Self-Sufficiency

48
30

John Cash

SNBTS : Product Development

From: "PETER FOSTER" <peterrfoster GRO-C
To: "John Cash" <cash3436 GRO-C
Sent: 01 July 2009 09:43
Attach: Introduction of Factor VIII Concentrates free from Transmission of Hepatitis C.docx
Subject: Re: Self Sufficeincy

John
Here is the table I mentioned re. the introduction of hep C safe FVIII by different manufacturers. This was actually in a presentation that I gave to the haemophilia soc in Nov 1999. The only date to update is the introduction of an '8Y' equivalent by CSL; this should be 1990 rather than 1989 (1990 is the date given in the hep C Investigation by the Australian Senate).
Peter

--- On **Sun, 28/6/09, PETER FOSTER <*peterrfoster* GRO-C wrote:

From: PETER FOSTER <peterrfoster GRO-C
Subject: Re: Self Sufficeincy
To: "John Cash" <cash3436 GRO-C
Date: Sunday, 28 June, 2009, 1:13 PM

John
I will e-mail the table in a couple of days - I am not at home at the moment and don't have the file with me. The different types of virus inactivation developed in the US and the dates of licensing in the US are all in a 1994 paper by Carol Kasper in Transfusion. The dates on which the products actually entered into general use are more difficult to ascertain, but I do have dates on which the first heat treated commercial products were licensed in UK - from Feb 1985.
Another aspect is how much was available - for example Beringwerke's pasteurised FVIII was 'available' from about 1980 - but the company continued to supply most of its FVIII unheated until 1985, because the yield of their pasteurised product was too low at first to make this their standard product.
The comercial companies all had various 'virus inactivated' products licensed in the US during 1983/84 but they were not taken up because they did not inactivate NANBH (and because of worries over inhibitors). It was not until late-1984 that the first data on inactivation of HIV became available and there was a step change to heat treated products. Because of our decision to heat our existing product - instead of waiting until we had made fresh (re-formulated FVIII) we led the way - the commercial companies did not do this - they had to make new batches and build up stock to meet demand - that's why unheated FVIII continued to be used in UK (England) well into 1985
Peter

--- On **Sun, 28/6/09, John Cash <*cash3436* GRO-C wrote:

From: John Cash <cash3436 GRO-C
Subject: Re: Self Sufficeincy
To: "PETER FOSTER" <peterrfoster GRO-C
Date: Sunday, 28 June, 2009, 9:13 AM

Peter
Thanks.
Could I have a look at the table you prepared for the Scottish Executive Investigation of 2000?
Is there any way we can provide comparative evidence that we had virus safe

Introduction of Factor VIII Concentrates free from Transmission of Hepatitis C.

YEAR	MANUFACTURER	VIRUS INACTIVATION METHOD	COMMENT	SAFETY STUDY*
1979	Behringwerke (Germany)	Pasteurisation	Very limited availability	1987
1985	BPL (England)	Advanced Dry Heat	Limited availability	1988
1985	NYBC (USA)	Solvent detergent	Not available in UK	1988
1986	Cutter (USA)	Pasteurisation	Not available in UK	-
1987	SNBTS (Scotland)	Advanced Dry Heat	Generally available in Scotland and N. Ireland	1993
1988	Baxter (USA)	Solvent-detergent	FDA approval, ? UK date	1992
1989	CSL (Australia)	Advanced Dry Heat	Australian 8Y	-
1989	Alpha (USA)	Solvent-detergent	FDA approval, ? UK date	1994
1989	Cutter (USA)	Solvent-detergent	FDA approval, ? UK date	-
1989	Armour (USA)	Pasteurisation	Generally available	1993

* Publication of study on low risk of NANB/HCV

concentrates at much the same time (before) the best of the commercials boys?
Thanks
John

----- Original Message -----
From: PETER FOSTER
To: John Cash
Sent: Saturday, June 27, 2009 6:56 PM
Subject: Re: Self Sufficeincy

John
Not quite sure what you are seeking in the way of a table - I can list SNBTS products and their dates of introduction, but I do not have UK-release dates for the commercial products. USA approval dates have been published for commercial products manufactured in the US. This would have almost certainly pre-dated UK-release.I did prepare a comparative table like this re. hep C safe FVIII for the Scottish Exec Investigation in 2000.

