thereafter ("post-2012 studies").[13] Among the 97 attachments referenced in the Petition, FDA has identified 35 such studies. FDA has also identified two post-2012 randomized controlled trials (RCTs) not cited in the Petition, for a total of 37 post-2012 studies.[14]

FDA reviewed each post-2012 study, considering design factors that included research objectives, selection and number of study participants, allocation of interventions, masking of intervention assignments, methods of data acquisition, duration of follow-up, and outcome ascertainment procedures. Studies were categorized as either informative or less informative for purposes of responding to the Petition and requiring a safety labeling change.[15]

Studies were considered informative if they 1) found a statistically-significant change (lower bound of 95% confidence interval [CI] $\geq$1.0) in the incidence of one or more of the following clinical safety signals associated with HES products: death, acute kidney injury (AKI), need for RRT,[16] or coagulopathy; and 2) did not have major methodological limitations.

[13] For purposes of responding to the Petition, FDA reviewed relevant scientific literature published through March of 2018. FDA conducts continuous surveillance; as relevant information is identified, it is considered regularly as part of routine surveillance activities. Since March of 2018, FDA has not identified any new data or studies that would change the assessment and conclusions in the current analysis.

[14] In this response, we address post-2012 studies referenced in the Petition, as well as additional studies that we identified as relevant. We do not address clinical studies that were cited, but not discussed, by the Petitioners unless these were either RCTs or observational studies in clinical settings for which there was a paucity of available information (e.g., trauma settings). We also do not address negative observational studies or clinical studies that were conducted only in the critically ill population.

[15] Studies not designed to assess clinical safety endpoints were classified as less informative a priori.

[16] RRT included hemodialysis, peritoneal dialysis and continuous hemofiltration.

Studies were considered less informative if they either 1) failed to find a statistically-significant change in the incidence of one or more of the clinical safety signals described above, or 2) were determined to have major methodological limitations. Failure to demonstrate statistical significance was associated with a number of features, including a study size too small to detect a safety signal had one been present (i.e., a study that lacked adequate power), inadequate study design, heterogeneity (I^2) that could have confounded the analysis (e.g., enrollment of elective surgery and critically ill surgery patients in the same study without a prespecified subgroup analysis), use of comparators whose safety profile overlapped with that of the HES product under investigation, changes in comparator/adjunctive therapy once the study had started, inappropriately low control event rates, limited product exposure, unclear methods of randomization and allocation concealment, pooling of data from different populations, and short duration of follow-up (typically 7-10 days). Less-informative studies did not permit FDA to draw any conclusions about product safety.

Of the 37 post-2012 studies, FDA considered 10 to be informative for purposes of this review; FDA considered the remaining 27 to be less informative.

The 10 post-2012 studies that FDA considered to be informative all found at least one safety signal indicating increased risk from HES compared with control solutions in one or more of four patient populations: noncardiac surgery, cardiac surgery, cardiac and noncardiac surgery, and trauma. See the Appendix for a brief description of each of these 10 studies and the safety signal(s) identified for each population. These studies are summarized in Table 2.

Table 2
Safety Signals in Informative Post-2012 HES Studies

Study Population	Safety Signal	Reference
Noncardiac surgery	Mortality	Green et al. 2016[17]
	Acute kidney injury (AKI)	Ahn et al. 2016[18] Kashy et al. 2014[19]
	Renal replacement therapy (RRT)	Green et al. 2016[20] Patel et al. 2015[21]
	Coagulopathy	Rasmussen et al. 2014[22,23]
Cardiac surgery	AKI	Lagny et al. 2016[24]
	RRT	Bayer et al. 2013[25]
	Coagulopathy	Lagny et al. 2016[26]
Noncardiac + cardiac surgery	RRT	Wilkes and Navickis 2014[27]
Blunt trauma	Mortality	Allen et al. 2014[28] Eriksson et al. 2015[29]
	AKI	Allen et al. 2014[30] Eriksson et al. 2015[31]

[17] Green RS, Butler MB, Hicks SD, et al. Effect of hydroxyethyl starch on outcomes in high-risk vascular surgery patients: A retrospective analysis. *J Cardiothorac Vasc Anesth*. 2016 Aug;30(4):967-972.
[18] Ahn HJ, Kim JA, Lee AR, et al. The risk of acute kidney injury from fluid restriction and hydroxyethyl starch in thoracic surgery. *Anesth Analg*. 2016 Jan;122(1):186-193.
[19] Kashy BK, Podolyak A, Makarova N, et al. Effect of hydroxyethyl starch on postoperative kidney function in patients having noncardiac surgery. *Anesthesiology*. 2014 Oct;121(4):730-739.
[20] Green RS, Butler MB, Hicks SD, et al. Effect of hydroxyethyl starch on outcomes in high-risk vascular surgery patients: A retrospective analysis. *J Cardiothorac Vasc Anesth*. 2016 Aug;30(4):967-972.
[21] Patel MS, Niemann CU, Sally MB, et al. The impact of hydroxyethyl starch use in deceased organ donors on the development of delayed graft function in kidney transplant recipients: A propensity-adjusted analysis. *Am J Transplant*. 2015 Aug;15(8):2152-2158.
[22] Rasmussen KC, Johansson PI, Højskov M, et al. Hydroxyethyl starch reduces coagulation competence and increases blood loss during major surgery: Results from a randomized controlled trial. *Ann Surg*. 2014 Feb;259(2):249-254.
[23] Rasmussen et al. was not referenced in the Petition.
[24] Lagny MG, Roediger L, Koch JN, et al. Hydroxyethyl starch 130/0.4 and the risk of acute kidney injury after cardiopulmonary bypass: A single-center retrospective study. *J Cardiothorac Vasc Anesth*. 2016 Aug:30(4):869–875.
[25] Bayer O, Schwarzkopf D, Doenst T, et al. Perioperative fluid therapy with tetrastarch and gelatin in cardiac surgery – A prospective sequential analysis. *Crit Care Med*. 2013 Nov;41(11):2532-2542.
[26] Lagny MG, Roediger L, Koch JN, et al. Hydroxyethyl starch 130/0.4 and the risk of acute kidney injury after cardiopulmonary bypass: A single-center retrospective study. *J Cardiothorac Vasc Anesth*. 2016 Aug:30(4):869–875.
[27] Wilkes MM and Navickis RJ. Postoperative renal replacement therapy after hydroxyethyl starch infusion: A meta-analysis of randomised trials. *Neth J Crit Care* 2014 Aug;18(4):4-9.
[28] Allen CJ, Valle EJ, Jouria JM, et al. Differences between blunt and penetrating trauma after resuscitation with hydroxyethyl starch. *J Trauma Acute Care Surg*. 2014 Dec;77(6):859-864.
[29] Eriksson M, Brattström O, Mårtensson J, et al. Acute kidney injury following severe trauma: Risk factors and long-term outcome. *J Trauma Acute Care Surg*. 2015 Sep;79(3):407-412.
[30] Allen CJ, Valle EJ, Jouria JM, et al. Differences between blunt and penetrating trauma after resuscitation with hydroxyethyl starch. *J Trauma Acute Care Surg*. 2014 Dec;77(6):859-864.
[31] Eriksson M, Brattström O, Mårtensson J, et al. Acute kidney injury following severe trauma: Risk factors and long-term outcome. *J Trauma Acute Care Surg*. 2015 Sep;79(3):407-412.

2. FDA Adverse Event Reporting System (FAERS) Review

In addition to reviewing clinical studies, we also searched the FDA Adverse Event Reporting System (FAERS) for serious adverse events reported after administration of HES products. Because the Agency had thoroughly reviewed all available information before the last FDA safety labeling change for HES products (November 2013), we focused our FAERS search on new clinical information that has appeared since that date.

We queried the database for reports submitted for all FDA-approved HES products received by FDA during the period November 25, 2013 to April 29, 2019.[32] We identified 122 serious adverse event reports, including 9 reports of death, 12 reports of AKI, 3 reports of need for RRT, and 3 reports of coagulopathy (the adverse events for which clinical studies have found safety signals associated with the use of HES products). These 27 reports were reviewed independently by two FDA medical officers, discussed in detail, and classified according to the WHO-UMC system for standardized case causality assessment.[33] See Table 3.

