BCS: implications on guidelines and policies for drug products approval world wide

(including ICH and regional)

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Joseph R. Robinson, University of Wisconsin, USA: The next speaker in this morning's session is Dr Iain McGilveray, who's going to speak on BCS, its implications on guidelines and policies for drug products approval world wide, including ICH (the International Conference on Harmonization) and regional.

Dr Iain McGilveray, McGilveray Pharmacon Inc., Ottawa, Canada: I want first of all to thank Vince Li and the organizers for inviting me here, it's a great pleasure to be in Hong Kong. Vince asked me why I was staying in Kowloon and I can tell him I'm a romantic, I like the ferry ride from Kowloon to the Island and it was very pleasant this morning to do that. But I'd better get, as we are running a little late.

You've already heard that there are problems when we consider moving US-evolved science-based regulations world wide, and I will be talking a little about that.

Figure 1 gives the outline of what I'm going to talk about. I'll try to go quickly through the BCS (biopharmaceutics classification system), to recap. I'll quickly mention SUPAC – Scale-up and Post-Approval Changes – which we heard about, and the BCS influences on it, as well as regional guidelines where the BCS touches on these; we heard a little about the European position already.

Then I'll move on to what ICH is trying to do, particularly when it comes to the Common Technical Document (CTD), and to some issues of and then some thoughts for the future. So it's rather a large mandate.

Outline

- BCS recap
- FDA SUPAC and BCS influences
- Regional guidelines (US, EU, Japan)
- ICH overview/steps
- ICH Q6A Specifications guideline
- Common Technical Document
- Some issues
- Future

Figure 1.

You stand on the shoulders of previous scientists when you give talks, and here I'm standing on the shoulders of Dr Ajaz Hussain of the Food and Drug Administration (FDA) with *Figure 2*, where he is saying why there was a need for the biopharmaceutics classification system (BCS). To some extent Gordon Amidon has already referred to that this morning.

The BCS attempts to identify when dissolution rate is likely to be rate-determining, and to assess when *in-vitro/in-vivo* correlations would be expected. And that would be, of course, the Class I type of drug, where dissolution is rapid and not the rate-determining step, plasma levels may not reflect product differences, and little or no difference would be expected between oral solutions and solid dosage forms.

The objective of the BCS is to help develop dissolution test methods that can assure bioequivalence, and to identify the good dissolution media for

Need for Biopharmaceutics Classification System (BCS)

AS Hussain FDA 1999

- To identify when dissolution rate is likely to be "rate determining" and to assess when IVIVC are expected
  - When dissolution is rapid and, not the rate determining step, plasma drug levels may not reflect product differences and little *in-vivo* difference would be expected between oral solutions and solid dosage forms
  - To develop dissolution test methods and specifications that can assure bioequivalence
  - Identify dissolution media composition that reflects *in-vivo* dissolution environment
- To identify and manage certain risks associated with the assessment of bioequivalence using in-vitro tests
  - Potential for "inactive ingredients" to alter gastrointestinal physiology such as transit time, metabolism, efflux, etc.

Figure 2.

that. The other side is to find out why the above is not happening and to look at areas such as a potential for inactive ingredients to alter gastrointestinal physiology. Although this is a Controlled Release Society (CRS) meeting, there's not very much CRS stuff in here but, of course, you do use excipients to affect the absorption and in that sense they are not inactive.

Figure 3 contains some opinions about dissolution. "Dissolution tests are over-discriminating", and the famous US Pharmacopeia (USP) preface, which I don't particularly like because there are examples when this is not true: "Products that dissolve about 70 percent in 45 minutes have no medically relevant bioequivalence problems". Therefore we don't need bioequivalence, folks! But of course people have not accepted that entirely.

Dissolution tests: Issues

- "Dissolution tests are over discriminating"
- "Products that dissolve about 70% in 45 minutes have no medically relevant bioequivalence problems" *USP preface*
- Dissolution tests are not sufficient to assure bioequivalence
- Demonstration of IVIVC is necessary
- IVIVC's are "Product Specific"

Figure 3.

"Dissolution tests are not sufficient to assure bioequivalence." Well, that's what BCS is about, trying to say when they would be sufficient, when not. "Demonstration of *in-vitro/in-vivo* correlation is necessary" – but, as we've often found, *in-vitro/in-vivo* correlations are product-specific. In the CRS area, with modified release, you're well aware of that.

When I was in the Canadian Health Protection Branch, we tested about 30 drugs and probably about 200 formulations, and we had no great success with dissolution. Often, as is said, it was over-discriminatory.

But, from that work, *Figure 4* shows a case of a reverse correlation. This was a sugar-coated reference product from Upjohn, the innovator, alongside two different sugar- and film-coated formulations from a generic manufacturer. The C-max (maximum plasma level) for those came out at about 70 percent. For the reference product, using USP paddle, 50 rpm, pH 7.2, dissolution was slower. It was 69 percent, at 45 minutes, compared with product A at 84 percent, and B at 92 percent.

