International Regulatory Perspectives on Guidelines for Drug Development and Testing*

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* The view expressed in this presentation reflect an individual perspective and are not necessarily those of the TGA as an agency

DR. SELIGMAN: Our next and final presenter of the afternoon is Andrew Bartholomaeus from the Therapeutic Goods Administration of Australia. Andrew, welcome, and we'll put this on and get you your slides.

DR. BARTHOLOMAEUS: Thank you very much for the invitation to talk. I must admit when John asked me to represent the entire regulatory community, outside of North America, I was wondering how it was that I drew the short straw until I got here and realized I'm the only straw in the audience. So I guess that answered that question for me fairly well.

If I talk quickly and look nervous it's because in Australia standing between an audience this size and a bar would be a suicidal act. (Laughter.) It doesn't look all that solid. I'm going to mention Hy's Law once, and I've just done it. (Laughter.)

My aim is to talk about how regulatory guidelines from agencies such as the FDA and EMEA are used internationally. Australia being a relatively small regulatory body, the TGA, have about 500 staff which is not insignificant but it certainly doesn't compare with the FDA's resources. We do need to work out how to put our resources to the task to get the biggest bang for our buck so to speak.

Issues

- Global markets need global requirements
- Market power influences regulatory practice
- Patient population a single species
- Harmonisation depends on engagement
- Use of international guidelines in smaller jursidictions
- Future of guideline development

The sort of issues I'm going to cover are issues that most of you should be well aware of. The pharmaceutical industry is a global market. So it needs global requirements. The market power of nations does drive to some extent the influence it can have on regulatory practice. At the end of the day, the patient population is a single species. Now, you know, as a toxicologist, I would love to have that luxury of just looking at one species but there isn't a lot of justification for multiple guidelines when you're dealing with a single population.

Harmonization depends on engagement, and I'll talk more about trying to facilitate engagements certainly in the future.

Using international guidelines in smaller jurisdictions is common although there are some jurisdictions that do tend for a variety of reasons, some of them more economic than scientific, to have local guidelines specific to their own population.

And I touch quickly on the future guideline development because I do think the international environment, particularly in pharmaceuticals is going to change in the next 10 to 20 years which will necessitate some changes in the way things are done.

Globalisation

- Pharmaceuticals are a truly global market
  - Top 4 pharmaceutical companies each have annual profits greater than total expenditure on pharmaceuticals by many smaller but prosperous developed nations
- With some few exceptions there is little justification for unique requirements in different jurisdictions
  - Variations in metabolic or other parameters between populations do occur but can generally be accommodated by appropriate clinical trial design or nonclinical studies

So globalization, you know, pharmaceuticals are truly a global industry. The top four pharmaceutical companies each have annual profits greater than the total expenditure on pharmaceuticals by many smaller but otherwise prosperous developed nations.

There are some exceptions. There are very few justifications for unique requirements in different jurisdictions. There are some population differences in metabolism, -- deficiencies and so on as an example of one and some differences in terms of -- metabolism and what have you but they tend to be able to be accommodated by an appropriate component in the clinical trial or by in vitro examination or other nonclinical studies. So they generally can be accommodated relatively easily within the overall package of clinical investigation and preclinical investigation.

Australia, like many jurisdictions, a small market

- Australian population 21 million (~7% of USA)
  - So a relatively small market
  - But high standard of living and health care
- Pharmaceutical Benefits Scheme subsidises medicines for all Australians
  - Current subsidy for non hospital pharmaceuticals US$ 6 billion pa
  - Total non hospital ~ $10 billion (~ US$500 per person pa)
  - So potentially profitable for the right drugs
- But net profit in 2007 for one company alone (Pfizer) was US$8 billion with revenues of $48 billion[1]
- Like so many smaller nations Australia does not have the market power to drive unique requirements
- More importantly, we do not generally see a need.
  - But do see a need to be engaged and involved

[1] Pfizer annual report 2007

So just looking at Australia specifically, which obviously here I have a little more familiarity with, we're a relatively small population, 21 million, approximately 7 percent of the United States. It's a relatively small market but the standard of living is high, and the expenditure on pharmaceuticals is about the same as throughout most of Europe, somewhat less than that per capita compared to the USA but it's got more to do with the drug subsidisation scheme and cost constraints rather than the nature of the pharmaceutical preparations used.

