Part II C:2.2 Monoclonal Antibody Column		For National Authority Use Only (Comments)
Objection 47	Further information is required to show that the risk of adventitious viral contamination from materials of biological origin used in cell culture has been minimised e.g. screening/selection of source materials and information on validation of viral inactivation processes. Bovine products should not be sourced from herds where ruminant proteins have been fed unless adequately justified. An assurance is required that the origin of batches of bovine materials is clearly documented.	
Response	Data on the screening/selection/treatment of source materials of biological origin used in the culture of Master Working Cell Banks 8608/8860 are presented as Attachment 47-1, Tables 1-6. As can be seen, these biological materials were sourced from USA, Australia, New Zealand and Canada. As stated in the original application, all of these countries are considered to be BSE free. The United States Department of Agriculture (USDA) maintains that there have been no reported cases of BSE in the United States, therefore, feed practices need not be legislated. It should be noted that it is accepted practice per USDA to allow ruminant protein in cattle feed. Therefore, a small percentage, less than 0.6% of the total food product, may consist of ruminant feed. The origin of batches of bovine materials that are collected from USDA certified (or equivalent) collection centers have a qualified, veterinary surgeon inspector always present. It should also be noted that Fetal Bovine Serum (FBS), as of December 1992, has been sourced exclusively from Australia. The Company has conducted audits to ensure traceability of all bovine-sourced constituents back to the geographical location of the source herd. Source material from European herds will not be used. Documentation of traceability is maintained on file at Baxter, Hyland. The origin of donors of human plasma can be determined because plasma is collected in accordance with FDA CFR requirements. Plasma is tested in accordance with current FDA specifications (i.e. for HBsAg; anti-HIV-1/2; anti-HCV). Specific validations on the efficacy of heat-treatments were not available from all suppliers, although it should be noted that heat-treatments (e.g. 10 hours at 60°C for albumin) are consistent with well accepted industry standards. Testing of each of the biological materials is as indicated on each table included in Attachment 47-1. (continued)	

Part II C:2.2 Monoclonal Antibody Column		For National Authority Use Only (Comments)
Objection 47 continued	The EC Guidance III/3298/91-EN, BSE, indicates risk categories which can be applied to the constituents of the MF-15 medium. These risk categories are stated in the tables found in Attachment 47-1. There is no definitive evidence regarding the transmission of spongiform encephalopathies inter-species, (i.e., human ⟷animal) through the human blood route and no evidence of transmission of BSE from bovine sources to humans by any route. A recent report (Esmond, et al., The Lancet, January 23, 1993) cited laboratory and epidemiological evidence that the risk factor of Creutzfeldt-Jakob disease (CJD) via the blood route is of little or no significance. This publication, found in Attachment 47-2, cites the infusion of 300 ml whole blood from a CJD patient into a chimpanzee, resulting in the animal having remained CJD-free for 8 years. Also, the incidence of CJD in patients having received whole blood transfusions was statistically equivalent to the incidence in the non-recipient population. It is also interesting that this report cites multiple blood donors (1 person donated blood up to 50 times) who later developed CJD. In the 9 to 23 years subsequent to these donations there has been no evidence of increased incidence of CJD in localities where these CJD-infected multiple donors resided at the time of donation. Summarizing the currently available information: 1. The biological constituents used by Hyland in MF-15 are of very low categorical risk with regard to BSE. 2. It is most likely that goat and cattle spongiforms are not transferrable to humans. 3. It is most likely that prion-related diseases are not transmitted by blood or plasma-derived products. 4. The materials used are at a very low concentration level in the mAb purification process and occur at a point in production which is significantly separated from the finished product. In view of the above, the Company believes that, while compliance to existing control measures is essential, there is not a need to achieve full compliance with the BSE Note for Guidance.	

Comment 47.