"Inverse" correlation :Ibuprofen

McGilveray, *1991 Book chapter*

- Sugar-coated reference
- A sugar, B film, Cmax 70%
- % Dissolved, paddle 50 rpm, pH7.2
  Ref = 69
  A = 84
  B = 92

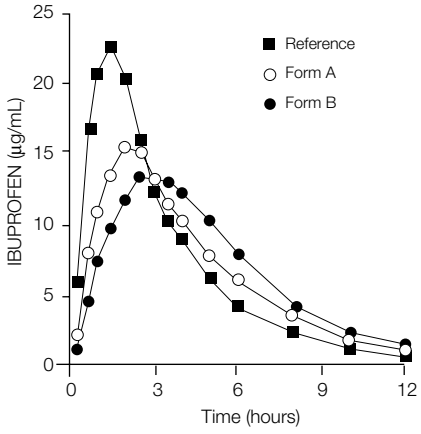

Figure 4.

Well, you'll say pH 7.2 isn't very good, but remember this drug doesn't dissolve very well below about pH 5, because of its pKa. But you can see that with this drug, which is used in analgesia, these differences (affecting speed of onset) might be significant to the patient, and therefore we should not rule out the possibility of medically relevant bioequivalence problems for this class of drugs: Class II, with high permeability/low solubility.

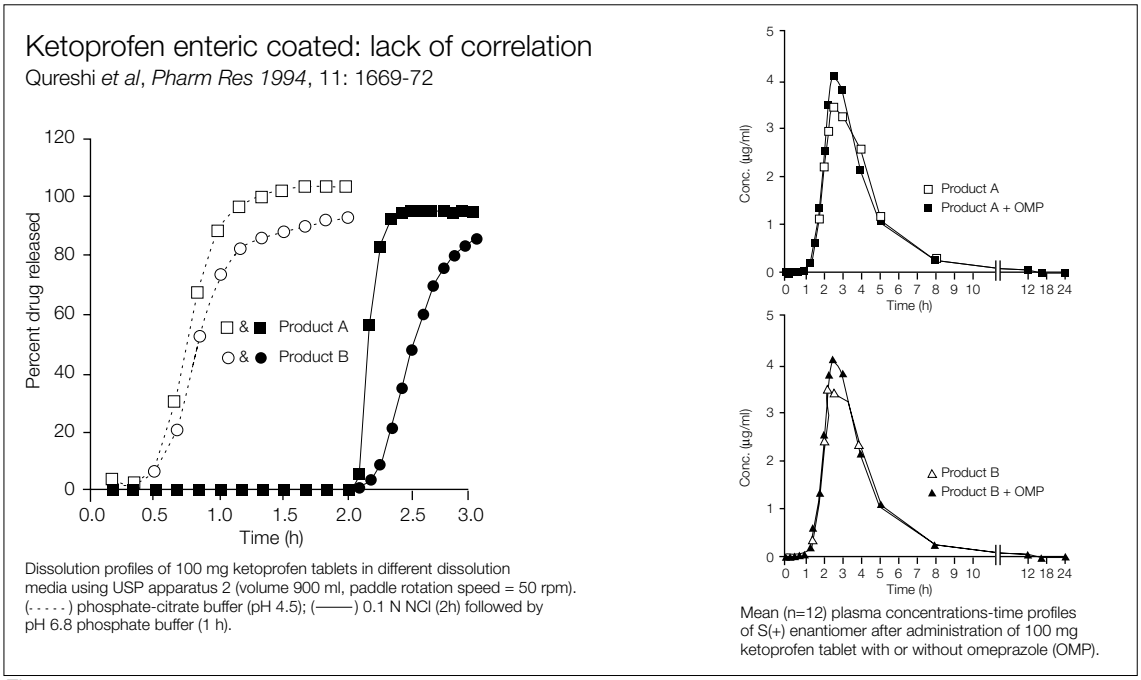

Figure 5.

Figure 5 shows another example where we tried to develop a model and it's not come out very well at all, with a net result for achlorhydria. These are two enteric-coated products that were tested at pH 4.5 in this case, using a typical USP method where they were exposed to acid for two hours, and then a pH 6.8 buffer. And you can see we get a difference in dissolution between these two formulations. For the *in-vivo* these are the ketoprofen average plasma profiles, and it's the S (+) enantiomer that we're showing in this figure (but the R- isomer provided almost identical profiles). There was no effect with either of these products *in-vivo*, they were the same with and without the omeprazole elevating the gastric pH. Over-discriminating dissolution, perhaps?

SUPAC-IR/MR and BCS waiver

- Based on FDA research at U.Maryland , Michigan, Uppsala
- Applies to NDA and ANDA post approval
- Some relevant to pre-approval

Change of:

- components or composition
- site of manufacture
- scaleup/scale down of manufacture
- manufacturing process or equipment

Figure 6.

And then in *Figure 6*, I wanted to mention the tremendous effort that Professor Amidon has been involved in, establishing the BCS scientific basis also applied in SUPAC, and also Hans Lennernäs and Professor Paalzow in Uppsala and Professor Augsburger at the University of Maryland. This is a tremendous effort. I call it the “Manhattan Project of pharmaceutical sciences”.

