One Year On: The Bioequivalence Guidelines

Interview by Helen Winsor, **Pharma IQ**

Helmut Schütz of BEBAC Consultancy and Anders Fuglsang of Fuglsang Pharma Consultancy, join Pharma IQ to discuss the impact of the bioequivalence guideline introduced in summer 2010 on the pharmaceutical industry.

Pharma IQ: First of all, just to put your roles into context, how many bioequivalence studies do you consult on per year? First of all, Helmut, could you take that question?

H Schütz: I would say roughly 30.

A Fuglsang: I think I'm at 15 so far. Most of the studies that I'm consulting on should perhaps be termed therapeutic equivalence studies rather than bioequivalence studies but, yes, 15.

Pharma IQ: Okay, so that's what we're working with. I'd like to have a look in more detail at the sort of consultancy that you do and some of your reflections on bioequivalence and the new guidelines that were introduced last year. In your opinion how well have the bioequivalence guidelines been received Helmut?

H Schütz: I think generally very well. People were waiting for these guidelines and there were a lot of discussions and draft guidance, etc, so people in the industry mostly, in my opinion, are really happy that there is something now they can rely on. The section on biowaivers was especially welcomed. This is my impression. I think generally well.

Pharma IQ: Anders, how have you seen the guidelines being received; do you think that there's good take up across the industry?

A Fuglsang: When we speak about the 2010 guideline for bioequivalence, yes, I think that people really welcomed that document. That is certainly my impression. We also had, the year before, a guideline on therapeutic equivalence for inhalation products and that's the type of product I mainly work with. I think a lot of people were very happy when that was published although when they got a bit in to the work the attitude became slightly more negative or perhaps it wasn't all gold that glittered.

Pharma IQ: What are the main changes in the guidelines in your opinion and has the industry been aware of these changes? Again, Helmut could you start off with this question?

H Schütz: For me it was very interesting that in the BE guidelines there was already a cross-reference to the bioanalytical guideline which will be finalised in the third quarter this year. This is very important because there was no guideline on bioanalytics at all in Europe so everybody was working according to FDA's; sections are already in the BE guideline. There is another section on statistics when you deal with highly variable drugs so it's possible to widen the acceptance range for the peak concentration.

I think the industry welcomed that very much but for me it's amazing that when I review protocols, even by very large players in the field, they still don't realise that the evaluation has not been done according to the code which was published by the FDA. There is a question and answers document which was published this March and you have to evaluate studies according to that. It's not only the guideline but there are other documents you have to adhere to also. Another thing is it's possible to go for two-stage designs, which is a major improvement; it wasn't possible according to the old guidelines. Yes, I think people are aware of that generally and it's a nice improvement.

Pharma IQ: Thanks Helmut. Anders, what do you regard as the main changes and how has industry responded to these?

A Fuglsang: I actually completely agree with Helmut regarding these bioanalytical aspects. Having been a regulator before I have been in the situation where I needed to assess outcomes of bioanalytical validations and where I didn't have any sort of regulatory reference for doing that kind of assessment. It seems a little unfair in such a situation that a European assessor would refer to a US document. I think it certainly paves the way forward now that the new guideline on bioequivalence are incorporating also on bioanalysis and referring to this new guideline, which is currently a draft.

Pharma IQ: Thanks Anders. Anders, are you aware of any specific problems experienced when it comes to implementing the guidelines?

A Fuglsang: That's a good question actually. There are some very good posts about this on the forum that is hosted by Helmut. Certainly I could mention there are some issues around statistics where I think perhaps some people believe regulators are in a bit of deep water or they have asked for things that are perhaps not well founded in the kind of science that at least the industry prefers to use. There are a few areas where things are a little greyish but as a whole I think the guideline is a step in the right direction.

Pharma IQ: Thanks Anders. Helmut, have you regarded any problems occurring when it comes to implementing the guidelines?

H Schütz: Yes. Actually it's a little bit difficult to see it because the guidelines are in force since last August and just last week I was at the BE Conference in Japan and right now we're close to day 210 so when we see problems they will appear right now. When people submit a study they go through the mill of the regulatory process and we will see coming now problems officially being published.

A Fuglsang: I can add perhaps that, for the types of products that I work with, some of these products are sometimes approved using that bioequivalence guideline. It has some specifics about batch sizes but for all inhaled product batch sizes can sometimes be a fuzzy area because 100,000 units is a little unclear; that means 100,000 inhalers or the amount of inhalers that contain 100,000 doses, something like that. This is the type of grey area that I encounter and I think you're absolutely right Helmut saying we are close to getting to a point where we will realise if there are any weaknesses they are about to surface now.