Bovine materials used in the manufacture of the MoAb are sourced from Australia, New Zealand **USA and Canada**. It is stated that BSE has not been reported in these countries. However 0.6% **ruminant** feed can be added to the diet in the USA. It may added in Canada as well. There is no ban on the use of ruminant feed in the USA. Since it is believed the it was ruminant feed which spread BSE, this practice is not acceptable. Material should be sourced from animals certified as not fed ruminant feed.

The view put forward that there is no evidence of BSE transmission to humans is not convincing, since it is too short a time from exposure to possible manifestation in humans for any view to be taken about transmissibility. The experience with the use of pituitary derived materials and duramater , which lead to CJD transmission, suggests a period of upto 15 years incubation is possible.

Experimentally blood cell fractions have been shown to transmit CJD, but it has not been recorded clinically. Even if transmission of encephalopathies across species barriers are at very low levels, the rise of BSE suggests it could be possible, ie sheep to cattle.

Baxter state that it is most unlikely that prion related disease is transmitted by blood or plasma derived products. In part that depends on their exposure to reagents which might be BSE or prion bearing. The best approach would be to avoid the causative agent's presence by ensuring that animal sourced reagents are derived from animals not fed ruminant feed.

Foetal calf serum is now sourced from Australia **acceptable**

The bovine insulin is sourced from Australia were ruminant feed is not used. **acceptable**

Human HL-1 components - tranferrin is obtained from suitably screened donors, pasteurised at 60^0C x10 hrs after triple 0.1µ filtration. No statement is made about the absence of stabilisers during the pasteurisation stage. No virus removal validation data are available, but some are quoted for bovine transferrin. The same data are quoted for both this source of transferrin and "transferrin [holo]" from the USA or Canada

Confirmation is required that the "HL-1 components" transferrin [Vendor - Ventrex] are pasteurised in the absence of stabilisers.

Bovine serum albumin [Canadian source] is pasteurised at 60^0 C x10 hr in the absence of stabilisers. No specific viral inactivation data are available. The issue of BSE removal is not covered.

An assurance is required that the "serum albumin (pancreatic?)", is sourced from cattle not fed ruminant feed. The fractionation process should be given as a fully annotated flow diagram. Details of any filtration stages should be given.

The Excyte 1 -serum lipoprotein is pasteurised as for the other components above. It is not clear whether the material is tissue or plasma derived, which might make a difference to the potential for BSE transmission.

An assurance is required that the Excyte 1 - serum lipoprotein is obtained from cattle not fed ruminant feed. The fractionation process should be given as a fully annotated flow diagram. Details of any filtration stages should be given. Confirmation is required that the source material is serum and not tissue derived.

Table 4

Materials of Biological Origin Used In Cell Culture

Constituent (of MF-15)	Source			Special Treatment Prior To Use in MF-15	EEC BSE Risk
	Species	Country	Vendor		
Serum Albumin (pancreatic)	Bovine	Canada	Waitaki	60°C for 10 hours (no stabilizing agents present)	IV

Comments

Tested by manufacturer according to 9 CFR 113.53 (Negative for BVD; IBR; PI3)

Manufactured from source plasma by cold ethanol fractionation, a process very similar to that used commercially to manufacture human albumin. Heat treatment of albumin solutions for 60°C for 10 hours is recognised to be virucidal - manufacturer has no specific viral validation data.

Refer to Certificate of Analysis, in Attachment 49-1.

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objection 47

Table 5

Materials of Biological Origin Used in Cell Culture

Constituent (of MF-15)	Source			Special Treatment Prior To Use in MF-15	EEC BSE Risk
	Species	Country	Vendor		
Excyte I -serum lipo-protein	Bovine	USA	Miles/Pentex	60°C for 10 hours (no stabilizing agents present)	IV

Comments

Cattle tested by manufacturer according to 9 CFR 113.53 (Negative for BVD; IBR; PI3).

The manufacturer has validated the heat-treatment process using five viruses in a transferrin product. Refer to Table 3.

Refer to Certificate of Analysis, in Attachment 49-1.

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Objection 4