Of course, SUPAC applies to post-approval ANDAs (abbreviated new drug applications), although some of it, as we will see, is also relevant to pre-approval new drug applications. SUPAC looks at four change areas: components or composition, site of manufacture, scale-up, and manufacturing.

Except for site of manufacture, the University of Maryland conducted the mapping of formulations and *Figure 7* shows one of their results that was typical for immediate-release (IR) products. In this case it was immediate-release metoprolol, but they looked at six drugs in total with different high permeability/ low permeability according to the classifications.

In this case we see for metoprolol that you get a very wide range of dissolution, Although the *in-vivo* peak concentration showed a trend in relation to dissolution, But all the *in-vivo* results are within the required bioequivalence limits of 80-125 confidence intervals.

FDA/UMAB study of IR metoprolol tablets
BE does not reflect dissolution

Rhekhi *et al*, *Pharm Dev Technol 1997*, 2: 11-24

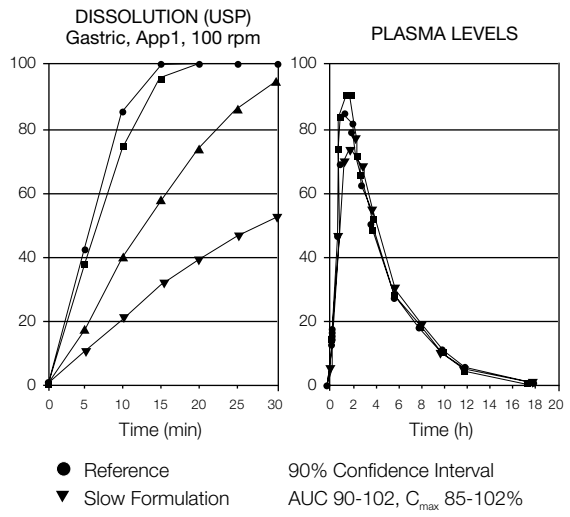

Figure 7.

Overall, the results of the University of Maryland research found that the dissolution is much more sensitive to the changes than the bioequivalence, and while major changes in the dissolution did indicate some trends, in terms of the C-max. None of them went outside the bioequivalence acceptance level for the six tested drugs.

Earlier this year, Ajaz Hussain set out his comments on why dissolution tests can fail – perhaps, through inappropriate acceptance criteria, in cases where one-point specification is set too late. That's certainly true of glibenclamide and possibly cimetidine. I think for some drugs, not all, the 45-minute time is too late, it needs to be 15 minutes.

Inappropriate test methods – Hussain proposes those based on media composition (pH), media volume, or hydrodynamics – are something that we can argue about. I mentioned previously my concerns about NSAIDs (non-steroidal anti-inflammatory drugs), and how do we deal with that?

Excipients affect drug absorption, he suggests. That has to be looked at. We certainly have had that in the past. The famous example is phenytoin in Australia, when a change from calcium sulfate 1to lactose did affect the drug absorption and cause patient toxicity problems.

So, improving the reliability of dissolution tests was the aim of the BCS, and trying to say when you would expect *in-vitro*/*in-vivo* correlation, which we know is rare for many IR products, as we found in our large Canadian series of studies. It certainly requires a lot of *in-vivo* studies and empirical work. Mapping, which they did at the University of Maryland, is a very expensive process to do for each group of formulations.

So can we come up with a Kiss system – keep it simple, stupid? Some way of classifying drugs that does not require additional studies and that is mechanistically-based, which is what Gordon talked about this morning? In fact, that has been very well done.

Gordon has already given you some of that with very exquisite triple integral equations, I noted. Anyway, the rationale for the BCS which he published in 1995 states that the major factors governing rate and extent of absorption of a drug that is stable in the GI tract are dissolution, solubility and intestinal permeability. We now have to worry more * about transporters and drugs with that type of active absorption, and that has an overlay effect.

Next is an outline of the FDA guidance for the waiver of *in-vivo* bioavailability studies for IR solid oral dosage forms containing certain active ingredients. This is to clarify the regulations, which will allow, as Gordon said, for some waivers from *in-vivo*, using dissolution, and it would apply to NDAs pre-approval as well as, hopefully, ANDAs – what we argued about earlier. And, as you know, a proposal has been put forward which would extend BCS from post-approval changes to changes at the development and pre-approval stages.

The proposed BCDS guidance document by Ajaz Hussain as well giving the solubility boundary – "highly soluble" requires the highest dose strength dissolve in 250mL, pH 1 to 8, also suggests diffe-

BCS proposed guidance

- Solubility- highly soluble requires highest dose strength dissolve in 250mL, pH 1 to 8
- Permeability determinations including:
  - extent of absorption >90% in humans or
  - application of human intestinal perfusion
  - studies of animal *in-vivo* or *in situ* perfusion
    - *in-vitro* permeation study of animal or human intestinal tissues
    - *in-vitro* permeation with cultured human intestinal cells

Figure 8.

rent methods of how to determine permeability. These include:

- extent of absorption >90% in humans or
- application of human intestinal perfusion
- studies of animal *in-vivo* or in situ perfusion
- *in-vitro* permeation study of animal or human intestinal tissues -*in-vitro* permeation with cultured human intestinal cells

We're still at an early stage of this, as Gordon mentioned earlier, but the methods would have to be validated if they are not based on human studies. The idea is to identify a class of drugs for which bioequivalence tests would only be *in-vitro* – the big aim is to reduce bioequivalence studies in healthy subjects. As Dr Malcolm Summers of the UK Medicines Control Agency has said, the Europeans have been struggling with this, but there are certainly elements of the BCS in their proposed note for guidance on bioavailability.

