

*The European Medicines Agency (EMA) has advised taking HES off the market.*

*There are numerous questions arising from this decision:*

*First, and most importantly, do you agree?*

*Then: Since 2013, we have already several limitations of HES (in duration, dose and indications), which have been –albeit still questionable– generally accepted. Currently, HES is indicated for surgical and trauma patients with hypovolaemia caused by acute blood loss when crystalloids alone are not considered sufficient. If the “ban” is accepted, (how) can we replace HES in these patients? Gelatins (Less effective), or albumin (money!!!), or can we assume/hope that there is no case where crystalloids are not sufficient? Indeed, don't we need any colloid anymore?*

*The arguments of EMA are another topic to discuss: a) doctors ignore contraindications, b) it is too difficult to distinguish between patients who might profit or be harmed from HES; c) further measures would be ineffective. Do you agree these arguments? The authority banning from utilizing a drug because of ignoring contraindications, is this not a limiting behavior one considers fit for immature? Furthermore: If you start with “doctors ignore contraindications”, can it be possible we can ban any existing drug? (Or where is the breaking point?)*

*HES's scientific history is shameful. Can it be possible, that maybe-just maybe- this fact has affected the recommendation of EMA? (A Turkish quote says (liberally translated): “Do not forsake the church, even if you are angry with the priest”). As a matter of fact, we need to be more suspicious about the studies comparing different types of fluids, no matter if the results are “pro” or “con” the use of HES. How do you comment different studies?*

**Editor**

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## The European Medicines Agency and the Authorization for Hydroxyethyl starch Containing Solutions–Killing the Cow to Get Rid of Ticks?

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After a long lasting review and consultation process, the European Medicines Agency (EMA) is currently considering taking hydroxyethyl starch (HES) containing solutions off the market. In order to the reader be able to understand how this situation was achieved, it is important to get back in the story of HES within the EMA.

Between 2008 and 2012, two seminal studies were published showing increased mortality in patients with sepsis who received HES, as compared to crystalloids containing solutions, for intravascular volume expansion (1, 2). Also, septic patients receiving HES have shown increased need for renal replacement therapy (1-3). These results promptly triggered action by the Coordination Group for Mutual Recognition and Decentralised Procedures–Human (CMDh), a medicines regulatory body representing the European Union (EU) Member States, which on 23 October 2013 endorsed the recommendation of the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) that HES solutions must no longer be used to treat patients with sepsis or burn injuries or critically ill patients. Of note, it has been considered that HES solutions may continue to be used in patients to treat hypovolemia caused by acute hemorrhage, when crystalloid solutions are not considered sufficient. In the same document, the PRAC recommended that “in these patients, HES solutions should not be used for more than 24 hours and patients' kidney function should be monitored after HES administration” (4). Also, the PRAC explicitly stressed that “further studies should be carried out on the use of these medicines in elective surgery and trauma patients”. Based on this recommendation, the pharmaceutical industry decided to conduct two independent, but interlinked trials on the use of HES, namely the so-called PHOENICS (Prospective, randomized, controlled, double-blind, multi-center, multinational study on the safety and efficacy of a 6% Hydroxyethyl starch sOlution versus an Electrolyte solutioN In patients undergoing elective abdominal Surgery) and TETHYS (PragmaTic, prospective, randomized, controlled, double-blind, mulTi-centre, multinational study on the safety and efficacy of 6% Hydroxyethyl starch Solution versus an electrolyte solution in trauma patients). Given the importance of these studies to patients and the Anesthesiology community, the European Society of Anaesthesiology (ESA) took the decision to build an Academic Contract Research Organization (ACRO) and coordinate the conduction of the trials. Effectively, PHOENICS and TETHYS were launched early/mid 2017.

After the release of the first recommendation from the PRAC, two drug utilization studies found that HES solutions were frequently used on an off-label basis, with septic patients receiving the compound. These findings released a discussion that included an EMA ad-hoc expert meeting on December 18<sup>th</sup>, 2017, when it was recommended to the PRAC to not suspend the commercialization of HES. The experts' opinion was based on different studies that were published after the initial recommendation of the PRAC. The first one was a large study conducted in intensive care patients, treatment of acute hypovolemia with colloids was not associated with increased 28 day mortality, and even better 90 day survival, as compared to crystalloids (5). Colloids were able to more effectively stabilize arterial blood pressure and were not associated with increased risk of acute kidney injury. The second one was a meta-analysis of 32 trials and including >16600 patients in total, which showed that colloids did not increase mortality in critically ill, surgery and trauma patients (6). Furthermore, compared to crystalloids, colloids did not increase the risk of acute kidney insufficiency in surgery patients, and even decrease it in trauma patients. Despite this overwhelming body of evidence and the fact that two large multicenter trials were being conducted, as suggested by the EMA, the PRAC recommended on January 12<sup>th</sup>, 2018, the suspension of HES from the European market, which was then approved by the CMDh two weeks thereafter. Since then, the discussion on the suspension of the market authorization has involved the European Commission, the PRAC and the CMDh, also with consultations with experts. Whether HES will be suspended is still unclear, but the steering committees of PHOENICS and TETHYS studies decided re-launching the trials. We fully support this decision.

It is important to highlight that the recommendation of the PRAC early in this year would not have affected the running studies. In a response letter addressed to the ESA, the EMA stated that any decision on the commercialization of HES would not interfere with the studies mentioned above. Despite this, a debate arose regarding ethical aspects of conducting clinical studies on a compound, whose authorization for commercialization was unclear. The conditions where HES was supposed to be tested, namely acute hypovolemia due to blood loss during abdominal surgery or trauma, are exactly the ones that have been recognized as favorable for this colloid. Furthermore, we are the opinion that the potential hazard of a premature withdrawal of the commercialization of HES can impact negatively on outcome of the target population. Alternative drugs, for example gelatins and dextrans, are associated with similar risks in terms of kidney functions (7), and carry others, for example anaphylactic reactions, which we, the authors, could unfortunately testify several times, and tend stay less longer than crystalloids in the circulation (8). The "more physiological" albumin containing solutions have a risk profile that is not fully understood, while

their costs may pose a burden to health systems and lead to their shortage in the middle term. One could even argue that balanced crystalloids might be sufficient, but those compounds are also not free of hazardous effects.

Since HES is prescribed and administered solely by physicians, instead of withdrawing a drug from the market due to inappropriate use, it makes more sense to raise the awareness of the medical personnel to the indications and contraindications of the product. This can be easily achieved by, for example, changes in labeling of the compound, educational material, possible the use of checklists, and by controlled delivery of HES from the hospital pharmacy to the operation and emergency theaters only, which would avoid its inadvertent use in intensive care units. Obviously, re-assessment of utilization must be conducted after those measures have been implemented and adapted as needed. Whatever the final decision from the EMA may be, stopping running trials that may give a definitive answer to the safety of the compound under appropriate indications is unconceivable, while the suspension of the commercialization of HES is also potentially hazardous. The best way for farmers to get rid of ticks is certainly not by killing the cow.

**Disclosures:** Dr. Jakob Wittenstein is local investigator and Dr. Marcelo Gama de Abreu is principal investigator of industry-sponsored studies on hydroxyethyl starch containing solutions at the University Hospital Carl Gustav Carus, Dresden, Germany.

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