Table 3
Adverse Event Reports Submitted to FAERS for All FDA-Approved HES Products from November 25, 2013 to April 29, 2019

Adverse Event	Number of Reports	Number of Unique Cases[34]	Causality Classification
Death	9	8	5 unlikely[35]; 3 unassessable[36]
Acute kidney injury (AKI)	12	8	8 unassessable
Renal replacement therapy (RRT)	3	3	3 unassessable
Coagulopathy	3	3	2 unlikely; 1 unassessable

[32] Since April of 2019, FDA has not identified any adverse event reports that would change the assessment and conclusions in the current analysis; as of March 31, 2021, there were no additional reports of death or serious adverse events of AKI, RRT, or coagulopathy.
[33] Uppsala Monitoring Center. The use of the WHO-UMC system for standardised case causality assessment, https://www.who.int/medicines/areas/quality_safety/safety_efficacy/WHOcausality_assessment.pdf; accessed 4/14/2021.
[34] Differences between the number of reports and the number of unique cases reflect duplicate reports.
[35] The WHO-UMC assessment criteria for the causality category "Unlikely" are: Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible); disease or other drugs provide plausible explanations. https://www.who.int/medicines/areas/quality_safety/safety_efficacy/WHOcausality_assessment.pdf.
[36] The WHO-UMC assessment criteria for the causality category "Unassessable/Unclassifiable" are: Report suggesting an adverse reaction; cannot be judged because information is insufficient or contradictory; data cannot be supplemented or verified. https://www.who.int/medicines/areas/quality_safety/safety_efficacy/WHOcausality_assessment.pdf.

FDA's review of the FAERS reports found that all reports of HES use that were associated with death, AKI, need for RRT, or coagulopathy were classified as either of unlikely causality (7 case reports) or of unassessable causality (15 case reports). These reports generally involved the use of HES products in the treatment of critical clinical situations involving shock. The role that HES administration may play in the treatment of patients with shock is difficult to independently assess and distinguish from the potentially poor clinical outcomes of the underlying disease process (e.g., renal failure, coagulopathy in the case of disseminated intravascular coagulation, death) and the overall medical condition of patients, and may be confounded by the many concomitant therapies administered. These cases were generally very complex, and there was insufficient information to assess causality in most of them.

FAERS is a spontaneous adverse event reporting system with inherent limitations, including underreporting, delayed reporting, and varying report quality (e.g., missing information, non-standardized terminology). Therefore, although causality was difficult to assess for these adverse event reports, we do not exclude the possibility that HES administration may contribute to the development of such events.

3. Data Mining Results

In addition to reviewing clinical studies and searching the FAERS database for data and information about the safety of HES products, FDA gathered and analyzed data mining results for adverse events associated with use of HES products.

FDA conducted a data mining query using the Empirica Signal 8.0 with a data lock point of April 28, 2019 to evaluate whether any events following use of HES products[37] were disproportionally reported compared to all products in FAERS.[38,39] The results showed that Voluven and HESPAN were associated with data mining signals for AKI,[40] and Hetastarch (including product names HESPAN and HEXTEND) was associated with signals for coagulopathy.[41]

Data mining findings evaluate whether adverse events following use of a drug are disproportionally reported compared to other drugs in the FAERS database. This does not imply causality and could be due to the effect of a drug or to an underlying predisposition for that event in patients who would normally receive the drug (confounding by indication).

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[37] Product Name (S): Voluven, Hespan, Hextend, Hetastarch, Hetastarch\Pentastarch, Hetastarch in sodium chloride, Hetastarch\Sodium chloride injection, and Hydroxyethyl starch.
[38] The threshold for signal detection is an EB05 value > 2. EB05 is the lower bound of the 90% confidence limit for the Empirical Bayesian Geometric Mean. *See* Data Mining at FDA – White Paper, available at https://www.fda.gov/scienceresearch/dataminingatfda/ucm446239.htm; accessed 4/14/2021.
[39] A subsequent data mining query with a data lock point of March 31, 2021 did not identify any additional data mining signals and thus did not change our conclusions.
[40] Voluven®: Acute renal failure, EB05=3.187; HESPAN®: Acute renal failure, EB05=2.698.
[41] Hetastarch: Coagulopathy, EB05=34.595.

B. New Safety Information Warrants a Safety Labeling Change for HES Products

FDA has become aware of new data and information about the safety of HES products since the HES products were approved, and has reviewed and analyzed this new information and data, including the results of the clinical studies referenced in the Petition. As discussed below, FDA considers this new data and information to be "new safety information" as defined in section 505-1(b)(3) of the FD&C Act. Based on this new safety information, and under the authority of section 505(o)(4) of the FD&C Act, FDA finds that safety labeling changes regarding certain risks associated with HES product use are warranted. Therefore, FDA is notifying holders of approved NDAs for HES products that FDA believes changes to the labeling of these products should be made to reflect this new safety information. Many of these labeling changes address the concerns expressed in the Petition, as discussed below.

It is FDA's view that, with the safety labeling changes that FDA is requiring, HES products are safe and effective for their intended use in the limited indications and the limited populations for which they are approved and labeled.

C. Analysis of Petitioners' Grounds for the Request

In support of your request that HES products be withdrawn from the market, you make the following assertions:

1) The unfavorable risk-benefit profile of HES products is not limited to critically ill patients (including those with sepsis), but also applies to surgical and trauma patients (Petition at 8-16);

2) Lower-molecular-weight HES products carry the same risks as their high-molecular-weight predecessors (Petition at 16-17);

3) The adverse effects of HES products cannot be avoided through the use of lower concentrations or doses (Petition at 17-18);

4) HES products need not remain on the market, given good alternatives for surgical and trauma patients (Petition at 18-21); and

5) Limited evidence on HES products' use in children indicates that it likely carries the same risks as in adult patients (Petition at 21-22).

We discuss each of these below.

1. The Risk-Benefit Profile of HES Products in Surgical and Trauma Patients

The Petition cites clinical studies on the use of HES products in surgical and trauma patients and argues that those studies demonstrate that the risks of HES products found when the products are used in critically ill patients (including those with sepsis) also apply to their use in surgical and

trauma patients. These studies include RCTs, systematic reviews and meta-analyses of RCTs, and observational studies.

a. Randomized Controlled Trials (RCTs)

In the Petition, you reference several RCTs, including the large CHEST study[42] (Petition at 13) and several small trials (Petition at 10).

FDA carefully considered the 2012 CHEST study in the context of the 2013 safety labeling change and referenced it in the June and November 2013 Safety Communications (2013 Safety Communications).[43]

We have examined the six smaller RCTs that you referenced. Petition at 10. One of these studies has been retracted.[44,45] Two were among those considered by the Agency in the context of the 2013 safety labeling change.[46,47] FDA has analyzed the remaining three RCTs[48,49,50]; because these studies failed to demonstrate a statistically-significant change in the incidence of one or more of the safety signals, FDA considers them to be less informative.

FDA has also identified and analyzed two other post-2012 RCTs in surgery patients, described below.

Rasmussen et al.: This study was a single-center, single-blind, RCT in patients undergoing cystectomy (N=33) to evaluate whether administration of 6% HES 130/0.4 affected coagulation

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[42] Myburgh, JA, Finfer S, Bellomo R, et al.; CHEST Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med*. 2012 Nov 15;367(20):1901-1911.

[43] FDA Safety Communication: Boxed Warning on increased mortality and severe renal injury, and additional warning on risk of bleeding, for use of hydroxyethyl starch solutions in some settings, November 25, 2013, https://wayback.archive-it.org/7993/20170112095648/http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ucm358271.htm; accessed 4/14/2021.

[44] Zeng K, Li Y, Liang M, et al. The influence of goal-directed fluid therapy on the prognosis of elderly patients with hypertension and gastric cancer surgery. *Drug Des Devel Ther*. 2014 Oct 29;8:2113-2119.

[45] Zeng K, Li Y, Liang M, et al. The influence of goal-directed fluid therapy on the prognosis of elderly patients with hypertension and gastric cancer surgery [Retraction]. *Drug Des Devel Ther*. 2017 Sep 6;11:2675.

[46] Allison KP, Gosling P, Jones S, et al. Randomized trial of hydroxyethyl starch versus gelatin for trauma resuscitation. *J Trauma*. 1999 Dec;47(6):1114-1121.

[47] James MF, Michell WL, Joubert IA, et al. Resuscitation with hydroxyethyl starch improves renal function and lactate clearance in penetrating trauma in a randomized controlled study: The FIRST Trial (Fluids in Resuscitation of Severe Trauma). *Br J Anaesth*. 2011 Nov;107(5):693-702.

[48] Szturz P, Kula R, Tichy J, et al. Individual goal-directed intraoperative fluid management of initially hypovolemic patients for elective major urological surgery. *Bratisl Lek Listy*. 2014;115(10):653-659.