Figure 8 shows the broad limits of the proposed guidance. The solubility suggested would be for a highly-soluble drug substance, and requires the highest-dose strength to dissolve at 250 mL, in a pH range of 1 to 8. Some of the permeability determinations are still to be validated fully, but the idea is that extent of absorption is greater than 90 percent in humans indicates "highly permeable". And one that's not on this Figure is, of course, the dissolution of the product, where 85 percent dissolved in 30 minutes appears to be what's said in the guidance, although I noticed that 15 minutes went up in one of Gordon's slides.

I won't dwell on *Figure 9* because Gordon has already talked about the impact of dissolution. But for the BCS class boundaries shown in *Figure 10*, rapid dissolution is 85 percent in 30 minutes, high solubility means that in 250 mL the highest strength would dissolve over a wide pH range, and we have already have noted what the step would be for high permeability, 90 percent absorbed.

The question is, can we bring in the system as shown in *Figure 11*? This is very important, as discovery is merging with development so much nowadays, in the rush to bring new candidates forward.

BCS class: Impact of Dissolution

- I. High P&S: When dissolution rate > gastric emptying - unlikely to be rate determining
- II. High P, low S: Dissolution likely to be rate determining and correlations possible
- III. Low P, High S: Same as I, but need to examine why absorption is incomplete
- IV. Low P&S: "Problem drugs": Correlation may be possible, but dissolution may not be reliable

Figure 9.

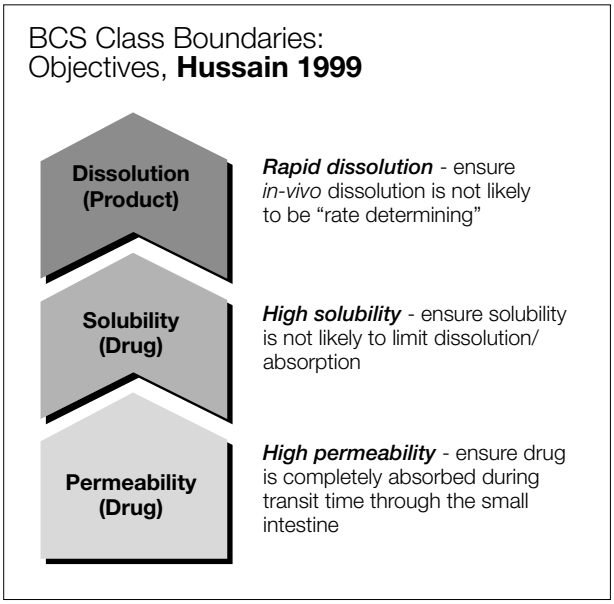

Figure 10.

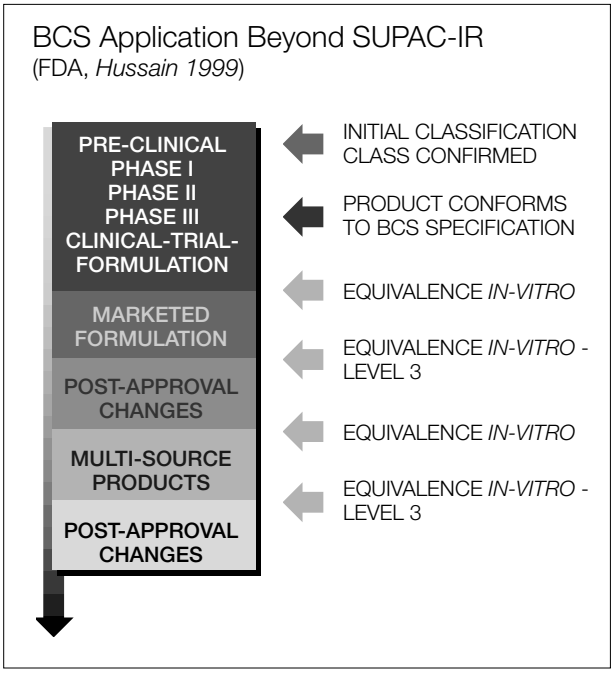

Figure 11.

I think preclinical is when you do your initial BCS classification. It would help you in the development later on and it would help you avoid *in-vivo* studies later on if you could do *in-vitro* equivalence.

So where does this fit in around the world? Where does BCS fit into region-specific and ICH guidances? The answer is very tentatively at the moment, really. We're hoping, and this is a fond hope, that maybe some time in the middle of the new millenium we will have a global dossier, but we're not there yet.