We have a Pharmaceutical Benefits Scheme which subsidies medicines for all Australians. The cost per item can be as low as $5 if you're on some sort of a welfare benefit or concession and about $32 per item maximum for the rest of the population. So the amount that we spend each year in terms of the subsidies is about 6 billion but then you need to add the personal contribution to that to get the total cost. It works out to something like about 10 billion a year for non-hospital based pharmaceuticals used.

If you compare that with something like the net profit for the one company, I'm sorry, Pfizer, I picked on you, but it just happened to be something I could find on the Internet, you know, Pfizer's profit last year was 8 billion from revenues of over 48 billion. Well, there's some countries that wouldn't have a GSP of that sort of size. So, you know, clearly the amount of buying power in Australia is insufficient to drive unique regulations.

Guideline Development

- Guidelines initially reflect the environment of those developing them:
  - Culture & politics both organisational and national
  - Experiences
  - Skill sets and corporate knowledge available
  - Legislative requirements
- Broad consultation ensures
  - Agency and other perspectives are tested openly
  - Resources of industry and academia are utilised
  - Broad ownership of guidelines is established

But more importantly, we don't actually see a need for most guidelines to be altered or to be unique for Australia's conditions. There are some perhaps related to environmental issues to do with stability of drugs and so on, and there are a few others that we don't adopt for a variety of reasons, often procedural but in general, it's fairly small.

When guidelines are developed they initially reflect the environment of those countries that are actually developing them. In culture and politics, both the organizational politics and culture and national culture and politics will drive a lot of the issues that come into a guideline.

Sara Goldkind mentioned in her talk that the focus is on the benefit to or the risk to the individual patient in the trial. Some cultures may have a slightly different perspective on that. So, you know, we shouldn't assume that the way we view it will be viewed the same way by every country that might have an interest in a particular guideline.

Skill sets and corporate knowledge available does vary very widely particularly in the smaller countries and the very small jurisdictions and they do rely on guidelines generated by areas like FDA and the EMEA, to provide support.

Broad consultation ensures that the Agency perspectives are tested openly, and forums like this are a tremendous way of getting open testing of paradigms that are driving a particular guideline. The fact that the transcripts are available on the Internet enables all of the discussions, those that can be heard on these microphones at any rate, to be shared around the world and I think that's a very positive thing.

Avenues for International Cooperation on Guidelines

- ICH
  - An important focus for dialogue between industry and the Key Regulatory Bodies of Europe, Japan and North America
  - Limited membership which currently **excludes**:
    - Regulators for the majority of the worlds population
    - Major developing nations with emerging Pharma industries
  - Little or no opportunity for engagement by non members
  - Australia has little involvement with ICH and does not adopt ICH guidelines directly - but
  - usually picked up via EMEA Guidelines and routinely considered
- Bilateral engagement – EMEA, FDA
  - EMEA engagement somewhat more formal in that Australia is routinely invited to comment on new guidelines under development

Australia certainly sees a need to engage in guideline development. It provides us, if you like, an inside view of the philosophies and the underlying data sets that are driving that, some of which may not be available to us through other sources.

It also creates broad ownership of the guidelines once they are actually established, and from industry's perspective, the more countries that are involved in the development of a guideline, the more agencies that actually have input into it, the greater their ownership is of the guideline when it comes out, the easier it is to actually get them to stick to that guideline and not go out on a tangent.

So what are the avenues for international cooperation on the guidelines?