[49] Kancir AS, Pleckaitiene L, Hansen TB, et al. Lack of nephrotoxicity by 6% hydroxyethyl starch 130/0.4 during hip arthroplasty: A randomized controlled trial. *Anesthesiology*. 2014 Nov;121(5):948-958.

[50] Kancir AS, Johansen JK, Ekeloef NP, et al. The effect of 6% hydroxyethyl starch 130/0.4 on renal function, arterial blood pressure, and vasoactive hormones during radical prostatectomy: A randomized controlled trial. *Anesth Analg*. 2015 Mar;120(3):608-618.

competence and perioperative blood loss compared to Ringer's lactate solution.[51] Sixteen patients were randomized to receive Ringer's lactate solution and 17 to receive HES. Among those receiving HES, thromboelastography (TEG) indicated reduced clot strength. There was no significant difference between the two treatment cohorts with regard to frequency of reoperations or length of hospital stay, but use of 6% HES 130/0.4 was less effective than Ringer's lactate in improving coagulation competence and perioperative blood loss. Administration of 6% HES 130/0.4 reduced clot strength and increased perioperative hemorrhage by more than 50%.

FDA's assessment is that the Rasmussen et al. RCT is informative because it found a statistically-significant safety signal for coagulopathy in patients undergoing cystectomy and did not have major methodological limitations.

Kammerer et al.: Researchers conducted a single-center, single-blind study in 100 patients undergoing cystectomy to evaluate whether administration of a balanced 6% HES 130/0.4 product vs. 5% albumin was associated with renal injury.[52] The primary endpoint was the ratio of serum cystatin C within an observation period of 90 days (i.e. between the first preoperative visit and the last visit at day 90). Secondary endpoints included estimated glomerular filtration rate until postoperative day (POD) 3, and the RIFLE scoring system category[53] at POD 3 and POD 90. No significant differences were found with respect to serum cystatin C concentrations, estimated glomerular filtration rate, or RIFLE criteria. Intraoperative transfusion requirements, transfusion rates per cohort until POD 3, and perioperative hemodynamics were similar in both groups. The authors concluded that, based on this study, albumin 5% and balanced HES 6% have comparable renal safety profiles in patients undergoing elective cystectomy.

FDA's assessment is that the Kammerer et al. RCT is less informative because it failed to demonstrate a statistically-significant change in the incidence of one or more of the safety signals.

In summary, having reviewed the relevant RCTs, FDA considers Rasmussen et al. to be an informative study that found a safety signal for coagulopathy in patients undergoing cystectomy.

[51] Rasmussen KC, Johansson PI, Højskov M, et al. Hydroxyethyl starch reduces coagulation competence and increases blood loss during major surgery: Results from a randomized controlled trial. *Ann Surg*. 2014 Feb;259(2):249-254.
[52] Kammerer T, Brettner F, Hilferink S, et al. No differences in renal function between balanced 6% hydroxyethyl starch (130/0.4) and 5% albumin for volume replacement therapy in patients undergoing cystectomy: A randomized controlled trial. *Anesthesiology*. 2018 Jan;128(1):67-78.
[53] RIFLE (an acronym of Risk, Injury, Failure, Loss of function, and End-stage renal disease) is a scoring system for AKI. *See* https://www.medscape.com/answers/1925597-112191/what-are-the-rifle-criteria-for-acute-kidney-injury-aki.

b. Systematic Reviews and Meta-Analyses of RCTs

The Petition also references a number of systematic reviews and meta-analyses of RCTs. Petition at 10-15.

FDA considered the meta-analysis by Navickis et al. (2012)[54] and the 2013 systematic review by Van der Linden et al.[55] in the context of the 2013 safety labeling change, and referenced them in the 2013 Safety Communications.[56] We address the other meta-analyses and systematic reviews that the Petition references here.

Mutter et al.: As you note, the 2010 Cochrane review[57] (referenced in the 2013 Safety Communications[58]) was updated by Mutter et al. in 2013.[59] Petition at 9. Mutter et al.'s database included 23 additional studies, which included surgical and trauma patients and patients with sepsis and burns. Although RRT and author-defined kidney failure were higher in the aggregate HES treatment cohort, risk of RRT in the surgical subpopulation was not significantly different between treatment arms. FDA considers Mutter et al. to be less informative because it did not demonstrate a statistically-significant change in the incidence of one or more of the safety signals in the surgical subpopulation.[60]

Martin et al.: You reference the 2013 meta-analysis by Martin et al. that included RCTs of patients undergoing cardiac and noncardiac surgery in which at least one study group received HES 130/0.4 products and at least one control group received a different solution.[61] Petition at

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[54] Navickis RJ, Haynes GR, and Wilkes MM. Effect of hydroxyethyl starch on bleeding after cardiopulmonary bypass: A meta-analysis of randomized trials. *J Thorac Cardiovasc Surg*. 2012 Jul;144(1):223-230.
[55] Van der Linden P, James M, Mythen M, et al. Safety of modern starches used during surgery. *Anesth Analg.* 2013 Jan;116(1)35-48.
[56] FDA Safety Communication: Boxed Warning on increased mortality and severe renal injury, and additional warning on risk of bleeding, for use of hydroxyethyl starch solutions in some settings, November 25, 2013, https://wayback.archive-it.org/7993/20170112095648/http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ucm358271.htm; accessed 4/14/2021.
[57] Dart AB, Mutter TC, Ruth CA, et al. Hydroxyethyl starch (HES) versus other fluid therapies: Effects on kidney function. *Cochrane Database Syst Rev*. 2010 Jan 20;(1):CD007594.
[58] FDA Safety Communication: Boxed Warning on increased mortality and severe renal injury, and additional warning on risk of bleeding, for use of hydroxyethyl starch solutions in some settings, November 25, 2013, https://wayback.archive-it.org/7993/20170112095648/http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ucm358271.htm; accessed 4/14/2021.
[59] Mutter TC, Ruth CA, and Dart AB. Hydroxyethyl starch (HES) versus other fluid therapies: Effects on kidney function. *Cochrane Database Syst Rev*. 2013 Jul 23;(7):CD007594.
[60] The 2013 Mutter et al. Cochrane review considered only a single additional trauma study: James MF, Michell WL, Joubert IA, et al. Resuscitation with hydroxyethyl starch improves renal function and lactate clearance in penetrating trauma in a randomized controlled study: The FIRST Trial (Fluids in Resuscitation of Severe Trauma). *Br J Anaesth*. 2011 Nov;107(5):693-702. As stated above, the James et al. RCT was among those considered by the Agency in the context of the 2013 safety labeling change.
[61] Martin C, Jacob M, Vicaut E, et al. Effect of waxy maize-derived hydroxyethyl starch 130/0.4 on renal function in surgical patients. *Anesthesiology*. 2013 Feb;118(2):387-394.

11-12. You point out that Wiedermann[62] identified limitations of this meta-analysis (use of another HES product or gelatin as the comparator; inclusion of only 21% of patients in a prior Cochrane meta-analysis[63]; short follow-up periods). Petition at 11-12. FDA agrees that the meta-analysis by Martin et al. has limitations, and considers it to be less informative because it had major methodological limitations.

Wilkes and Navickis: The Petition also references the 2014 meta-analysis by Wilkes and Navickis[64] of RCTs of adult subjects (N=4409) undergoing surgery, including the CHEST surgery cohort, comparing HES vs crystalloids/non-HES colloid solutions.[65] Petition at 12-13. The authors found an increased need for RRT associated with HES use, even though analysis of the CHEST surgery cohort alone did not. FDA considers the Wilkes and Navickis meta-analysis to be an informative study because it found a statistically-significant safety signal for need for RRT in surgical patients and did not have major methodological limitations.

Gillies et al.: In the Petition, you also reference the 2014 meta-analysis by Gillies et al., which included RCTs with subjects undergoing surgery in which perioperative administration of 6% HES products was compared with that of any non-starch fluid.[66] Petition at 13. The authors found no significant differences in hospital mortality, need for RRT, or AKI between the two groups. FDA considers the Gillies et al. meta-analysis to be less informative because it did not demonstrate a statistically-significant change in the incidence of one or more of the safety signals.