"Regional" guidances involving BCS

EMEA-CPMP
- NfG investigation of BA&BE (draft).
- NfG Quality of modified release products:A. Oral and Transdermal Dosage forms; Section 1 (Quality)

MHW Japan
- Guideline for Bioequivalence Studies of Generic products

U.S. FDA
- SUPAC -IR, -MR, Dissolution–IR, –MR (*in-vivo/in-vitro* correlations), proposed BE waiver using BCS

Figure 12.

And you have to remember that there are regional guidances in existence and BCS should fit in with them (*Figure 12*). We've talked about the European Union's note for guidance (NfG) draft, which is having its troubles. And while its note for guidance on the quality of modified-release products does not mention the BCS, it is very concerned with *in-vitro/in-vivo* correlations, and very similar in this regard to the US, where they also have that in their guidance.

The guidance from the Ministry of Health and Welfare in Japan doesn't mention permeability, but I did notice from what was available in English that it features as a decision tree. They do, in fact, allow for *in-vitro* bioequivalence in some cases, but it depends on a lot of dissolution studies. In particular, they're concerned about achlorhydria.

The FDA as we've mentioned has a whole variety of guidances: SUPAC -IR, -MR and there's Dissolution -IR, -MR (*in-vitro/in-vivo* correlations), and the BCS underlies all of these.

And by this time you'll be saying guidelines, guidances, heaven help us, we need to hire more people. Maybe that's true, but we hope that the guidances will help to avoid delays in getting drugs to market, because they spell out what is going to be acceptable.

European (EU) Registration Procedures

Mutual recognition procedure
- Authorisation in one member state (MS) 1st MS is the "reference MS"
- Other MS can only object to acceptance on serious "public health" grounds

Centralised procedure
- Assessment by the Committee for Proprietary Medicinal products (CPMP)
- CPMP appoints a member as coordinator and primary assessor (rapporteur)

Figure 13.

And we have to remember that each area, each region if you will, has its own different means of approving drugs. In the European Union (EU), where they've been working on this now for some 20 years, they've narrowed it down in the last couple of years, to two procedures from three (*Figure 13*). There's a mutual recognition procedure in which first authorization is given in one member state, then that state becomes a kind of guide through the system, and other member states can object on various grounds.

Then there's a centralized procedure that has been used since 1995 and the idea there is that the EMEA (the European Medicines Evaluation Agency), through its Committee for Proprietary Medicinal Products will put the drug to a country and that member state acts as co-ordinator and primary assessor. If approved, the product should then be accepted in all countries. However, there are still teething problems with this.

This summarises only one region. Many of you know the US system, and Japan also has its complexities. So it isn't always easy to graft this science into the regulations.

The idea of ICH, (*Figure 14*) of course, aims to eliminate the need for duplicate studies to meet these different regulatory requirements, and it's certainly moving along that way. It is concerned with the more efficient use of resources in the research and development process, whether that be human or animal material and, as a consequence, with giving patients quicker access to safe and effective new medicines – without compromising public safety, one may say.

The ICH structure, probably many of you are aware, encompasses the 16 member states of the

Figure 14.

European Union, plus Japan and the USA, representing North America, as well as their respective research industry associations and the regulatory authorities. They make up the so called six-pack of the people who are running ICH. The steering committee members are from that six-pack. Then there are observers from the Canadian therapeutic products program – which some of you know as TPP, others as HPB – and from the World Health Organization. The WHO is important in this because ICH is an attempt at bringing about globalization.

The guidelines have recently been extended to the generic and over-the-counter industries because in the US they had begun to use the guidance for stability and impurities on generics, which were not represented, and that seemed very undemocratic, so it has now been addressed.

And the ICH steps start with technical discussions in a working group. You arrive at a consensus – step two – which is published, for example, in the US Federal Register. Then there is formal consultation for a while and a finalized text is then again published in the different regions, the US Federal Register being one that you know. Then after that it's up to the regulatory agencies to implement these guidances.

I'm not going to talk about all 40 guidances, I'd be here for 40 days and nights, I guess. But I will mention the quality topics (*Figure 15*), which include stability, analytical validation and impurities. The Q4 pharmacopeial harmonization is a special one, as is biotech-specific Q6b, and I'm going to spend time on the specifications involved, and Q7 GMP is a new one that is just started.

The Q6A specification is very important, it's where BCS might be applied and the Q4 pharma-

ICH Quality Topics

- Q1 Stability, Q2 analytical validation, Q3 Impurities, Q4 Pharmacopeial harmonization, Q5 Biotech specific, Q6 specifications, Q7 GMP active substances
- Q6A Specifications of new chemical entities and products from them is where BCS will be applied
- Q4 Pharmacopeial Harmonization Project should provide equivalent or mutually recognized test methods

Figure 15.

copeial harmonization is important because of the need to provide equivalent mutually-recognized test methods. It has been an area of controversy with people in the industry, who say well, if we use the USP it should be accepted in Japan and Europe, and so on. But it is moving along.