Well, the ICH is an obvious one but it really only represents North America, Europe and Japan. So the ICH does not have representation for the regulators that regulate the bulk of the world's populations. Major developing nations have emerging PhRMA industries. The per capita consumption of pharmaceuticals is rising very rapidly, and I wonder whether in 10 to 20 years time, whether that is actually going to be sustainable. I gather the ICH is actually aware of this issue and is considering ways to engage more broadly but I think it's going to be essential in the future.

Australia tends to draw most of its guidelines from the EMEA, and it's not any reflection on the FDA. It's got to do with bilateral arrangements that we have, but we do seek to engage with the FDA as much as we possibly can.

Nation Specific Guidelines

- Generally considered undesirable in Australia as they:
  - Act as a barrier to free trade in pharmaceuticals
  - Tend to delay introduction of new medicines
  - Are resource intensive if done well
  - Are counterproductive if not done well
  - Difficult to justify scientifically
    - With some specific exceptions

Australia does not believe that nation specific guidelines are desirable. They act as a barrier to free trade and the whole Pharmaceutical Benefits Scheme actually depends on competition and the ability to purchase drugs that provide a particular indication at the lowest per capita cost for a given event. So we have significant reasons for not wanting to create barriers. It tends to delay the introduction of new medicines. It's resource intensive to develop good guidelines. Well, just look at this meeting and the work that's actually gone into it, how much work will come out of it in terms of, you know, the material posted on the Internet and so on, and smaller jurisdictions do not have those resources.

If they're not done well, they're counterproductive because it just creates confusion in the marketplace. They're also difficult to justify scientifically, although there are some smaller exceptions as I mentioned earlier.

Use of FDA, EMEA, ICH guidelines in Australia

- Guidelines provide conceptual frameworks for the knowledgeable.
- Australia has a flexible approach to the use of guidelines, essentially using the best available, or a combination, for any given circumstance regardless of origin.
- Formal adoption only of EMEA guidelines which are the default in most cases

In Australia, we take guidelines as simply presenting a conceptual framework within which to examine and evaluate data presented to us. We have a very flexible approach. We take guidelines from anywhere, you know, if there are a selection of guidelines and one is better, more recent, better documented, we'll use that in preference to one that's less useful to us or inappropriate to a specific circumstance.

We do formally adopt only EMEA guidelines, and I'll talk a little bit about why that is, and we generally adopt most of them although we do actually post on our Internet lists of guidelines we haven't adopted for various reasons.

Why EMEA Guideline

- The multinational nature of the EU and EMEA tends to lead to guidelines with maximal input across stakeholder sectors.
- Scientific capacity, like that of the FDA, is high although more dispersed.
- EMEA routinely seeks input from Australia on all new guidelines (semi formal arrangement)
- Need to pick one set rather than mix and match
  - Simpler and more transparent to internal and external stakeholders
  - But confusion remains due to differences between regulatory jurisdictions (eg FIH nonclinical data requirements)
- An extensive set of Guidelines covering most circumstances

Why EMEA? The multinational nature of the EU and EMEA tends to lead to guidelines with maximal input across stakeholder sectors, and that's got more to do with a multiplicity of nation states being involved.

The scientific capacity, like the FDA, is high although it is more dispersed and there are some issues there for the EMEA in particular. The EMEA routinely seeks input from Australia on all new guidelines. It's not so much a formal bilateral arrangement, but some of their documentation regarding the guideline development actually sets out that Australia should be consulted at the draft stage in every case. So for no other reason than that, we tend to lean more towards the EMEA Guidelines. But, you know, if there's a defficiency in those Guidelines, or there is that doesn't exists, then we'll use the FDA Guidelines and if the FDA Guidelines is similar to the EMEA, we'll look at both. You know, it's not that we ignore them. It's just that in terms of giving guidance to industry and what they should think about in trials in Australia or presenting an eCTD submission to Australia, we try to be consistent by sticking with one consistent set of guidelines and that at the moment is the EMEA.