Jacob et al.: In the Petition, you reference the 2014 meta-analysis by Jacob et al.,[67] which reviewed RCTs of HES products versus other fluids in subjects undergoing cardiac surgery. Petition at 14. The authors found that, while higher-molecular-weight (HMW) HES products were associated with greater blood loss and transfusion requirements than comparator fluids, this risk was not seen with lower-molecular-weight (LMW) HES products. The LMW HES products were associated with less blood loss and fewer transfusion requirements than albumin, but no significant differences on these outcomes when compared with crystalloids or gelatin. Overall, in studies comparing HES products to albumin, blood loss and transfusion requirements either were statistically higher, or trended higher, in studies using HES products with MW >200 kDa than in studies using HES products with MW <200 kDa. Although 6% HES 130/0.4 significantly decreased blood loss and transfusion requirements compared with albumin, the

[62] Wiedermann CJ. Correspondence: Hydroxyethyl starch 130/0.4: Safe for the kidney in surgical patients? *Anesthesiology*. 2013 Sep;119(3):735-736.
[63] Mutter TC, Ruth CA, and Dart AB. Hydroxyethyl starch (HES) versus other fluid therapies: Effects on kidney function. *Cochrane Database Syst Rev*. 2013 Jul 23;(7):CD007594.
[64] Wilkes MM and Navickis RJ. Postoperative renal replacement therapy after hydroxyethyl starch infusion: A meta-analysis of randomised trials. *Neth J Crit Care* 2014 Aug;18(4):4-9.
[65] Myburgh, JA, Finfer S, Bellomo R, et al.; CHEST Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med*. 2012 Nov 15;367(20):1901-1911.
[66] Gillies MA, Habicher M, Jhanji S, et al. Incidence of postoperative death and acute kidney injury associated with i.v. 6% hydroxyethyl starch use: Systematic review and meta-analysis. *Br J Anaesth*. 2014 Jan;112(1):25-34.
[67] Jacob M, Fellahi JL, Chappell D, et al. The impact of hydroxyethyl starches in cardiac surgery: A meta-analysis. *Crit Care*. 2014 Dec;18(6):656.

authors cautioned that this was based on only 3 studies and thus should be viewed as preliminary. The authors noted "borderline sufficient data were available for some of [the] analyses" but did not quantify this number, which is a limitation of the study.

The Jacob et al. meta-analysis is problematic due to confounding (use of gelatin as a comparator fluid in a large proportion of trials), limited data to support superiority of 6% HES 130/0.4 vs. albumin, and questions surrounding completeness of the data. Because Jacob et al. had major methodological limitations, FDA considers it to be a less-informative study.

Raiman et al.: Finally, you reference the 2016 meta-analysis by Raiman et al., which analyzed RCTs that compared HES products with crystalloid solutions in subjects undergoing noncardiac surgery.[68] Petition at 14-15. In this negative meta-analysis, the authors found a nonsignificant trend towards increased 90-day mortality with HES products. Because Raiman et al. did not demonstrate a statistically-significant change in the incidence of one or more of the safety signals, FDA considers it to be less informative.

In summary, having reviewed the meta-analyses and systematic reviews referenced in the Petition, FDA considers the 2014 Wilkes and Navickis meta-analysis to be an informative study that found a safety signal for an increased need for RRT in surgical patients receiving HES.

c. Observational Studies

In the Petition, you reference a number of observational studies. Petition at 15-16. We address these studies below.

Kashy et al.: The Petition references the 2014 study by Kashy et al. of postoperative AKI in patients undergoing inpatient noncardiac surgery and receiving either HES products or a crystalloid (N=29,360).[69] Petition at 15. The authors found that the risk of AKI was significantly higher among the HES group. This retrospective study is the largest to date in patients undergoing noncardiac surgery and receiving HEXTEND. Despite the potential for residual confounding inherent in nonrandomized observational studies such as this one, findings from a study of this size lend support to a causal relationship between HEXTEND and kidney injury. FDA considers Kashy et al. to be an informative study because it found a statistically-significant safety signal for AKI in the noncardiac surgery patient population and did not have major methodological limitations.

Allen et al.: You reference the 2014 retrospective study by Allen et al. that assessed the risk of AKI and 90-day mortality among blunt (N=959) or penetrating (N=451) trauma patients who

[68] Raiman M, Mitchell CG, Biccard BM, et al. Comparison of hydroxyethyl starch colloids with crystalloids for surgical patients: A systematic review and meta-analysis. *Eur J Anaesthesiol*. 2016 Jan;33(1):42-48.
[69] Kashy BK, Podolyak A, Makarova N, et al. Effect of hydroxyethyl starch on postoperative kidney function in patients having noncardiac surgery. *Anesthesiology*. 2014 Oct;121(4):730-739.

received 6% HES 450/0.7 products and/or blood products.[70] Petition at 15-16. In blunt trauma patients, HES use was associated with a significantly increased risk of AKI and mortality. These risks were not seen in penetrating trauma patients. FDA considers the Allen et al. observational study to be an informative study because it found a statistically-significant safety signal for mortality and AKI in the blunt trauma (but not penetrating trauma) patient population and did not have major methodological limitations.

Patel et al.: In the Petition, you reference the 2015 prospective observational study by Patel et al. that assessed the impact of HES products administered to kidney donors after neurologic determination of death on recipient renal graft outcomes.[71] Petition at 16. Kidneys from donors who received HES products had a higher rate of delayed graft function in recipient patients (N=411) compared with kidneys from donors who did not receive HES products (N=575). After accounting for the propensity of donors to receive HES products, the authors found that HES product administration was independently associated with an increased risk of delayed graft function in recipients. A dose-response relationship was also evident. Although evidence of harm from this study is indirect, the results support the conclusion that exposure of kidney donors to an HES dose >750 mL is strongly associated with increased need for dialysis in kidney transplant recipients within the first week after kidney transplantation. FDA considers Patel et al. to be an informative study because it found a statistically-significant safety signal for RRT in the renal transplant surgery population and did not have major methodological limitations.

Eriksson et al.: The Petition references the 2015 observational study by Eriksson et al.[72] Petition at 15; footnote 93. This retrospective cohort study investigated kidney injury in severely injured trauma patients aged 15 years and older (N=413) admitted to the ICU, most of whom (89%) were blunt trauma patients, comparing those exposed to 6% HES 130/0.4 and those who were not. Diabetes, male sex, and severe injury were identified as strong risk factors, but age, nondiabetic comorbidity, massive transfusion, and resuscitation with 6% HES 130/0.4 were also associated with postinjury AKI. Multivariable regression analysis showed that HES exposure was independently associated with AKI, which, in turn, was associated with increased 30-day mortality and 1-year mortality. FDA considers Eriksson et al. to be an informative study because it found a statistically-significant safety signal for AKI and mortality in the trauma patient population and did not have major methodological limitations.

Green et al.: You also reference Green et al. (Petition Attachment 31), a 2016 single-center, retrospective case series of adult vascular surgery patients with peripheral vascular disease (N=1395; complete records available: N=796) that compared outcomes between patients who received 6% HES 130/0.4 (N=170) or 10% HES 200/0.45 (N=63) and patients who received

[70] Allen CJ, Valle EJ, Jouria JM, et al. Differences between blunt and penetrating trauma after resuscitation with hydroxyethyl starch. *J Trauma Acute Care Surg*. 2014 Dec;77(6):859-864.
[71] Patel MS, Niemann CU, Sally MB, et al. The impact of hydroxyethyl starch use in deceased organ donors on the development of delayed graft function in kidney transplant recipients: A propensity-adjusted analysis. *Am J Transplant*. 2015 Aug;15(8):2152-2158.
[72] Eriksson M, Brattström O, Mårtensson J, et al. Acute kidney injury following severe trauma: Risk factors and long-term outcome. *J Trauma Acute Care Surg*. 2015 Sep;79(3):407-412.

only crystalloids (N=583).[73] After adjustment for potential confounders, the study found that receiving an HES product was associated with increased likelihood of 30-day mortality, postoperative requirement for hemodialysis, intensive care unit admission, and mechanical ventilation. FDA considers Green et al. to be an informative study because it found statistically-significant safety signals for mortality and need for RRT in the vascular surgery patient population and did not have major methodological limitations.

In summary, FDA concludes that these informative observational studies found the following increased risks in those receiving HES products:

- In trauma patients:
  - Mortality (trauma[74]; blunt trauma[75]); and
  - AKI (trauma;[76] blunt trauma[77])
- In noncardiac surgery patients:
  - Mortality (vascular surgery)[78];
  - AKI[79]; and
  - Need for RRT (renal transplantation surgery[80]; vascular surgery[81]).

d. Summary

FDA has carefully reviewed the results of available studies, including those referenced in the Petition, as well as other available information and data about the safety of HES products. The Agency has concluded that clinical studies conducted since the products' approvals have found safety signals associated with the use of HES in the surgery population and the blunt trauma population.