The decision trees which I will speak about are very useful, and that's where BCS is somewhat reflected in the Q6A, although permeability is not mentioned. Specifications do derive from the other guidelines such as analytical methods, impurity and stability (Q1-3) and they also, as I've said, depend on the harmonization of the pharmacopeias (Q4). One caveat is that this does not address clinical research at development stages, although valuable information is gained from formulation at that stage.

The next three Figures, a decision tree setting acceptance criteria for drug dissolution, have been produced by ICH, not by me. Walking you through it, I would point out that *Figure 16* starts off: “Is the dosage form designed to produce modified release?” If yes, you go to another series of things, which I'll mention.

Is the drug solubility 370 C, and the physiological pH range, 1.2 to 6.8? Does it dissolve in 250 mls and is the dosage form rapid? These are two of the things in BCS that you will find in ICH Decision Tree 7.

It's talking of dissolution 80 percent in 15 minutes. I suspect this comes from glibenclamide which Henning Blume worked on a lot, and which the Europeans are very sensitive to. In contrast, I see that the BCS is 30 minutes, so there is a difference there.

Has a relationship been determined between disintegration and dissolution? I think there was a little bit of a frisson in North America when ICH wanted to go back to disintegration but I guess as long as all this is working out well, one might be able to accept the disintegration. Otherwise, in

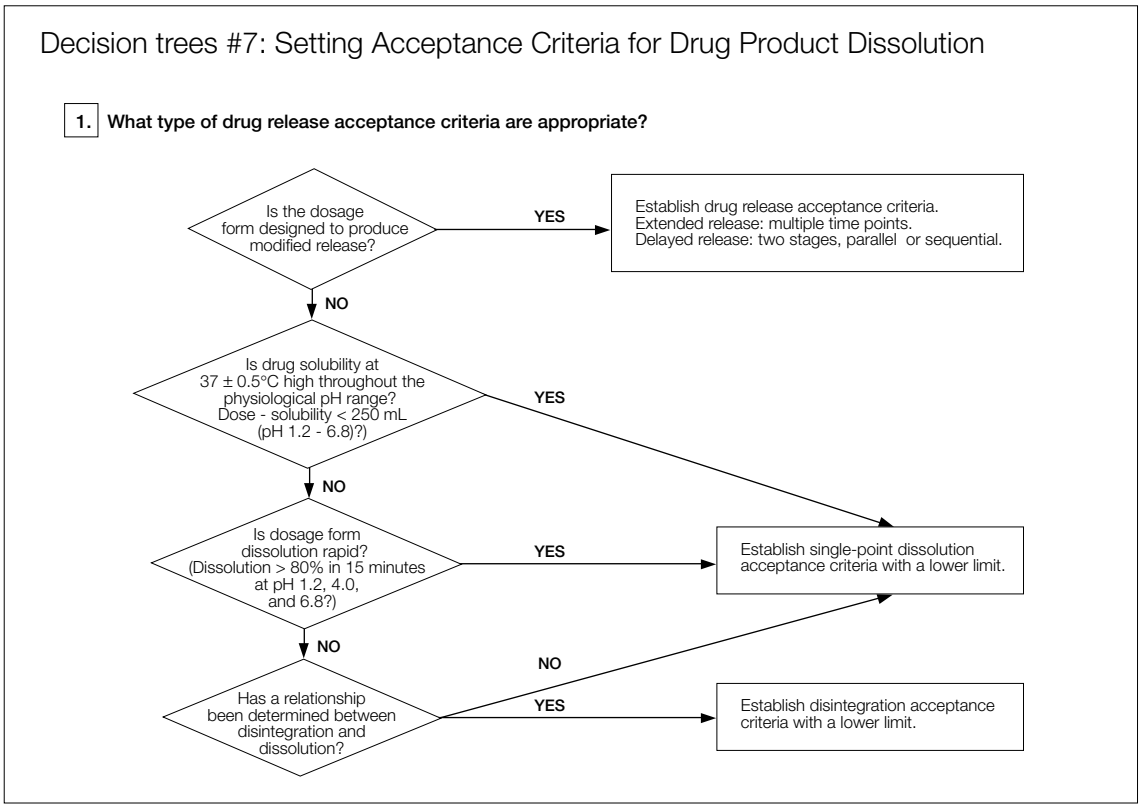

Figure 16.