The Process of adoption

- All EMEA guidelines are considered both technically, as drafts, and for adoption as finals
- Industry, internal and other external stakeholders in Australia and New Zealand are provided opportunity to comment
- Process related guidelines are generally not considered
- If adopted specific aspects not relevant to Australia or specific aspects requiring amendment for Australian circumstances are annotated (eg climatic issues around stability)
- Very few Australian specific requirements
- Some technical guidelines not adopted

We look at them as drafts and at that stage, we actually have wide consultation with local stakeholders, industry, interested patient groups, academics. We also formally invite New Zealand to comment because if we do, in fact, adopt a guideline, it has some potential impact on the New Zealand environment. So that's really a courtesy that we extend.

Generally we don't adopt guidelines related to procedure or to process and how to get it through the system.

If we do adopt them, specific aspects not relevant to Australia which is often procedural or aspects requiring amendments for specific Australian circumstances, are annotated on our website when we put them up. We have very few specific Australian requirements but there are some. There are quite a number of guidelines which are simply not adopted because they're not relevant to the Australian environment.

Guidelines Not Adopted

some examples[1]

- Guideline on the Acceptability of Invented Names for Human Medicinal Products processed through the Centralised Procedure
- Guideline on the Acceptability of invented names for human medicinal products processed through the centralised procedure
- Core SPC for Human Normal Immunoglobulin for Subcutaneous and Intramuscular Use
- Core SPC for Human Anti-D Immunoglobulin for Intravenous and / or Intramuscular Use
- Note for Guidance on Core SPC for Human Immunoglobulin for Intravenous Administration (IVIg)
- Core SPC for Human Plasma Derived and Recombinant Coagulation Factor VIII Products
  Core SPC for Human Plasma Derived and Recombinant Coagulation Factor IX Products
- Core SPC for Human Plasma Derived Antithrombin
- Note for Guidance on the Warning on Transmissible Agents in Summary of Product Characteristics (SPCs) and
- Package leaflets for Plasma-Derived Medicinal Products
- CPMP Position Statement on the Quality of Water used in the production of Vaccines for parenteral use
  Guideline on Requirements for Plasma Master File (PMF) Certification
- Points to Consider on the Manufacture and Quality Control of Somatic Cell Therapy Medicinal Products
- Guideline on Development and Manufacture of Lentiviral Vectors
- CPMP Position Statement on Creutzfeldt-Jakob Disease and plasma-derived and urine-derived medicinal products
- Note for Guidance on Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs
- Note For Guidance on Good Manufacturing Practice for Active Pharmaceutical Ingredients
- NB. This guideline has not been adopted in this format. Sponsors should refer to the Therapeutic Goods (Manufacturing Principles) Determination No. 1 of 2002 on Active Pharmaceutical Ingredients , which was adopted by the TGA with effect from 29 May 2002.
- Rapid Alert System (RAS) in Pharmacovigilance
- Notice to Marketing Authorisation Holders: Pharmacovigiliance Guidelines

[1]http://www.tga.gov.au/docs/html/euguidenotad.htm

Highlighted in green, however it comes up on the web I guess, but this is just an example of guidelines that we've not adopted and it's a relatively small set. A lot of them relate to blood supply. The Australian blood supply is very highly regulated. It's all volunteer donors. It's all collected by the Red Cross and I believe there are some other groups doing it now but because it's got such a highly controlled and well managed environment, a lot of the guidelines related to blood supply just aren't relevant to us.

Guidelines adopted with notation

- CPMP/ICH/300/95 **Note for Guidance on Duration of Chronic Toxicity Testing in Animals (Rodent and Non-rodent Toxicity Testing)**
  Published: TGA Internet site with amendment effective: 30 August 2001
  See also: CPMP/SWP/1042/99 (Adopted by TGA 23 February 2001)

