



Leveraging Regulatory Opportunities for Biotech Development in the Asia-Pacific *Case Studies*

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Topics

- Review recent status for clinical development in the region
- Compare opportunity for conducting early biotech trials in Australia
- Review the special challenges for bringing complex biological products into clinical trials
- Discuss case studies for successful clinical trial strategies and experience in Australia

Challenges for Biotech / High-tech Products

- Biological or technically complex products need special attention in development compared to conventional, small molecule drugs
 - Experience in special requirements in manufacturing and control is essential
 - Case-by-case non-clinical strategies are needed
 - Particular understanding of regulatory expectations for data packages is crucial
- A robust regulatory system for clinical trials can offer both oversight AND opportunity

Regulatory Landscapes in the Asia-Pacific Region for Clinical Development

- Japan has a consolidated agency since 2004 - the Pharmaceuticals and Medical Devices Agency (PMDA)
 - Established to promote new drug development and approvals
 - Increasing acceptance of data from multi-national studies
 - Many clinical trial consultations are now held each year
 - PMDA accepted 508 clinical trial applications in 2007
- In Singapore, the Health Sciences Authority (HSA) granted about 250 clinical trial certificates in 2007
- The Korean FDA (KFDA) encourages pre-submission consultations to support clinical trial applications

Regulatory Landscapes in the Asia-Pacific Region for Clinical Development (cont)

- In Australia, the established regulatory system and authority (TGA) provides a strong environment for conducting clinical studies
 - These trials will support global development programs
 - TGA has experience with all types of products, including novel biological / biotech products and biosimilar medicines
- In accordance with ICH GCP, ethical review and approval is required in Australia and the Asia-Pacific countries
 - Ethics Committee review processes in Asia generally take from 1 to 4 months, with varying regulatory review times

Activity in the Asia-Pacific Region: New Listings of Clinical Trials (NIH site)

COUNTRY	2006	2007
Australia	278	266
Japan	158	180
Korea	156	177
Singapore	69	59
UK	460	437
USA	2,505	2,966

From: clinicaltrials.gov



Biological Product Opportunities in Australia

Australia made an early move in Biosimilars

- In addition to the well-established clinical trial system in Australia, there is also the TGA's extensive experience in biological product review and registration
- Omnitrope[®] (human growth hormone, Sandoz) – the first biosimilar product to gain registration
- First approval for Omnitrope[®] worldwide was granted in Australia - on the basis of an application to the TGA in September 2004
 - On the market in Australia 2 years ahead of any other country.....
- Australia follows the EU guidelines for the evaluation of biosimilar medicinal products

Clinical Trial Opportunity in Australia for Asian Companies

- Clinical data from Australian trials meet international GCP standards
- Australia offers the convenience of a nearby time-zone
- Accelerated access to the clinic is usually possible via the *Notification* (CTN) route
 - A first-in-man (FIM) study does not require investigational product to be manufactured in a GMP facility
 - Subsequent studies require GMP drug
- Caucasian subjects are available for Asian companies to conduct comparative studies on the potential impact of intrinsic factors such as differences in pharmacokinetic profiles or pharmacodynamic sensitivities

Advantages of the Australian CTN Scheme

- Covers studies from Phase 1 – Phase 3
- Based on approval by an Ethics Committee, supported as needed by scientific advisory groups, usually in 6-8 weeks
- CTN available to industry, not just academia
- No similar pathway exists in the major markets
 - All clinical trials in the USA and Europe must undergo regulatory agency review
 - Possible exceptions for investigator-initiated trials in some Asian countries
- **NOTE:** CTN route is not suitable for products representing high risks to subjects - these go through the CTX application

Comparing Clinical Trial Applications

- Approximate order for the amount of information and data required internationally in the clinical trial submission:
CTN (Australia) << CTA (EU) < CTX (Australia) < IND (USA)
- Review of a US IND application takes 30 calendar days, less than for a CTA, but a deficient IND is put on a formal CLINICAL HOLD by the US FDA (which has other major disadvantages)
- Within the Asia-Pacific region Japan, for example, follows a US IND application model with similar review time, but an IND application to the Korean FDA (KFDA) will enjoy a longer review period
- Timeframes favour the Australian CTN

Utilising the CTN Route - *Biologicals*

- Ethics Committees review the clinical study protocol.....
 - For biotech products, this includes highly technical CMC data, and non-standard pharm/tox studies
- Investigator’s Brochure – a crucial document, but a summary
- Use an integrated pre-clinical assessment to support and expedite ethical review of a trial
 - Detailed and critical evaluation of quality and safety documentation together, dealing with any “hot topics”
 - Assures a Company has taken the most diligent approach to protect subjects and gain useful clinical information

What are HOT CMC Issues with Biotech Products?