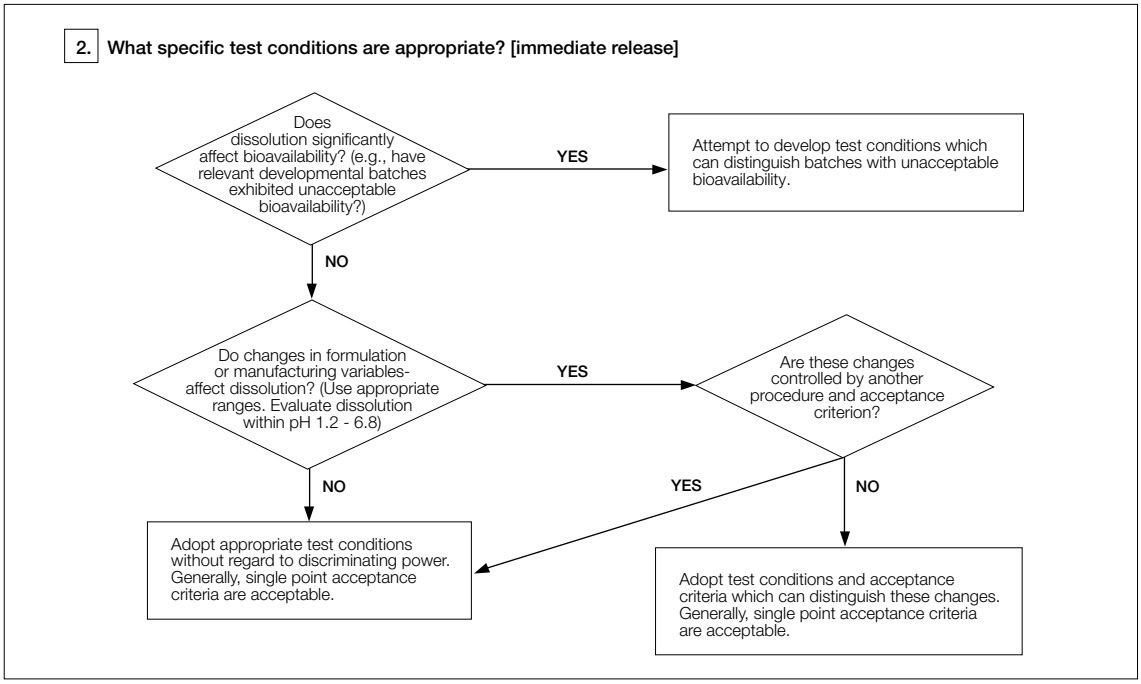

Figure 17.

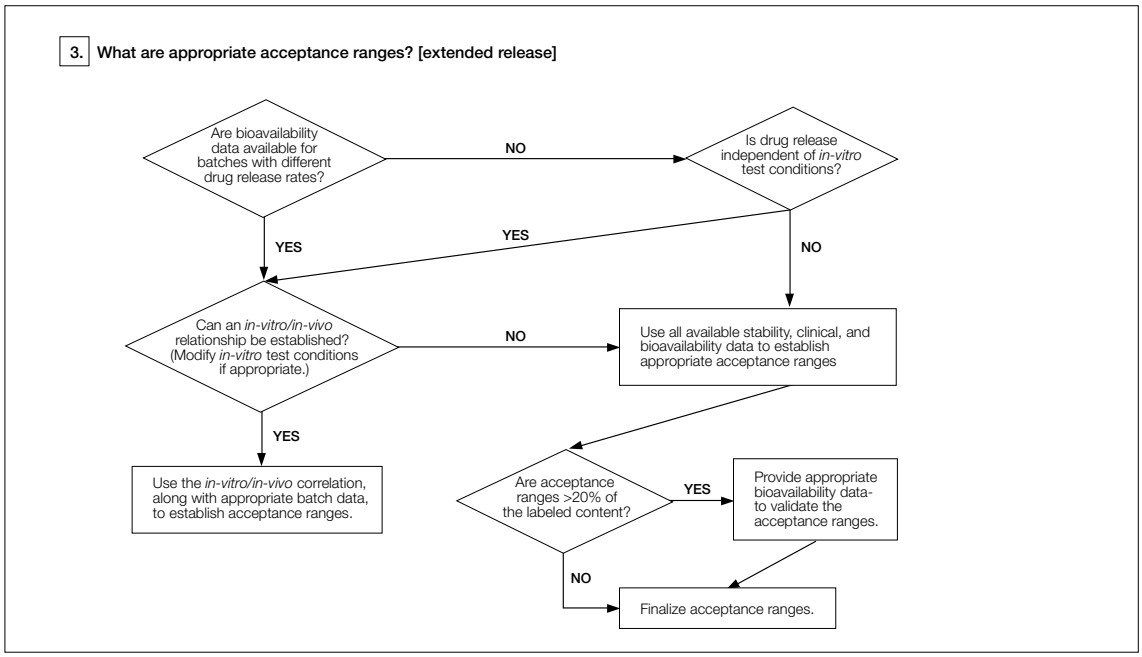

Figure 18.

these cases you're looking at a single-point acceptance for dissolution (*Figure 17*).

Figure 18 is just a very quick rundown for the ICH decision tree for extended release formulations. If you've got an *in-vivo/in-vitro* correlation, you're in business, that's what this decision tree implies, really. And if you don't have correlation you're going to have more difficulties in gaining approval if you make a change. That's what this means in simple terms.

The ICH M4 common technical document (CTD) is a great idea (*Figure 19*), it would be a step towards the global dossier. The idea is to have a common technical information package with the same format and content, for submission in all the regions. The benefits clearly are a more logical order, a reappraisal of data needs for approval – need to know versus nice to know could be sorted out here. There are certainly resource efficiencies to be gained, both in compilation and in review. And, of course, the big thing these days is electronic submissions, and the CTD would make it easier to do that. The idea is that this scheme would represent the way each report would be set up (There will be CTDs for efficacy, safety and quality). For quality I have some information obtained recently.