So far Penrose has only asked SNBTS for an account of the documentation it holds (from 1974) and for details of its administrative arrangements since 1970. I think the same requests have been made to the Scottish Health Dept. Beyond that I have no idea what SHD are planning for Lord P as they are keeping SNBTS very much at arms length.

I am not sure "what took us to Lille". You and David Mac paid them a visit - this may have been prompted by Theirry submiting a manuscript to Vox. Following your visit Chris, Duncan, Ron and I made the journey. The Lille process was chosen because it was easier (quicker) to implement and much less expensive than monoclonal purification (which BPL opted for and had to make a £3M downpayment) and as far as ion exchange is concerned was ahead of Johnson in that routine production was undweray and clinical data were available - although there were a number of manufacturing disadvantages cf. Johnson, our practice of doing our utmost to satisfy the demands of Scottish clinician's ASAP meant that Lille was chosen over Johnson.
Peter

--- On **Sat, 27/6/09, John Cash <*cash3436*** GRO-C > wrote:

From: John Cash <cash3436 GRO-C >
Subject: Re: Self Sufficeincy
To: "PETER FOSTER" <peterrfoster GRO-C >
Date: Saturday, 27 June, 2009, 12:08 PM

Peter

Thanks again!

I'm sure you will have guessed that at the moment I'm trying to develop a riposte to the stated policy position in the DOH's publication on self-sufficiency in E/W (1973-1991) in which it is claimed that reliance on a single supplier of coagulation concentrates (BPL) would 'stifle new developments (many of which came from the commercial sector) and thereby expose England and Wales to the possibility of inadequate **volumes** of product for effective treatment'.

Against that official policy background I suggest there is good reason to make it clear to Lord Penrose (if we believe it is true) that in Scotland research at PFC was not stifled and indeed, when compared to that of huge commercial concerns, was competitively highly productive. I happen to believe this is a fact but would like to see it presented more clearly and succinctly. Can you have a shot? I had wondered whether you could give a succinct summary in table form - with key activities down the left and (say) timing of consequential market release along the top.

It is a fact that in the period under consideration SHHD was subservient to DHHS. Have you any idea whether the current DOH (Scotland) intends to produce it own statement for Lord Penrose on self-sufficiency?

One last question. Can you remind me what took us to Lille? In retrospect do you think this was a good idea?

John

----- Original Message -----
From: PETER FOSTER
To: John Cash
Sent: Thursday, June 25, 2009 5:49 PM
Subject: Re: Self Sufficeincy

John
It might be helpful if I try to summarise events through out the period in question.
You will remember that during the 1970s we were investigating removal of the hepatitis virus(es) by precipitation (FIX - Johnson's method) and that we began research on heat treatment of FVIII and FIX by pasteurisation in 1981. Pilot batches of our pasteurised FVIII product (ZHT) were available in late-1983 for inital examination of efficacy and tolerability. Two patients in Glasgow tolerated the product well but one in Edinburgh did not. Christopher advised (Jan 1984) that the reaction was unacceptable (his patient went on to react to other products). Our strategy to resolve this was to increase purity, working in collaboration with Johnson (a collaboration that we had begun to set-up in 1983 but because of confidentiality could not begin practical work on until mid-1984).
In parallel with this (late-1984) we heated our existing product (NY) as much as it would tolerate (ie 68 degrees/2hr) as soon as there was any evidence that this might be effective against HIV (a level of dry heating that was already known to be ineffective against NANBH) . Sufficent 68 degree NY for all patients was distributed throughout Scotland on 10th Dec 1984 - making Scotland, as far as I can establish, the first country to provide heated FVIII (HIV-safe) for all patients. The time of heating was increased to 24 hours by our discovery to a change in the formulation of NY and we began to make this change in manufacture in Jan 1985. At the same time all of our unheated FVIII was recalled and this plus all of our stocks was heated at 68/2hrs. Because we had almost 12 month stock (good evidence that we had achieved self-sufficiency) we effectively back-dated heating to donations that had been collected from Oct 1983.
During 1985 our main efforts were directed towards developing high purity as this was consistent with either (a) an improved pasteurised

