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Department of Health and Human Services
Food and Drug Administration

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Revisions to Labeling and Storage Requirements for Blood and Blood Components, Including Source Plasma

The above mentioned document was published for consultation in the Federal Register / Vol. 68, No. 146 on July 30, 2003. In the document changes of storage requirements are proposed, pertaining also to source plasma (plasma for fractionation).

The European Pharmacopoeia (PhEur), a part of the European Department for the Quality of Medicines (EDQM) located in Strasbourg (France), is the competent regulatory authority laying down requirements for plasma for fractionation, which are mandatory in all member states of the Council of Europe, which include all member states of the European Communities and further countries within and beyond the European continent. In order to enable the exchange of plasma for fractionation, intermediates and medicinal products produced thereof, it appears desirable to avoid discrepant regulatory requirements, which might hinder that exchange. To this end, the proposals laid down in the above mentioned document would have an impact on the possibility of importation of source plasma and derivatives into the area covered by the Council of Europe. Therefore, the PhEur takes the opportunity to respectfully submit the following comments worked out by its expert group 6B (chair: Prof. Rainer Seitz, Paul-Ehrlich-Institut), and to suggest that the FDA may considers the requirements laid down in the relevant PhEur monograph on Human Plasma for Fractionation.

1) For source plasma used for injectable products, the FDA proposes a change to the storage temperature from –20°C to –30° or colder.

In this proposal, there is no differentiation between the initial freezing of the plasma following its collection, and the further storage of the frozen plasma. There are, however, experimental data showing that particularly the process of initial freezing is crucial for the quality of the plasma. Such early studies (Smith et al., 1977; Farrugia & Prowse, 1985), assessing the preservation of labile proteins such as coagulation factor VIII (FVIII) show that the freezing conditions should be such that at a low

surrounding temperature (e.g. in those experiments –40°C) freezing to the core of the plasma container is reached as rapidly as possible. The study of Åkerblom et al., 1992, found a highly significant difference of FVIII activity comparing slow freezing at -20°C with rapid freezing within 40 minutes at -40°C.
This suggests that the freezing should proceed in a short time at temperatures well below –20°C. Such freezing conditions were shown to increase the yield of labile products as FVIII, but can be considered as favourable for the plasma quality in general. Though it is hard to show experimentally, it can be anticipated that the decrease of e.g. FVIII activity could be associated with the generation of break-down products, which might not only be inactive impurities, but potentially detrimental. The situation appears to be different, if only certain fractions of the plasma are used for manufacture of non-labile proteins such as albumin or immunoglobulins.

It is therefore suggested that the FDA may consider the requirements laid down in the relevant PhEur monograph:

"When obtained by plasmapheresis, plasma intended for the recovery of proteins that are labile in plasma is frozen by cooling rapidly in a chamber at -30 °C or below as soon as possible and at the latest within 24 h of collection.
When obtained by plasmapheresis, plasma intended solely for the recovery of proteins that are not labile in plasma is frozen by cooling rapidly in a chamber at -20 °C or below as soon as possible and at the latest within 24 h of collection.
When obtained from whole blood, plasma intended for the recovery of proteins that are labile in plasma is separated from cellular elements and is frozen by cooling rapidly in a chamber at -30 °C or below as soon as possible and at the latest within 24 h of collection.
When obtained from whole blood, plasma intended solely for the recovery of proteins that are not labile in plasma is separated from cellular elements and frozen in a chamber at -20 °C or below as soon as possible and at the latest within 72 h of collection."

2) For source plasma used for injectable products, the FDA proposes a change to the shipping temperature from –5°C to –15° or colder.

The above mentioned studies, and a more recent report by Kotitschke et al., 1999, show that the temperature limit for further storage can be set at –20°C without significant decrease of coagulation factor activities, provided the initial freezing was performed rapidly at low temperatures, as outlined above.
In principle, the plasma should be kept at a suitably low temperature all the time between initial rapid freezing and start of manufacture. Therefore, the PhEur monograph does not prescribe different temperature limits for storage and transport.

The available experience suggests that a slightly warmer temperature for a relatively short period of time, e.g. during defrosting of freezers, is not critical. Therefore, a temperature of –15°C or colder appears to be acceptable for shipment completed within a confined period of time. However, transport of plasma in ships across oceans may take considerable time, during which technical problems with the cooling equipment might occur. It appears therefore to be a reasonable approach to require

in principle a temperature limit in line with the normal storage conditions, but to foresee on the other hand, criteria of acceptance of deviations.

It is therefore suggested that the FDA considers the requirements laid down in the relevant PhEur monograph:

"STORAGE AND TRANSPORT
Frozen plasma is stored and transported in conditions designed to maintain the temperature at or below -20 °C; for accidental reasons, the storage temperature may rise above -20 °C on one or more occasions during storage and transport but the plasma is nevertheless considered suitable for fractionation if the following conditions are fulfilled:
— the total period of time during which the temperature exceeds -20 °C does not exceed 72 h;
— the temperature does not exceed -15 °C on more than one occasion;
— the temperature at no time exceeds -5 °C."

The PhEur appreciates the opportunity to comment. The PhEur secretariat will be happy to respond to any questions the FDA might have concerning the above comments.

References:

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