The quality of the aggregate database used to identify these safety signals is primarily based on nonrandomized observational studies, along with meta-analyses of RCTs and an RCT. Despite

[73] Green RS, Butler MB, Hicks SD, et al. Effect of hydroxyethyl starch on outcomes in high-risk vascular surgery patients: A retrospective analysis. *J Cardiothorac Vasc Anesth*. 2016 Aug;30(4):967-972.
[74] Eriksson M, Brattström O, Mårtensson J, et al. Acute kidney injury following severe trauma: Risk factors and long-term outcome. *J Trauma Acute Care Surg*. 2015 Sep;79(3):407-412.
[75] Allen CJ, Valle EJ, Jouria JM, et al. Differences between blunt and penetrating trauma after resuscitation with hydroxyethyl starch. *J Trauma Acute Care Surg.* 2014 Dec;77(6):859-864.
[76] Eriksson M, Brattström O, Mårtensson J, et al. Acute kidney injury following severe trauma: Risk factors and long-term outcome. *J Trauma Acute Care Surg*. 2015 Sep;79(3):407-412.
[77] Allen CJ, Valle EJ, Jouria JM, et al. Differences between blunt and penetrating trauma after resuscitation with hydroxyethyl starch. *J Trauma Acute Care Surg.* 2014 Dec;77(6):859-864.
[78] Green RS, Butler MB, Hicks SD, et al. Effect of hydroxyethyl starch on outcomes in high-risk vascular surgery patients: A retrospective analysis. *J Cardiothorac Vasc Anesth*. 2016 Aug;30(4):967-972.
[79] Kashy BK, Podolyak A, Makarova N, et al. Effect of hydroxyethyl starch on postoperative kidney function in patients having noncardiac surgery. *Anesthesiology*. 2014 Oct;121(4):730-739.
[80] Patel MS, Niemann CU, Sally MB, et al. The impact of hydroxyethyl starch use in deceased organ donors on the development of delayed graft function in kidney transplant recipients: A propensity-adjusted analysis. *Am J Transplant*. 2015 Aug;15(8):2152-2158.
[81] Green RS, Butler MB, Hicks SD, et al. Effect of hydroxyethyl starch on outcomes in high-risk vascular surgery patients: A retrospective analysis. *J Cardiothorac Vasc Anesth*. 2016 Aug;30(4):967-972.

limitations in the informative studies, the strength, consistency and clinical importance of safety signals found in heterogeneous populations and across diverse clinical settings are persuasive. Furthermore, the safety signals that have now been found in the surgery population (mortality, need for RRT, AKI and coagulopathy) and the blunt trauma population (mortality and AKI) are those that were previously found in the critically-ill population.

Based on our analysis of these data and information, FDA agrees with the Petitioners that there is evidence that the risk-benefit profile of HES products used in critically-ill patients (including those with sepsis) also applies to the use of HES products in surgery and blunt-trauma patients.

FDA has become aware of data and information about the safety of HES products that have become available since the products' approvals, including the results of the studies referenced in the Petition; has considered these data and information; and has concluded that they constitute new safety information as defined in section 505-1(b)(3) of the FD&C Act. Under the authority of section 505(o)(4) of the FD&C Act, as described above, FDA is requiring changes to the labeling of HES products to reflect the new safety information discussed in this and subsequent sections of this letter. Based on our analysis of this new safety information, FDA finds that safety labeling changes are warranted for HES products regarding increased risk of mortality, AKI, RRT, and coagulopathy in surgery patients and increased risk of mortality and AKI in blunt trauma patients.

It is FDA's view that the labeling revisions that FDA is requiring will be effective in informing health care providers of the increased risks associated with the use of HES products in the surgery patient population (mortality, need for RRT, AKI and coagulopathy) and blunt trauma patient population (mortality and AKI). In light of the safety labeling changes, it is FDA's view that HES products remain safe and effective when used in the limited populations and under the limited conditions of use reflected in the labeling.

2. Lower-Molecular-Weight HES Products

In the Petition, you argue that the new LMW formulations of HES (specifically Voluven) cause the same adverse effects as do older HMW HES products. Petition at 16-17. You cite several studies as evidence of the risks of LMW HES products.

Three of the studies you cite[82,83,84] were considered by FDA at the time of the 2013 safety labeling change; two of these[85,86] were referenced in the 2013 Safety Communications.[87] You also cite Mutter et al.[88]; as discussed above, FDA considers this to be a less-informative study.

We address here the 2014 meta-analysis by Wilkes and Navickis.[89] We also consider Eriksson et al.[90] in regard to this issue.

Wilkes and Navickis: You state that the 2014 Wilkes and Navickis meta-analysis found that "HES solutions significantly increased the need for renal replacement therapy (pooled RR 1.44; 95% CI 1.04 – 2.01).[91] Ten (67%) of the 15 trials, comprising 90% of analyzed subjects, used only low-molecular-weight HES (130/0.4) solutions." Petition at 17; footnote renumbered.

Eleven of the 15 studies that Wilkes and Navickis analyzed investigated 6% HES 130/0.4 and four investigated other HES formulations. Comparators included 4% gelatin, 6% HES 200/0.62, 10% HES 250/0.45, 5% HSA and/or crystalloid. Wilkes and Navickis found a significant increase in need for RRT in groups receiving HES compared to groups receiving a comparator solution.

The Agency considers Wilkes and Navickis to be an informative study because it found a statistically-significant safety signal for the need for RRT associated with all HES products, including LMW formulations, and did not have major methodological limitations.

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[82] Myburgh, JA, Finfer S, Bellomo R, et al.; CHEST Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med*. 2012 Nov 15;367(20):1901-1911.
[83] Perner A, Haase N, Guttormsen AB, et al. for the 6S Trial Group and the Scandinavian Critical Care Trials Group. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *N Engl J Med*. 2012 Jul 12;367(2):124-134.
[84] Bellmann R, Feistritzer C, and Wiedermann CJ. Effect of molecular weight and substitution on tissue uptake of hydroxyethyl starch: A meta-analysis of clinical studies. *Clin Pharmacokinet*. 2012 Apr 1;51(4):225-236.
[85] Myburgh, JA, Finfer S, Bellomo R, et al.; CHEST Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med*. 2012 Nov 15;367(20):1901-1911.
[86] Perner A, Haase N, Guttormsen AB, et al. for the 6S Trial Group and the Scandinavian Critical Care Trials Group. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *N Engl J Med*. 2012 Jul 12;367(2):124-134.
[87] FDA Safety Communication: Boxed Warning on increased mortality and severe renal injury, and additional warning on risk of bleeding, for use of hydroxyethyl starch solutions in some settings, November 25, 2013, https://wayback.archive-it.org/7993/20170112095648/http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ucm358271.htm; accessed 4/14/2021.
[88] Mutter TC, Ruth CA, and Dart AB. Hydroxyethyl starch (HES) versus other fluid therapies: Effects on kidney function. *Cochrane Database Syst Rev*. 2013 Jul 23;(7):CD007594.
[89] Wilkes MM and Navickis RJ. Postoperative renal replacement therapy after hydroxyethyl starch infusion: A meta-analysis of randomised trials. *Neth J Crit Care* 2014 Aug;18(4):4-9.
[90] Eriksson M, Brattström O, Mårtensson J, et al. Acute kidney injury following severe trauma: Risk factors and long-term outcome. *J Trauma Acute Care Surg*. 2015 Sep;79(3):407-412.
[91] Wilkes MM and Navickis RJ. Postoperative renal replacement therapy after hydroxyethyl starch infusion: A meta-analysis of randomised trials. *Neth J Crit Care* 2014 Aug;18(4):4-9.

Eriksson et al.: FDA also notes that Eriksson et al.'s 2015 retrospective cohort study[92] (discussed above), which investigated kidney injury in severely injured trauma patients, is relevant. In that study, the authors identified risk factors associated with AKI development, which was in turn associated with increased mortality. One of the risk factors associated with postinjury AKI was resuscitation with 6% HES 130/0.4, an LMW HES product.

a. Summary

FDA has considered the information and data that have become available since the HES products' approvals, including the results of the studies referenced in the Petition. FDA concludes that there is evidence now available that the risks associated with LMW HES products, such as 6% HES 130/0.4, are comparable to risks associated with HMW products.

The new safety labeling that FDA is requiring, discussed in other sections of this letter, applies to all HES products, including LMW ones. Because the new labeling will not be limited to HMW formulations of HES products, FDA expects that it will effectively provide health care providers with the information they need to make appropriate decisions about the use of all HES products, including LMW HES products, in their patients.