product ie. improved ZHT (b) an s/d-treated product (which NYBC were just developing) (c) 80 degree dry heat (which BPL introduced routinely during Sept 1985 (in the belief that increased purity allowed increased heating) and (d) a higher temp than 80 (as the purity we were aiming for was 10-to 20 times greater than 8Y (if a higher temp was needed to inactivate NANBH and BPL were correct that purity was what mattered.)

A number of things happened in late-1985 to cause us to review our strategy.

(i) we discovered that the secret to dry heat at 80 was in the freeze drying not the purity.

(ii) there were rumours from the States that dry heat at 60-68 might not be sufficient to destroy HIV - this was Fred Prince's study of the Armour process which did in fact transmit HIV in 1986 in UK (iii) BPL were now manufacturing 8Y and their routine product had been shown to be effective and well tolerated.

We decided to shelve our work on high purity and to develop an 80 degree dry product ASAP instead using procedures with which we were aleady familiar from our work on ZHT. This proposal was ratified by the FVIII Study Group in Feb 1986. A completely new product (Z8) had to be developed, so we had to go through all the stages of a product deveopment, including lab-scale and pilot-scale studies. We ceased the manufacture of NY (68/24) in July 1986 and began full-scale trial production of Z8 in August. It was not until Oct 1986 that BPL presented preliminary data (to HCDO) to suggest that heating at 80 might inactivate NANBH. Batches of Z8 for clinical trial were available at the end of Dec 1986. (bear in mind that it takes about 3 months to manufacture a batch of FVIII). The clinical studies (tolerability and efficacy) were done in March/April 1987 and Z8 was issued routinely from April 1987. However the introduction of Z8 was phased with a rundown of NY in in order to maintain batch dedication as (in the absence of proof re. NANBH safety) HCDs still viewed that as important. As far as I can establish this made Scotland the first country to be able to provide HCV-safe FVIII for all patients.

As we had developed Z8 so quickly we still had a lot to learn and so moved on to develop an improved version S8 (a more robust process and higher yielding) - we also continued work on Johnson's high purity method but not as a priority.

S8 was was ditched just before clinical trials in favour of introducting a Lille-type high purity FVIII which we introduced in 1990/91. Lille had not attempted to move from dry-heat at 68 to dry heat at 80 and had gone straight for high-purity (with s/d). I think they introduced this in France in 1988/89, so I would guess that we had a Hep C safe-FVIII about 12 months before them, but as a consequence lost the race to develop high purity, despite the Lille process being inferior to Johnson's (ie. much lower yield using NIBSC standards/assays).

60-68 degree commercial dry products continued to be used in the UK in the late 1980s and remained licensed in UK until 1992 (interesting that in 1988/89 Scottish HCDs bought some of Alpha's 60 degree 20 hr product, despite this having been shown to transmitt NANBH).