Pharma IQ: Thanks Anders, that's a great point. Anders, do you think that there is anything missing from the guidelines that you would like to have seen included?

A Fuglsang: Yes. Helmut mentioned before two-stage approaches; as the guideline is written now it opens up the use of these two-stage approaches but it does very little in terms of specifying which model for two stage approach to use and how to validate that. I would like to have seen a bit more specific information there. In addition to that I can mention that the requirement about using Good Laboratory Practice in the bioanalysis, sometimes I think that requirement has sort of outlived itself. It's in the guideline now for historical reasons but GLP – Good Laboratory Practice – was actually never intended to be used for these purposes. I think today a lot of regulators apply the principles of GLP and they don't always fit very well with bioanalysis. To give an example of, say, quality control – the GLP guideline does not in any way mention quality control but regulators can actually crack down on that if they think that quality control is missing or interpreted to be lacking.

Pharma IQ: Helmut, is there anything, in your opinion, missing from the guidelines?

H Schütz: Yes. First, I agree with Anders. What I really miss is that this widening or scaling is only allowed for C_{max}. There are examples of drugs, like bisphosphonates which have low absorption, some of these drugs lower than 1% and they are highly variable, so C_{max} is only one part of the problem. We have also very high variability for the area under the curve. For the FDA, if a drug or drug product is highly variable scaling is allowed for C_{max} *and* AUC so actually allowing it only for C_{max} is just the opposite of global harmonisation because now it's different; in Europe it's only C_{max}. Really, I miss that because for some products we still have

to run large studies of 150 subjects or something like that. It was a first step but I'm not totally satisfied.

Pharma IQ: Thank you. How do you predict the landscape changing over the next five years Helmut?

H Schütz: Good question. Next question? The next five years, it's so far in the future. The next step will be the modified release guideline; we can expect the draft coming out in the first quarter next year and this will be a very important document and we will discuss the draft again when it is finalised. I don't know; maybe there is another year and when it comes into force maybe two years or so. This is very important because so many products on the market are not immediate release but modified release and I think the ratio of these types of products will change towards modified release products because just from compliance and from the pharmaceutical technology these are better products, in my opinion, for many drugs.

Pharma IQ: Sure. Thank you. Anders, what changes do you expect over the next few years?

A Fuglsang: I fully agree with Helmut here that modified release is going to be important and that's an area where we're likely to see some changes. Apart from that I would say that we are going to see some changes in the landscape in the US for inhaled products and for nasal products. In the US they don't have any guidelines yet for equivalence for all inhaled products, although the FDA has been working on that for more than ten years. The industry is quite desperate to actually get those guidelines and have something complete to base the work on. I think we will see that within five years, and perhaps even within a much shorter timeframe. We will also see some nasal guidelines being published, I'm quite sure of that, and that could be both in the EU and in the US.

Pharma IQ: Thanks for your reflections. Both of you are going to be presenting at our second annual Bioequivalence and Bioavailability Studies Conference in September. I'd like to use this opportunity to just get a quick snapshot about what you're going to be talking on in your presentations. Anders, could you give us a quick overview of what you'll be covering?

A Fuglsang: At the moment I'm lined up to speak about two aspects; one will be the two stage approaches, where I might do a little bit of work with Helmut, and another topic that I'll be covering is development of nasal hybrids or nasal generics and which territory they are supposed to be submitted in.

Pharma IQ: Thank you. Helmut, what are you going to cover in your presentation?

H Schütz: Actually we will do some co-work and we will somehow improvise a little bit, keep it quite open, but mainly I will speak on power calculation which means to calculate the sample size of studies. In my opinion this is a point where many companies either waste money because they have just a one size fits all approach, meaning we do a study in such and such subjects, and their product has a low variability so they are just burning money; on the other hand they say they have a fixed sample size. I've seen that; all their studies were in 24 subjects – as if carved from stone, and many studies failed because the subject number was just too low. I hope to shed some light; it's not rocket science but you have to follow some points which are important.

Helmut Schütz and Anders Fuglsang will be delivering presentations at the forthcoming 2nd Annual Bioequivalence and Bioavailability Studies Conference, due to take place from 19th – 21st September 2011 at the Four Points Sheraton, Brussels, Belgium. For further details please visit http://www.bioequivalenceevent.com/, call 0800 652 2363 or email enquire@iqpc.co.uk.