3. Lower Concentrations and Doses of HES Products

In the Petition, you argue that adverse effects of HES products cannot be avoided by using lower concentrations or doses of HES products, and cite several studies in support of your claim. Petition at 17-18. One of these studies[93] was considered by FDA at the time of the 2013 safety labeling changes, and was referenced in the 2013 Safety Communications.[94] You also cite Mutter et al.[95]; as discussed above, FDA considers that study to be less informative. With regard to the study by Meybohm et al.,[96] we note that the authors' suggestion of an algorithm for limiting HES administration to immediate hemodynamic stabilization has not been studied.

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[92] Eriksson M, Brattström O, Mårtensson J, et al. Acute kidney injury following severe trauma: Risk factors and long-term outcome. *J Trauma Acute Care Surg*. 2015 Sep;79(3):407-412.
[93] Patel A, Waheed U, and Brett SJ. Randomised trials of 6% tetrastarch (hydroxyethyl starch 130/0.4 or 0.42) for severe sepsis reporting mortality: Systematic review and meta-analysis. *Intensive Care Med.* 2013 May;39(5):811-822.
[94] FDA Safety Communication: Boxed Warning on increased mortality and severe renal injury, and additional warning on risk of bleeding, for use of hydroxyethyl starch solutions in some settings, November 25, 2013. https://wayback.archive-it.org/7993/20170112095648/http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ucm358271.htm; accessed 4/14/2021.
[95] Mutter TC, Ruth CA, and Dart AB. Hydroxyethyl starch (HES) versus other fluid therapies: Effects on kidney function. *Cochrane Database Syst Rev*. 2013 Jul 23;(7):CD007594.
[96] Meybohm P, Van Aken H, De Gasperi A, et al. Re-evaluating currently available data and suggestions for planning randomised controlled studies regarding the use of hydroxyethyl starch in critically ill patients – A multidisciplinary statement. *Crit Care.* 2013 Jul 26;17(4):R166.

In addition, you reference three retrospective observational studies published in 2016[97,98,99] and state that these studies "found increased risks of acute kidney injury and need for renal replacement therapy in surgical patients at relatively low median or mean infusion volumes (< 50 mL/kg) of HES solutions." Petition at 18. We discuss these three studies here.

Albrecht et al.: This was a retrospective, single-center, nonrandomized cohort analysis of patients admitted to a surgical intensive care unit over a period of several years that compared use of HES, gelatin, or crystalloid alone for fluid resuscitation. The analysis found that significantly larger volumes of colloids than crystalloid were needed, with cumulatively larger volumes administered of gelatin than of HES. Although no difference was noted between HES and gelatin in the incidence of acute renal failure, the incidence was higher using colloids than using crystalloid. Mortality and maximum daily dose of HES and gelatin were significantly correlated, but mortality and total amount of crystalloids or total fluid intake were not. Need for RRT and 30-day mortality were significantly higher, and intensive care unit and hospital stay was longer, for both colloid solutions compared with crystalloids. The authors concluded that treatment with gelatin did not reduce the rate of acute renal failure or mortality in surgical critical care patients compared to treatment with HES, and that both colloids appeared to have dose-dependent effects on renal function.[100]

Albrecht et al. enrolled, and was designed to study, all patients admitted to a surgical ICU, a population that included both postoperative surgery patients requiring ICU admission (who were not necessarily critically ill at time of admission) and critically ill patients. Due to these major methodological limitations (i.e., the heterogeneity of the population and the fact that the study was not designed to analyze the effect of HES in the surgery subgroup), FDA considers Albrecht et al. to be a less-informative study.

Ahn et al.: In this retrospective study, subjects (N=1442) were patients intentionally fluid-restricted during thoracic surgery procedures.[101] Postoperative AKI was diagnosed in 5.1% of patients within 72 hours after surgery based on the AKIN criteria. Crystalloid restriction was unrelated to AKI, even in patients with abnormal renal function at baseline. Mean volume in patients who received HES was only 526 ± 219 mL. AKI occurred more often when HES was administered to patients with decreased renal function or to patients with normal renal function having more than two risk factors (use of angiotensin-converting enzyme inhibitor; use of

[97] Ahn HJ, Kim JA, Lee AR, et al. The risk of acute kidney injury from fluid restriction and hydroxyethyl starch in thoracic surgery. *Anesth Analg*. 2016 Jan;122(1):186-193.
[98] Lagny MG, Roediger L, Koch JN, et al. Hydroxyethyl starch 130/0.4 and the risk of acute kidney injury after cardiopulmonary bypass: A single-center retrospective study. *J Cardiothorac Vasc Anesth*. 2016 Aug:30(4):869–875.
[99] Albrecht FW, Glas M, Rensing H, et al. A change of colloid from hydroxyethyl starch to gelatin does not reduce rate of renal failure or mortality in surgical critical care patients: Results of a retrospective cohort study. *J Crit Care*. 2016 Dec;36:160-165.
[100] Albrecht FW, Glas M, Rensing H, et al. A change of colloid from hydroxyethyl starch to gelatin does not reduce rate of renal failure or mortality in surgical critical care patients: Results of a retrospective cohort study. *J Crit Care*. 2016 Dec;36:160-165.
[101] Ahn HJ, Kim JA, Lee AR, et al. The risk of acute kidney injury from fluid restriction and hydroxyethyl starch in thoracic surgery. *Anesth Analg*. 2016 Jan;122(1):186-193.

angiotensin receptor blocker; open thoracotomy; pneumonectomy/esophagectomy; albumin <4.3 g/dl; diabetes mellitus; cerebrovascular disease; serum creatinine >1.2 or GFR <60), with each 500-mL aliquot increasing the odds of AKI 7-fold. The type of HES product (LMW or HMW) did not affect AKI frequency.

FDA considers Ahn et al. to be an informative study because it found a statistically-significant safety signal for AKI in thoracic surgery patients that was associated with lower doses of HES products and did not have major methodological limitations.

Lagny et al.: In this retrospective study (N=606), 6% HES 130/0.4 was used both as pump prime and for intraoperative fluid replacement in cardiac surgery patients and was compared to a balanced crystalloid solution.[102] Total HES volume for the first 48 hours was 1563 ± 1844 mL (20 mL/kg). Patients who received HES were twice as likely to develop postoperative AKI as those treated with crystalloid. In addition, surgical re-exploration for rebleeding was more frequent in the HES cohort. This association remained after propensity score matching. Results from this study suggest that lower HES doses (e.g., 10-20 mL/kg or 700-1400 mL) are not necessarily safer than higher doses (e.g., 40-50 mL/kg or 2800-3500 mL), especially in those at risk of AKI.

The Agency considers Lagny et al. to be an informative study because it found a statistically-signficiant safety signal for AKI and coagulopathy in cardiac surgery patients that was associated with lower doses of HES products and did not have major methodological limitations.

a. Summary

FDA has considered the information and data that have become available since the HES products' approvals, including the results of the studies referenced by the Petitioners. Based on this analysis, FDA concludes that there is evidence that the adverse events associated with the use of HES products are not limited to the products' administration at higher concentrations or doses, but are also associated with their administration at lower concentrations and doses. Post-2012 data from retrospective observational studies in the thoracic surgery and cardiac surgery populations suggest that HES doses as low as 10 mL/kg are associated with the same risks as are higher concentrations and doses of HES products, especially in populations with decreased renal function or in populations with normal renal function and more than two risk factors.

The new safety labeling that FDA is requiring, discussed in other sections of this letter, applies to HES products at all concentrations and doses, including at low concentrations and doses. Because the new labeling will not be limited to high concentrations or doses of HES products, FDA considers that it will effectively provide health care providers with the information they

[102] Lagny MG, Roediger L, Koch JN, et al. Hydroxyethyl starch 130/0.4 and the risk of acute kidney injury after cardiopulmonary bypass: A single-center retrospective study. *J Cardiothorac Vasc Anesth*. 2016 Aug:30(4):869–875.

need to make appropriate decisions about the use of HES products at all concentrations and doses.

4. Alternatives to HES Products for Surgical and Trauma Patients

In the Petition, you take the position that there is no need for HES products to remain on the market given available alternatives. Petition at 18-21. Insofar as HES results in greater intravascular pressures at lower infusion volumes than do crystalloids, you question whether these differences are clinically significant and outweigh the known risks of HES. Petition at 18.

