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nvCJD and Biological Products
Managing the Risks

For manufacturers of biological medicinal products, the latter half of the twentieth century has epitomized the ancient Chinese curse "may you live in interesting times." On one hand we have benefited from the unprecedented scientific and engineering advances, which have permitted substantive improvements in the purity and efficacy of existing products, and the development of a range of new therapeutics. On the other, we have encountered significant and unanticipated adverse events associated with the use of these therapeutics. Of these adverse events, the exposure of patients to new and newly emerging pathogens has been the most problematic. To survive in the current environment of newly emerging pathogens, biopharmaceutical companies have had to develop a comprehensive strategy of risk management, to provide effective guidance in the development, manufacturing and marketing of these biological products.

The approach to risk management utilized by Baxter is comprised of four key elements: risk evaluation, exclusion, elimination and education. The application of this strategy will be illustrated with regards to some of our blood products and the new variant Creutzfeld Jakob disease (nvCJD). Creutzfeld Jakob disease is the most common human transmissible spongiform encephalopathie (TSE). Given its relatively uniform and ubiquitous distribution within diverse human subpopulations, the causative agent for this disease is likely to be an ancient pathogen. Although many aspects of the etiology of this disease still remain obscure, it is clearly transmissible by exposure to contaminated biological materials. Iatrogenic transmission by human sourced medicinal products such as pituitary derived growth hormone and dura mater was an unanticipated risk associated with the use of these materials. Unlike CJD, nvCJD is clearly a new pathogen. At present its geographic distribution is limited to Europe, primarily the U.K. While transmissible to humans the more common host for nvCJD appears to be cattle in which it is responsible for bovine spongiform encephalopathy (BSE). Human to human transmission of this agent has yet to be observed.

Given the potential for the transmission of TSE through infected biological materials, our first step in risk management was to evaluate the potential for transmission by blood products. While a theoretical possibility of iatrogenic transmission of CJD by blood or blood products exists, epidemiological data indicate that the actual potential for transmission is zero or very remote. While this observation is comforting, there remains a possibility that the agent responsible for nvCJD would have different biological characteristics which could permit blood products to be a vector for transmission. To explore this possibility we have initiated studies in non-human primates, squirrel monkeys and mice. In these studies, the infectivity of cellular components and plasma derived from individuals infected with nvCJD is examined.

Whatever the results of these studies, it will be important to erect barriers to the entry of the nvCJD into our production processes. As bovine derived materials represent the most likely potential source of infection we have put in place a risk reduction program which is comprised of the following: 1) Essential bovine derived materials to be sourced from animals from BSE-free countries, 2) Replacing some bovine materials with similar materials of non-bovine origin, and, 3) Elimination of non-essential bovine materials.

For essential bovine materials presently required in the manufacture of our products, we have undertaken extensive validation studies to examine both the potential for removal of TSE agents during the production of the bovine derivatives and TSE elimination during the manufacture of the therapeutic material . Examples of representative clearance factors are tabulated below:

Material	TSE Clearance* During Manufacture
BSA	16.2
Aprotinin	17.3
Recombinant Factor VIII	8.6
Plasma Derived Factor VIII	8†

* Log_{10} ID50

† Study in progress

As observed in the above table, there is extensive clearance of the experimental TSE agent in both the manufacture of the bovine derivatives and the production of products. The aggregate clearance factors of >24 logs provide and excellent assurance of safety.

Another risk exclusion/elimination strategy revolves around the use of leukodepletion in the preparation of blood products. At present, the role leukocytes play in the pathology of nvCJD is the subject of intense investigation. Whatever the eventual conclusion of these studies, it is clear that for plasma and plasma products, leukocyte contamination is detrimental. For this reason, Baxter has committed to moving to the use of leuko-depleted source plasma as the primary type of plasma for fractionation.

In conclusion, I would like to comment on the aspect of education with respect to risk. Blood and blood products appropriately prescribed provide excellent benefit to risk ratios. It is very important that the value of these therapeutics and the relative rarity of adverse consequences be thoughtfully presented so that physicians and patients can make appropriate decisions.