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Dr C V Prowse
Director of the SNBTS National Science Laboratory
Edinburgh & South East Scotland
Blood Transfusion Service
Royal Infirmary
Lauriston Place
EDINBURGH

Dear Chris

PROCESS OPTIONS FOR HIGH PURITY FVIII

Many thanks for the draft copy of the report(s) that you are preparing with John on this topic. There are a number of specific and general comments that I can make which may be helpful to you.

I will list the specific points first as these do not affect your overall conclusions which are very much in keeping with our previous conclusions on this subject. My general points will deal with our different perceptions concerning product development and the development of NSL itself as a scientific force in Transfusion Medicine.

1. **SPECIFIC COMMENTS** (Report by J D Cash and C V Prowse)

   1.1 **Page 2 Paragraphs 1 (c) and 1 (d)**

   You make it clear in these paragraphs that your selection process will ignore the issues of inhibitor formation and the presence of mouse protein.
While clinicians are in a position to change their prescribing habits with virtually every issue of the Lancet we do not have that luxury. We are involved in longer term planning and must make judgments that will stand the test of time. It is for this reason that I prefer, if at all possible, to avoid the use of reagents which could represent a future hazard to the patient (eg. toxic chemicals, mouse protein). The same logic applies to inhibitors and activation both of which may be emerging as major quality issues.

Page 3

You define "two key areas" which affect the interpretation of process yield but you have chosen not to mention here the problems of assay discrepancies and product activation. By not including this point here the yield comparisons which follow (page 6) may be inconsistent.

My view is similar to that in 1.1 above; we have to make a judgment that will stand the test of time as to whether we want a non-activated product or an activated product. We should then interpret everything on that common basis.

Page 5 (Solubility)

The observations from Dr Savidge concerning the solubility of the Lille product are quite different from the solubility problems experienced with Z8 and it may be incorrect to say that it is "still much better than Z8".

From Dr Savidge's description the Lille product goes fully into solution but some protein then comes out of solution again. This is almost certainly due to the lack of a defined formulation step at Lille and as such represents a flaw in their process design (it may also say something about their actual product purity).

By contrast poorly soluble Z8 is difficult to get "into" solution but once in solution it is a stable product. The problem with Z8 was caused by not following the correct manufacturing procedure and was not due to any intrinsic flaw in the process design. This is now appreciated and a soluble product is now being manufactured (solubility time will of course be reduced further with a correctly formulated high purity product).
1.4 Page 5 (Viral Risk)

The "extensive pedigree" that you ascribe to the Armour product is based on terminally heated Monoclate. The safety of products prepared without terminal V.I depends substantially on procedural controls. The success or failure of these controls will be determined by the quality of each manufacturers operation and cannot be covered by generalised statements except to say that transmission of HCV and HIV is inevitable by processes of this type. The question is not if they will transmit virus, but when? It could well be happening already, but passing undetected because of limited patient monitoring.

1.5 Page 6 (Yield)

The yield figures have been obtained in a different manner for different products. These inconsistencies could result in misleading projections (page 7).

For example the Z8 yield is a precise figure calculated from 62 consecutive production lots, covering good days and bad, FA plasma and FB plasma. By contrast yields for Lille have been estimated from only 1 lot taking selected UK assay values. The basis for the Baxter and Armour figures is not known (ie. how many consecutive batches) and it should be appreciated that manufacturers sometimes provide "good" data in circumstances like this.

The yield figures for Baxter do not take into account the 40% mark-up from activation (see 1.2 above) and I would not regard this as "modest" (page 8).

1.6 Page 10 (Delivery)

You state earlier in the paper that our poor performance concerning Z8 and S8 was "complex and multifactorial" (page 4), yet here you imply that these problems will be resolved by "management changes in the context of PFC product development".

I have to disagree. The management changes that I think you are referring to do not address any of the issues required to improve the overall PFC performance.
There are fundamental issues which relate to operational constraints (e.g., hours of work) and to the control and supervision of manufacturing operations. While the first of these is being addressed (the consequences of progress here could be quite profound), I see little or no prospect of improvement elsewhere. In these circumstances the only way of "significantly and favourably affecting our future performance" will be to allow R&D staff a stronger role in the overall design, specification and implementation processes. In the past it has been PFC policy for R&D to withdraw sooner rather than later, leaving manufacturing staff to tidy up any loose ends. In retrospect this has been self-defeating and has been the root cause of many of the problems experienced with Z8 which then followed through to S8.

Page 11 (Timescale)

The timescale shown here is that estimated from the Permaste Plan. That plan is based on the use of PFC technology integrated with the solvent/detergent and ion exchange steps of Lille.

We have considerable experience of ion-exchange at PFC both in the routine manufacture of Factor IX (since 1970) and in development studies for high purity Factor VIII (since 1984). Hence there is considerable experience and expertise within the Centre concerning ion exchange. This is not the case with the alternative methods that you are considering as we have no experience of either gel filtration or immunopurification at a process scale. Consequently I would not assume that "the overall timescale will not be significantly different for other options".