To support your position, you reference several studies that measured differences in the volume of colloid versus crystalloid solutions used to restore or maintain hemodynamic stability in studies of surgical and critically-ill patients. FDA considered two of these studies[103,104] at the time of the 2013 safety labeling change, and referenced one[105] in the 2013 Safety Communications.[106] Here, we consider the other studies that you reference in the Petition.

Proponents of colloid solutions such as HES claim that these are therapeutically superior to crystalloid solutions because colloid solutions restore hemodynamic stability more quickly, require smaller volumes to achieve the intended goal, and remain in the circulation for longer periods of time.[107] Studies, including those referenced by the Petitioners, bring those claims into question.

With regard to infusion volumes, a 1:3 colloid:crystalloid ratio has generally been held to apply, i.e., three times as much crystalloid solution would need to be infused in order to obtain the effect of a given volume of colloid solution on hemodynamic stability.[108] However, the trials that you cite, conducted in surgical and critically-ill patients, who generally are at risk of cellular glycocalyx barrier disruption, found colloid: crystalloid ratios of only 1:1.7,[109] 1:1.4,[110] and

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[103] Myburgh, JA, Finfer S, Bellomo R, et al.; CHEST Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med*. 2012 Nov 15;367(20):1901-1911.
[104] Hartog CS, Kohl M, Reinhart K. A systematic review of third-generation hydroxyethyl starch (HES 130/0.4) in resuscitation: Safety not adequately addressed. *Anesth Analg*. 2011 Mar;112(3):635-645.
[105] Myburgh, JA, Finfer S, Bellomo R, et al.; CHEST Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med*. 2012 Nov 15;367(20):1901-1911.
[106] FDA Safety Communication: Boxed Warning on increased mortality and severe renal injury, and additional warning on risk of bleeding, for use of hydroxyethyl starch solutions in some settings, November 25, 2013, https://wayback.archive-it.org/7993/20170112095648/http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ucm358271.htm; accessed 4/14/2021.
[107] Jacob M, Chappell D, Hofmann-Kiefer K, et al. The intravascular volume effect of Ringer's lactate is below 20%: A prospective study in humans. *Crit. Care*. 2012 May 16;16(3):R86.
[108] *Id.*
[109] Yates DR, Davies SJ, Milner HE, et al. Crystalloid or colloid for goal-directed fluid therapy in colorectal surgery. *Br J Anaesth*. 2014 Feb; 112(2):281-289.
[110] Bayer O, Schwarzkopf D, Doenst T, et al. Perioperative fluid therapy with tetrastarch and gelatin in cardiac surgery – A prospective sequential analysis. *Crit Care Med*. 2013 Nov;41(11):2532-2542. In this observational

1:1.5.[111] An updated review[112] of trials comparing HES to crystalloid in critically ill patients with sepsis, trauma or hypovolemic shock found even lower ratios of 1:1,[113] 1:1.2,[114] and 1:1.3.[115] Therefore, the trials referenced in the Petition, as well as other studies, lend only modest support to the therapeutic superiority of colloid solutions with regard to volumes required.

More importantly, RCTs have been unable to show that colloids confer a survival advantage. For example, Finfer et al. showed that mortality was no different between ICU patients randomized to 4% albumin and those randomized to normal saline.[116] In a subgroup analysis of an RCT comparing colloid vs. crystalloid in critically ill surgical patients, researchers were unable to find any difference in mortality.[117] Two of the studies referenced in the Petition reached the same conclusion.[118,119] These results collectively support the Petitioners' argument that there is no demonstrated survival advantage of using colloids instead of crystalloids.

a. Summary

FDA has carefully reviewed the results of available clinical studies, including those referenced in the Petition, as well as other available information and data about alternatives to HES. The Agency agrees with the Petitioners that, in most surgical and trauma situations, alternative volume expanders are readily available for treatment of hypovolemia. FDA has also concluded that there is now evidence that these alternatives are, in most situations, as effective as HES products in restoring plasma volume without the risks of nephrotoxicity associated with HES products. For these reasons, we agree with the Petitioners that, in most surgical and trauma settings, alternative volume expanders are readily available for treatment of hypovolemia, and the risks of HES products outweigh their benefits.

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study of patients undergoing cardiac surgery, the authors found that HES increased risk for RRT, but not for mortality. FDA considers the study informative, but of limited interpretability because of its sequential, historically-controlled design.

[111] Orbegozo Cortés D, Gamarano Barros T, Njimi H, et al. Crystalloids versus colloids: Exploring differences in fluid requirements by systematic review and meta-regression. *Anesth Analg*. 2015 Feb;120(2):389-402.

[112] Zazzeron L, Gattinoni L, and Caironi P. Role of albumin, starches and gelatins versus crystalloids in volume resuscitation of critically ill patients. *Curr Opin Crit Care*. 2016 Oct; 22(5):428-436.

[113] Perner A, Haase N, Guttormsen AB, et al., for the 6S Trial Group and the Scandinavian Critical Care Trials Group. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *N Engl J Med*. 2012 Jul 12;367(2):124-134.

[114] Myburgh JA, Finfer S, Bellomo R, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med*. 2012 Nov 15;367(20):1901-1911.

[115] Brunkhorst FM, Engel C, Bloos F, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med*. 2008 Jan 10;358(2):125-139.

[116] Finfer S, Bellomo R, Boyce, N, et al.; SAFE Study Investigators. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med.* 2004 May 27;350(22):2247-2256 (SAFE Study).

[117] Heming N, Lamothe L, Jaber S, et al. Morbidity and mortality of crystalloids compared to colloids in critically ill surgical patients: A subgroup analysis of a randomized trial. *Anesthesiology*. 2018 Dec;129(6):1149-1158.

[118] Bayer O, Schwarzkopf D, Doenst T, et al. Perioperative fluid therapy with tetrastarch and gelatin in cardiac surgery – A prospective sequential analysis. *Crit Care Med*. 2013 Nov;41(11):2532-2542.

[119] Yates DR, Davies SJ, Milner HE, et al. Crystalloid or colloid for goal-directed fluid therapy in colorectal surgery. *Br J Anaesth*. 2014 Feb;112(2):281-289.

However, FDA is aware that surgical and trauma situations exist in which health care providers may find HES products to be an appropriate option. In particular, the availability of HES products may be important in austere, remote settings or when routine therapy is not effective, for example on a battlefield or during an emergency involving agents of military combat where adequate alternative therapy is not available. Given the existence of safe and effective alternatives, however, it is FDA's view that HES products should be reserved for those situations in which no adequate alternative treatment is available.

In summary, FDA has become aware of data and information about the safety of HES products that have become available since the products' approvals, including the results of the studies referenced in the Petition. FDA has considered the new data and information, and concludes that data and information on the increased morbidity and mortality risks of HES products relative to those of alternative products in surgery and trauma patients constitute new safety information as defined in section 505-1(b)(3) of the FD&C Act. Under the authority of section 505(o)(4) of the FD&C Act, FDA is requiring changes to the labeling of HES products to reflect the new safety information discussed in this and other sections of this letter. Based on our analysis of this new safety information, FDA finds that safety labeling changes are warranted for HES products warning that these products should not be used when adequate alternative treatment is available.

FDA believes that the labeling revisions that FDA is requiring will be effective in informing health care providers of the risks of HES products relative to those of alternative products. In light of the safety labeling changes, it is FDA's view that HES products remain safe and effective when used for the limited indications and in the limited populations for which they are approved and labeled.

5. Use of HES in Children

In the Petition, you argue that "[t]he increased risks of HES solutions seen in adults may also apply to children." You note that "there are relatively few studies evaluating the risks and benefits of HES products in pediatric patients," and reference an RCT by Van der Linden et al.[120] and a meta-analysis by Li et al.[121] Petition at 21.

As stated above, Voluven is the only HES product with a pediatric indication.

Van der Linden et al.: This study was a 2013 postmarketing RCT conducted by the manufacturer of Voluven (Fresenius Kabi) that compared its product (6% HES 130/0.4) to 5%

[120] Van der Linden P, De Villé A, Hofer A, et al. Six percent hydroxyethyl starch 130/0.4 (Voluven®) versus 5% human serum albumin for volume replacement therapy during elective open-heart surgery in pediatric patients. *Anesthesiology*. 2013 Dec;119(6):1296-1309.

[121] Li L, Li Y, Xu X, et al. Safety evaluation on low-molecular-weight hydroxyethyl starch for volume expansion therapy in pediatric patients: A meta-analysis of randomized controlled trials. *Crit Care*. 2015 Mar 10;19:79.

albumin for volume expansion in pediatric patients undergoing elective open-heart surgery.[122] An imbalance in safety measures between the two treatment cohorts was not found; however, as you point out, this study was not powered to reach a conclusion about safety.