Commercial high-purity products began to enter UK during the late 1980s/early 1990s - but the first (Monoclate) was not virus

inactivated and did transmitt NANBH. Pasteurised Monoclate was then developed (I think this also transmitted NANBH). All other high purity products were s/d treated in the belief (as expressed by Christopher) that non-enveloped viruses were not a problem. Hepatitis A infections then emerged (1994) probably due to the removal of neutralising antibody in conjunction with a VI method that was ineffective against non-enveloped viruses. So from that point of view high-purity was a step backwards.
You will remember that the clinical driving force for high-purity was the idea that lower purity products were causing immunological abnormalities and that HIV-infected patients would do better on high-purity. This was eventually shown to be false. From today's perspective the real benefit of high-purity may be a greater capacity for prion removal.
Disappointly we chose to drop dry heat instead of having a high-purity FVIII with both s/d and 80 degree dry heat - we could have been first in the world by a number of years to have a dual inactivated FVIII (something which Baxter's high-purity FVIII still cannot tolerate because its partially activated). We took a different decision with FIX as yield was not an issue. We did eventually develop Liberate with both s/d and 80 degree dry heat but fell foul of the ban on UK plasma (which delayed the clinical trials) and the switch to recombinant (with a 3x higher risk of inhibitors).
As Lord Penrose is concerned with how patients were infected with HIV and HCV I am not sure he will want to spend time considering subsequent product developments, even so, its better to prepared.
Sorry to be so long winded. Hope this is helpful
Peter

--- On **Thu, 25/6/09, John Cash <*cash3436*** GRO-C > wrote:

From: John Cash <cash3436 GRO-C >
Subject: Re: Self Sufficeincy
To: "PETER FOSTER" <peterrfoster GRO-C >
Date: Thursday, 25 June, 2009, 9:23 AM

Peter
Extremely helpful; thanks for that.
Can I now take you to a later stage when our customers wanted a high purity product that matched that available from the commercial boys..
Looking back, how do you think we got on? I'm thinking of the Alan Johnson saga and thence to Lille.
Finally, could you remind me again when our heat treated products 'went live'?
Best to you
John

----- Original Message -----
From: PETER FOSTER
To: John Cash
Cc: Ian Franklin ; BRIAN MCCLELLAND ; Robert Perry
Sent: Wednesday, June 24, 2009 2:52 PM
Subject: Re: Self Sufficeincy

John
The title of my talk was ' we made it safe just in time?' - During the talk I considered progress to self-sufficiency and the development and introduction of heat treatment and my answer to the question in the title was No. (I still have the slides).

As far as self-sufficiency is concerned, I would argue that we did achieve it during 1983 - but it was always a moving target and it depends on your definition of self-sufficiency. For the Investigation by the Scottish Exec in 2000 I defined this as supplying the quantity of FVIII needed to provide treatment at a level equivalent to UK clinical practice at the time. HCDO returns tell us the amount of FVIII used in the UK each year since 1969. So its possible to work out how much was used each year per head of population - comparing this with SNBTS output shows that we were at or close to providing this amount from 82/83 onwards. We fell back slightly for a short time in the late 1980s as we could not keep pace with the year-on-year growth in Scottish demand. The critical period was of course in the late-1970s - early 1980s before commercial products had been made safe(r). I am not sure that we have complete data on commercial purchases, but from the figures we have it looks to have been around 20% during the early 1980s when the risk from HIV was at its greatest - it might be argued that the 80% from SNBTS could have been 'sufficient' if users had been more cautious in their use of commercial products (bearing in mind that we also supplied cryo on demand).
Hope this is helpful
Peter

--- On **Wed, 24/6/09, John Cash** <***cash3436*** GRO-C > wrote:

> From: John Cash <cash3436 GRO-C >
> Subject: Self Sufficeincy
> To: "Peter Foster" <peterrfoster GRO-C >
> Cc: "Ian Franklin" <ian.franklin GRO-C >,
> "BRIAN MCCLELLAND"
> <brianmcclelland561 GRO-C >, "Robert
> Perry" <robert.perry7 GRO-C >
> Date: Wednesday, 24 June, 2009, 12:53 PM
>
> Peter
> I remember at my retiral symposium you kindly
> contributed and recall to the rhetorical question on self
> sufficiency - did we make it?- you finally responded
> 'no'. This would have been my conclusion too.
> Am I right? If so, could briefly enlarge where you felt
> we failed?
> Thanks
> John