- Bioanalytical package should be robust even at Phase I
 - Purity / impurity profile of the active substance
 - Absence of process-related contaminants
 - Stability
- Quality of any biological materials used in manufacturing
 - Virus safety
 - TSE risk



What are HOT PHARMACOLOGY Issues with Biologics?

- Pharmacokinetics often more challenging for proteins, and not just at Phase I of clinical development
- Case study: Erbitux[®] (cetuximab)
 - ImClone Systems (subsidiary of Eli Lilly & Co and Bristol-Myers Squibb) sought two new indications for cetuximab in supplemental applications (sBLA's) to US FDA
 - Clinical studies for the new indications used material manufactured in Europe in partnership with Merck KGaA
 - CMC comparability concerns identified by FDA
 - Pharmacokinetic comparability not considered proven
 - Result: both sBLA's in early 2009 were found not approvable

What are HOT SAFETY Issues with Biologics?

- Estimation of safe starting dose in humans
 - Toxicology relevant?
 - Pharmacodynamics *versus* adverse pharmacological effects
- Probability of immunogenicity
 - 34/52 biopharmaceuticals elicit a humoral immune response (1% to 70% or more) Koren et al. Curr. Pharm. Biotech. 3, 349, 2002

How to Manage Risks?

- Be aware why the regulators may have concerns!
- Prepare a rationale for the trial based on comprehensive scientific data package that has been reviewed critically
 - Crucial for high tech/biotech products
- An *integrated pre-clinical assessment* can help by providing
 - Appropriate justifications for moving to the clinic
 - A strategy by which deficiencies can be corrected
 - Content for the relevant sections of a rational drug development plan, for management or due diligence

Case Study – Facilitating Ethics Committee Review for CTN

- A university-based research group developing a cancer vaccine for a first-in-man study
 - Complex biologic, not produced under GMP
 - Limited relevant animal immune response/safety data
 - Ethics Committee required expert opinion regarding quality (CMC) and immunology issues
 - Specialist assessment report was prepared to support the Ethics Committee review
 - Ethics approval was granted for the trial
 - CTN successfully submitted

Australian Clinical Trials - *Data that can travel*

- Clinical trials conducted in Australia can generate data suitable for submissions *worldwide*
 - TGA adopts ICH guidelines, as well as most guidances from the European Union
- Australian trials may represent regulatory advantages to Asian companies moving products from the local to global markets
 - Robust environment of oversight and compliance
 - Conducted in a largely Caucasian population
 - Conducted and reported in English (the “first language” of regulatory affairs in Europe and the USA)

Case Studies of Australian Clinical Data for Export...

- Case #1: European company with cell therapy agrees Phase I trial design with FDA – study in Australia under a CTX
 - Data suitable for IND submission and for later stage trials in Europe
- Case #2: US company with combination biologic/device product sets up sites in Australia to support their IND Phase II studies
 - CTN route used, data to be pooled with US data for statistical analysis for IND
 - Data became basis for CTA in Germany for next Phase II trial

Case Studies of Australian Clinical Data for Export...

- Case #3: US company with a monoclonal antibody product sets up Australian site for Phase I study, CTN route
 - Data will be included in both a CTA to be filed in the UK and in a Phase II IND submission
- Case #4: Australian company with novel delivery oncology product performed Phase I and Phase II studies in Australia, using the CTN route
 - Successfully opened an IND for Phase III trial to support registration in the US

Summary.....

- Australian companies should consider opportunities in Asia for clinical studies, especially to access Asian subjects and determine early if there are PK/PD differences
- Asian companies with biological products under development can benefit from the advantages of the Australian system for the timely conduct of clinical trials
 - Opportunity to gather PK/PD data in Caucasian subjects
 - Suitability of clinical data to support regulatory submissions in the major international markets
- Australia provides an established and sophisticated regulatory environment for development of both novel biologics and biosimilar medicines



Thank you!

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