Li et al.: In this 2015 meta-analysis, the authors analyzed RCTs in pediatric patients given a 6% LMW HES product (130/0.4 & 200/0.5) or a comparator fluid.[123] The meta-analysis found that HES products significantly decreased platelet count and increased length of ICU stay; no significant differences were reported in mortality, serum creatinine, activated partial thromboplastin time, or blood loss. However, most of the underlying studies had significant weaknesses, including small sample size (fewer than 100 patients in 11 of the 13 studies), inadequate follow-up, and systematic bias (allocation concealment was unclear in 7/13 studies, sequence generation was unclear in 6 studies, blinding methodology was unclear in 5 studies, and the number of patients who withdrew or dropped out was unclear in 7 studies).

a. Summary

FDA has considered the results of clinical studies, including the studies referenced in the Petition, on the use of HES products in pediatric patients. Based on our analysis, including our re-evaluation of existing information regarding safety of HES products in pediatric populations in light of the serious safety concerns with the use of HES products in adults, we conclude that studies conducted in children have not been of sufficient size or follow-up duration to assess the risks of mortality, AKI (including need for RRT), and coagulopathy in this patient population. FDA considers this to be new safety information as defined in section 505-1(b)(3) of the FD&C Act. FDA has also determined that information regarding the limited nature of such data should be included in the labeling for HES products. As a result, under the authority of section 505(o)(4) of the FD&C Act, FDA is requiring changes to the labeling of HES products to reflect the new safety information discussed in this and other sections of this letter.

FDA believes that the labeling revisions that FDA is requiring will be effective in alerting health care providers to the lack of information about the safety of HES products in pediatric populations, and will enable them to make appropriate decisions about the use of HES products in their pediatric patients. In light of the safety labeling changes for HES products, it is FDA's view that the products remain safe and effective when used for the limited indications and in the limited populations for which they are approved and labeled.

[122] Van der Linden P, De Villé A, Hofer A, et al. Six percent hydroxyethyl starch 130/0.4 (Voluven®) versus 5% human serum albumin for volume replacement therapy during elective open-heart surgery in pediatric patients. *Anesthesiology*. 2013 Dec;119(6):1296-1309.
[123] Li L, Li Y, Xu X, et al. Safety evaluation on low-molecular-weight hydroxyethyl starch for volume expansion therapy in pediatric patients: A meta-analysis of randomized controlled trials. *Crit Care*. 2015 Mar 10;19:79.

IV. Conclusions

We have carefully considered the information submitted in the Petition and other relevant studies, data, and information relating to the safety of HES products. We have concluded that information and data that have become available since the approvals of the HES products constitute new safety information as defined in section 505-1(b)(3) of the FD&C Act. Based on the existence of this new safety information, and under the authority of section 505(o)(4) of the FD&C Act, FDA is requiring changes to the labeling of all HES products to reflect this new safety information.

Much of the new safety labeling that FDA is requiring directly addresses the issues raised in the Petition, including labeling to reflect safety signals identified in the surgery patient population (mortality, need for RRT, AKI and coagulopathy) and blunt trauma patient population (mortality and AKI). The labeling changes also directly address the limited nature of information relating to the safety of HES products in the pediatric population. The new labeling is not limited to HMW formulations of HES products, or to their use in high concentrations or doses.

Based on the available data, it is FDA's view that, with labeling changes to inform prescribers of new safety information, the benefits of HES products continue to outweigh their risks in the limited populations and under the limited conditions of use reflected in the labeling. Therefore, we decline to withdraw approval of HES products at this time.

For the reasons discussed above, the Petition is denied. FDA will, however, continue to monitor and review available safety and efficacy information related to HES products and will act within our authority as appropriate.

Sincerely,

Peter Marks, MD, PhD
Director
Center for Biologics Evaluation and Research

cc: Dockets Management Staff

APPENDIX

Safety Signals Identified in Informative Post-2012 Clinical Studies of HES Products

This Appendix describes safety signals identified in clinical studies of HES products published after 2012, including those referenced in the Petition, that FDA considered informative.[124]

A. Noncardiac Surgery Studies

1. Ahn HJ, Kim JA, Lee AR, et al. The risk of acute kidney injury from fluid restriction and hydroxyethyl starch in thoracic surgery. *Anesth Analg*. 2016 Jan;122(1):186-193. A single-center, three-arm (Voluven, Volulyte,[125] HEXTEND) retrospective study in 1442 thoracic surgery patients found a safety signal for AKI using the AKIN criteria.
2. Green RS, Butler MB, Hicks SD, et al. Effect of hydroxyethyl starch on outcomes in high-risk vascular surgery patients: A retrospective analysis. *J Cardiothorac Vasc Anesth*. 2016 Aug;30(4):967-972. A single-center, three-arm (Voluven, pentastarch, crystalloids) retrospective study in 796 high-risk vascular surgery patients found safety signals for mortality and need for renal replacement therapy (RRT).
3. Kashy BK, Podolyak A, Makarova N, et al. Effect of hydroxyethyl starch on postoperative kidney function in patients having noncardiac surgery. *Anesthesiology*. 2014 Oct;121(4):730-739. A single-center, two-arm (HEXTEND with crystalloids vs. crystalloids) retrospective study with propensity score matching in 29,360 noncardiac surgery patients found a safety signal for AKI.
4. Patel MS, Niemann CU, Sally MB, et al. The impact of hydroxyethyl starch use in deceased organ donors on the development of delayed graft function in kidney transplant recipients: A propensity-adjusted analysis. *Am J Transplant*. 2015 Aug;15(8):2152-2158. A multicenter prospective observational study in 529 kidney transplant donors who received HES found a safety signal for RRT.
5. Rasmussen KC, Johansson PI, Højskov M, et al. Hydroxyethyl starch reduces coagulation competence and increases blood loss during major surgery: Results from a randomized controlled trial. *Ann Surg*. 2014 Feb;259(2):249-254.[126] A single-center, two-arm RCT of 33 cystectomy patients found a coagulopathy safety signal.

B. Cardiac Surgery Studies

1. Bayer O, Schwarzkopf D, Doenst T, et al. Perioperative fluid therapy with tetrastarch and gelatin in cardiac surgery – A prospective sequential analysis. *Crit Care Med*.

[124] FDA found these informative for purposes of responding to the Petition and requiring a safety labeling change for HES products; see section III.A.1 above.
[125] Volulyte® is 6% HES 130/0.4 in an isotonic electrolyte injection, not approved in the U.S.
[126] Rasmussen et al. was not referenced in the Petition.

2013 Nov;41(11):2532-2542. A single-center, three-arm, prospective, observational, sequential study in 6,478 post-cardiac surgery patients found a safety signal for RRT.

2. Lagny MG, Roediger L, Koch JN, et al. Hydroxyethyl starch 130/0.4 and the risk of acute kidney injury after cardiopulmonary bypass: A single-center retrospective study. *J Cardiothorac Vasc Anesth*. 2016 Aug:30(4):869–875. A single-center, two-arm (Volulyte, crystalloid) retrospective study in 606 cardiac surgery patients found safety signals for AKI and coagulopathy.

C. Cardiac and Noncardiac Surgery Studies

1. Wilkes MM and Navickis RJ. Postoperative renal replacement therapy after hydroxyethyl starch infusion: A meta-analysis of randomised trials. *Neth J Crit Care* 2014 Aug;18(4):4-9. A meta-analysis of 15 RCTs (HES vs. crystalloids/non-HES colloids) conducted in cardiac, noncardiac, hepatic and renal transplant patients (N=4409) found a safety signal for RRT.

D. Trauma Studies

1. Allen CJ, Valle EJ, Jouria JM, et al. Differences between blunt and penetrating trauma after resuscitation with hydroxyethyl starch. *J Trauma Acute Care Surg*. 2014 Dec;77(6):859-864. A single-center, two arm (HEXTEND, no HEXTEND) retrospective study (N=1410) of blunt (N=959) and penetrating (N=451) trauma patients found safety signals for mortality and AKI in blunt trauma.

2. Eriksson M, Brattström O, Mårtensson J, et al. Acute kidney injury following severe trauma: Risk factors and long-term outcome. *J Trauma Acute Care Surg*. 2015 Sep;79(3):407-412. A single-center, single arm, retrospective cohort study of blunt (89%) and penetrating (11%) trauma patients admitted to the ICU (N=413) found safety signals for mortality and AKI.