The first part of such a package will be out in time for ICH 5, to be held in San Diego in November 2000. Figure 20 shows the portion of the content format that has so far been agreed, so there's rather a long way to go.

Figure 20, CTD-Quality Content, describes the drug product, rather than the drug substance. You can see that BCS would be expected in the pharmaceutical development report (P2), and you would also expect to see some BCS elements – dissolution, certainly – in the control of the drug product (P5).

I hope that the above indicates the pivotal role the basic science in the BCS will now play in drug product regulation worldwide

And there are going to be more guidance documents to help you to fill in the CTD- Quality Content.

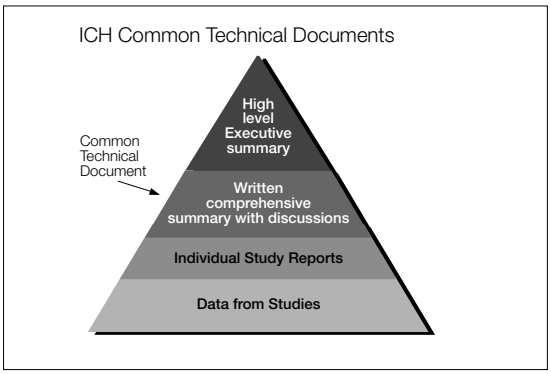

Figure 19.

CTD-Quality Content (Drug Product)

- P-Product
- P1 Description and composition
- P2 Pharmaceutical development report
- P3 Manufacture
- P4 Control of excipients
- P5 Control of drug product
- P6 Container closure system
- P7 Stability

Figure 20.

One of those that would concern some BCS, I'm sure, is the description of the manufacturing process and process controls for drug substance, another being the pharmaceutical development report guidance and the description of the drug product manufacturing process and controls.

I want to talk about some disharmony that's been expressed by industry over the last year by companies that have been submitting in different regions. A comment was made in London, I guess in April 1999, that dissolution remains a major topic for harmonization, and I would say one of the reasons might be the clay feet of dissolution, which is calibration.

In the US, they're using USP calibrators, which are not used world wide. I believe that for certain drugs, you will not get the same answer if you do your study in Osaka, in Frankfurt, in New Jersey and in the FDA lab at St Louis. You may end up with quite different answers for dissolution because of problems in calibration. There needs to be training in this.

It doesn't matter for the highly-soluble/highly-permeable class of drugs, however, because they're just dissolving in a flash. But for those where there is an element of a slower release, such as carbamazepine, it can be problematic.

Another comment is that the FDA often have more concerns than authorities elsewhere, and that they don't stick to the ICH, they push more the SUPAC BCS philosophy. In one case, when they came to Europe, where they had developed a sort of correlation, I guess, they came up with a dissolution spec based on two time-points, whereas the European Union wanted to have a USP-Q at 80 percent or something. So again they came up with two different specifications, one for Europe and one for the US.

The use of enzymes for the dissolution of gelatin capsules has been an interesting issue. It seems to be well accepted, if not demanded, by the FDA. The European Union is less happy with that, and it doesn't appear to be permitted in Japan. I'm sure Capsugel has concerns about that.

Can such disharmony be resolved through ICH? Steps 4 and 5 of its Q6A may provide greater harmony. The CTD should stimulate more agreement, although it's likely to be easier for the drug substance – a drug product may be handled in a variety of ways, in the light of differences between regulatory agencies and pharmacopeias. And there's some movement to mutual recognition.

Down the road I think we're going to do well, because it's only eight years since the initiation of ICH and already they've got nearly 40 guidelines and guidances. These have been integrated within regulatory policies and implemented in the regions. I think the CTD will promote this further. Meeting the ICH goals brings clear advantages in efficiency to regulators and industry.

Now, I realize I have gone over this very quickly. If you wish to ask for further information, my e-mail address is: mcgilveray@ottawa.com Thank you very much.

Roland Daumesnil, Capsugel AG, Switzerland: Some questions? We still have a few minutes.

Gordon Amidon, University of Michigan, USA: Iain, thank you for your excellent overview of a very complicated set of standards that are evolving rapidly. One question I have is, when I looked at the EMEA guidance on bioequivalence, posted in December 1998, it allowed for a waiver. But one of the requirements, in addition to the solubility dissolution requirements, was for less than 70 percent first-pass metabolism. Whereas we have left metabolism out because metabolism occurs after absorption. Can you comment on that?

Iain McGilveray, McGilveray Pharmacon Inc., Canada: Yes, they may have copied it from the Canadians. But I think the concern is that you've got a highly variable drug when you have that situation and also you've often got dose-dependent kinetics. We realized that these are more difficult to look at for bioequivalence and, however nice it would be to simplify, we have concerns.

I think the concerns will have to be at the front end though. If you've got a highly-soluble/highly-permeable drug that has high first-pass, which you mentioned with propanolol, then it's less important. I recall that propanolol SR – because it has more chance to be chewed up – is only about 60 percent bioequivalent to the IR. And in that case we saw, with the Inderal LA, I think it was, that it showed clinical effectiveness.