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Internal Memorandum

Date: 11-24-09

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APPROVED
By Jaro Vostal at 4:51 pm, Nov 24, 2009

To: Salim Haddad, MD
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Subject NDA 080041, Evaluation of extractables from plastics used in PAS III storage containers,

Background

InterSol Platelet Additive solution, also referred to as Platelet Additive Solution III (PAS III) is a buffered solution that was developed by Fenwal to support storage of S59 pathogen reduced platelets (S59 PRP). S59 psoralen is a chemical additive of a pathogen reduction process developed by Cerus Corporation with support from Fenwal (then Baxter). The S59 pathogen reduced platelets were evaluated in a US Phase III clinical trial in the year 2001 (SPRINT trial). The pathogen reduction process includes re-suspension of platelets collected by apheresis on an AMICUS instrument in a ratio of 35% plasma and 65% PASIII, addition of the S59 to the platelets, illuminating the mixture with UV A light, incubating the illuminated mixture with an absorption device to remove un-reacted S59 and storage of the cells in the plasma additive solution mixture for up to 5 days at room temperature. PASIII alone was evaluated as a part of the pre-clinical evaluation of S59PRP in several animal studies where it served as the control vehicle. Fenwal is proposing using PASIII as a stand alone additive solution for the storage of platelets without pathogen reduction processing.

Plastic component formulation of containers

Plastics used in storage and administration of PASIII are PL 2411, b(4) and b(4). These plastics are manufactured by b(4) and manufacturing information has been submitted under b(4)

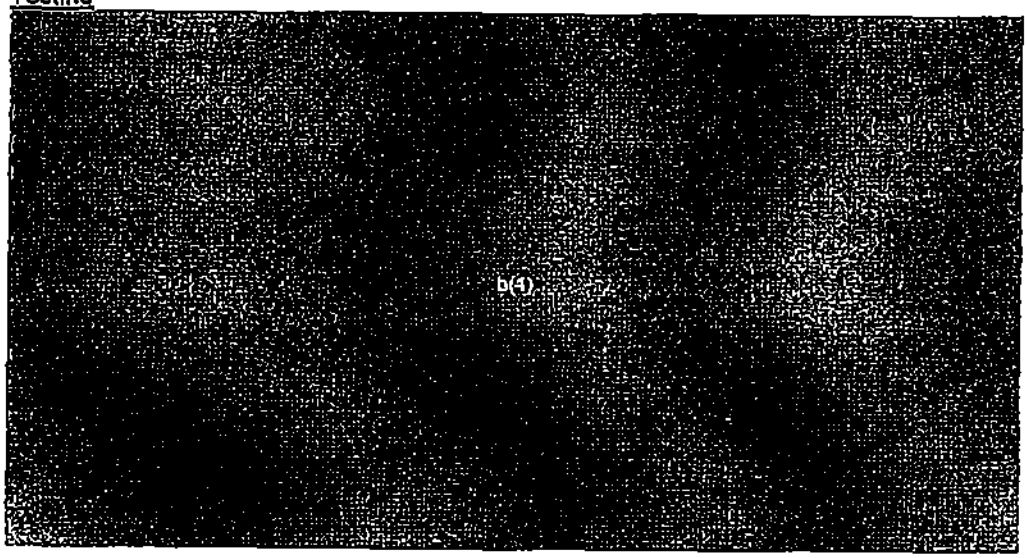
PL 2411 is a an alloy blend b(4) plastic sheeting (does not contain PVC or b(4)(6)). It is the main body of the container and potentially the largest source of extractables.

b(4) is the plastic used in the port tube. The surface that would come into contact with PAS III is covered with b(4)

b(4)

b(4) is the twist off protector plastic. It is a b(4) plastic with b(4) as plasticizer and has been previously approved under NDA b(4)

Testing



Safety assessment of the materials and extractables

Calculated safety margins were acceptable for human use. For b(4) and b(4) the NOAEL levels were based on oral dosing. The estimate of b(4) human exposure from PASIII solution was 0.0002 mg/kg. The WHO maximum intake oral limit is b(4) This is an estimate for oral dosing and may not apply to IV dosing.

Letter ready comments to the sponsor:

The toxicological evaluation of leachables from PL 2411 plastic platelet additive storage bag should be based on animal studies that defined a toxic dose of an IV administered compound and on the anticipated clinical application of the device. The WHO allowable daily intake for b(4) applies to oral dosing and is not appropriate for IV application. Please calculate the safety margin for b(4) based on toxicity reports (LD50) of an IV administered benzoic acid. The calculation should be based on leachables from a 500 ml bag stored with platelets for up to 5 days and a 70 kg patient.

Please perform the same calculation for b(4) and b(4) using an IV toxic dose (LD50) derived in animal experiments.

Please identify the source of b(4) and b(4) Could the ink or the adhesive of the label be a source of these compounds?

Have the ink and the adhesive been FDA-approved for use on other bags?

What is the measured level of b(4) in a platelet products stored up to 5 days at room temperature?