- **Adopted by the TGA with the following notation**:
- It should be noted that while the ICH guidance recommends 9-month chronic toxicity studies in non-rodents, the TGA considers 9-month studies in non-rodents acceptable for most drug development programs, shorter studies may be equally acceptable in some circumstances and longer studies may be more appropriate in others, as follows:
- Six-month studies may be acceptable for indications of chronic conditions associated with short-term, intermittent drug exposure, such as bacterial infections, migraine, erectile dysfunction, and herpes.
- Six-month studies may be acceptable for drugs intended for indications for life-threatening diseases for which substantial long-term human clinical data are available, such as cancer chemotherapy in advanced disease or in adjuvant use.
- Twelve-month studies may be more appropriate for chronically used drugs to be approved on the basis of short-term clinical trials employing efficacy surrogate markers where safety data from humans are limited to short-term exposure, such as some acquired immunodeficiency syndrome (AIDS) therapies.
- Twelve-month studies may be more appropriate for new molecular entities acting at new molecular targets where post-marketing experience is not available for the pharmacological class. Thus, the therapeutic is the first in a pharmacological class for which there is limited human or animal experience on its long-term toxic potential.

http://www.tga.gov.au/docs/html/euguide/euad_nonc.htm

So this is an example of a guidelines that has been adopted with annotations, just describing how Australia used this particular preclinical guideline. I selected it because it was in my area and not for any other purpose but just as an illustrative example. And the only point I really make here is that if we do have some issues with a particular guideline, we document them fairly well on the Internet and if there, you know, particularly if you see a guideline that hasn't been adopted and it has relevance to a particular product you want to bring to the Australian market, the best thing is just to ring up and have a chat or, you know, come to a meeting. It's a nice place to visit. We need tourist trade. So come and ask us what you would like us to have you do in that situation.

The Future

- Within 10 to 20 years the pharmaceutical market in India and China may be worth as much or more than the entire world sales currently ?
  - Current average per capita expenditure on pharmaceuticals in Europe is ~ US$500 [1]
  - X 2 billion + population ~ US $1 trillion
- A growing domestic pharmaceutical industry in those countries will seek to take some of this market
- Clinical and non clinical development capacity is emerging rapidly in East and central Asia
- Better to engage in international guideline development earlier rather than later ?

1 DEPT OF HEALTH DISCUSSION PAPER: THE PHARMACEUTICAL PRICE REGULATION SCHEME (SEPT 2003). Comments from the Association of the British Pharmaceutical Industry 27 Oct, 2003

In the future, I think, you know, within 10 to 20 years, the pharmaceutical markets in India and China particularly, but all of Eastern and Central Asia, is going to grow enormously, and it may well be worth more than the entire world sales currently. If their current rate of growth continues and, you know, who knows, but if it does, and they would have an average per capital expenditure similar to that in Europe, you know, a couple of billion people plus, getting $500 a head in drugs a year, boy, that's a lot of money.

So I think the growing pharmaceutical industry in those countries is starting to grow quite markedly. There's a lot of capacity going into preclinical testing, a lot of clinical trials are being run in these markets. I think it's only a matter of time before significant pharmaceutical industries start to emerge from those countries, and I will say they already have a significant pharmaceutical industry.

I think there's going to be a need to better engage those countries. There's not much point having a guideline in just one country if most of the market is elsewhere. You know, the market will drive the guidelines that industry needs to work with. So it's better to engage earlier and get better consistency across the world despite the fact that this is actually quite a complicated exercise. It does delay the development guidelines because there are far more stakeholders to engage but it will lead to a much more consistent and certain environment for industry. So I certainly think there's going to be a need for far less single nation guidelines and far more, you know, international guidelines.

Currently, having EMEA and the FDA both generating guidelines is actually quite puzzling in a sense because in terms of drug-induced liver injury, the EMEA has produced a nice guideline in terms of a preclinical and nonclinical investigation. We now have, you know, a clinical guideline from the FDA, where if it was only one agency developing all of them, well, they may not have have the resources necessarily in a given time to do both. So I don't see necessarily that it's a bad thing but it would be nice if there was greater engagement on these guidelines particularly across those two large agencies. So thank you very much. I hope I haven't offended too many people.

DR. SELIGMAN: Thank you very much. (Applause.)