SPECIFIC COMMENTS (Report by C V Prowse)

Page 4 (Quality)

In the absence of data to the contrary surely it is just as valid to argue that "purer is worse" as it is to argue "purer is better". I'm sure an immunologist could construct that argument quite easily.
1.9 Page 6 (big table on Process Yields)

Again there may be some inconsistencies here. The Lille plasma figure (0.68 iu/ml) seems to be from their sample taken at entry to fractionation while your SNBTS figure (0.78 iu/ml) is from low level sampling carried out at RTC’s during 1986 (PFC’s equivalent figure was 13% less).

These differences could be significant for recovered plasma in contrast to source plasma where the choice of the sampling points should not matter.

Similarly the PFC recovery into cryo extract is based on a large number of consecutive batches, including FB as well as FA plasma. Figures for other manufacturers are based either on a single batch (Lille) or on casual information (see 1.8 above).

1.10 Page 7, Table 3

Surely it would be more correct to list the specific activity seen by the patient, leaving the pre-formulation value in parenthesis. Perhaps it should also be noted that these are values quoted by the manufacturers and they have not been verified by any control authority.

2. GENERAL COMMENTS

My general comments stem initially from the problem that I have in equating a product with a process. We seem to have reached a point where the two terms are being used almost interchangeably with no clear distinction being made between them and with processes being used to market products and vice-versa.

I find this trend profoundly disturbing for two reasons. First the two terms are not interchangeable. It is quite possible to prepare products with the same characteristics using different processing technologies. It is also possible to prepare products with quite different characteristics using the same process technology. Hence the notion that there is some simple relationship between a process method and the product characteristics is a serious misconception. Of course there is a relationship, but it is a complex relationship rather than a simple one.
As we explore this further, another key issue emerges and leads to the second reasons for my concern. Before we can examine the relationship between a product and a process we have to consider how a product is defined and how a process is defined.

The Product

In modern medicine, pharmaceutical products are defined according to their clinical and chemical or biochemical pharmacology. This is the basis on which prescribing physicians are trained and also provides the fundamental basis for the statutory regulation of drug substances. The only statutory qualification (i.e. the "Qualified Person") required for pharmaceutical manufacture is a professional qualification covering subjects such as Pharmacology and Toxicology (this is awarded in the UK by the Institute of Biology and the Royal Institute of Chemistry). Membership of bodies such as the CSM is based on similar disciplines both in the UK and overseas.

The Process

Plasma Fractionation is a Process Industry and the discipline that underpins the design and operation of its processes is Chemical Engineering. Biochemical Engineering is formed from a synthesis of Process Biochemistry, Industrial Microbiology and Chemical Engineering. As Biochemical Engineering is a relatively young discipline it is still often necessary to employ people from each of the formative disciplines to fully cover the ground in the biochemical process sector.

In most critical areas of human activity (e.g. Medicine, Law, Architecture, Civil Engineering) professional qualifications are a statutory requirement. Although Biochemical Engineers can achieve professional status (i.e. Chartered Engineer) there are no statutory requirements in this country concerning the use of professional staff in the design and operation of industrial chemical or biochemical processes, including Plasma Fractionation. That this should be the case in the manufacture of pharmaceutical drugs seems surprising. Of course the safety of this approach in pharmaceutical manufacturing depends almost entirely on the "Qualified Person" (above) being able to filter out any potential problems. For this approach to work all aspects of a product's safety and efficacy must be encompassed in its pharmacological specification as it is only in this area that the "Qualified Person" is actually professionally qualified by definition.
Where the safety and efficacy of a product are expressed in terms of the process design then virtually all regulatory and statutory controls disappear. A process can be designed and operated by any Tom, Dick or Harry. The "Qualified Person" and the Regulatory Authorities will not be qualified to judge Process Engineering or Biochemical Engineering issues, leaving prescribing Physicians in the unenviable position of having to take decisions and make judgements in areas in which they are neither academically trained nor professionally qualified.

This is the situation in which to some extent we now find ourselves, partly as a consequence of some of the commercial companies attempting to market new products in terms of a "glamorous" process technology rather than by the defined characteristics of a product.

How can we resolve the situation? I believe there are two options:

(a) Regulate the design and operation of manufacturing processes by making the use of appropriate professionally qualified staff obligatory and by incorporating wider disciplines into Regulatory bodies (despite the fact that we are a Process Industry there is little or no professional Process Engineering representation in the regulatory framework).

(b) Develop product specifications to a point where clinicians can take decisions on the basis of defined product characteristics (as is the case in virtually every other branch of medicine) without recourse to details of manufacturing technology.

The first of these options would be welcome but is one over which we have little or no control (it may evolve through European harmonisation). However the second option is one which we can pursue and to my mind this represents the challenge of the '90's for Transfusion Medicine and Transfusion Science.

You will remember in previous discussions concerning Product Development and the role of NSL, both Ron and I have gone on at great length about the importance of developing comprehensive product specifications. We regarded this as necessary for the provision of safe and effective products and also to enable cost-effective processes to be designed in a manner whereby quality could be correctly monitored and controlled. In this letter I have indicated why this is also important if the industry is to manufacture products in a safe and fully professional manner.
I believe that with the emerging NSL and the close clinical community which we enjoy, the SNBTS has a genuine opportunity to lead the world in this area. The first step is to recognise its importance.

I apologise for such a lengthy letter, but I hope you will find my specific points helpful and I'm sure we will return to the subject of my general comments again.

Best wishes.

Yours sincerely

PETER R FOSTER

CC. R J Perry
     J D Cash