

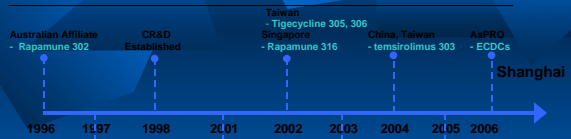
Research in the New World – Competition or Opportunity

Dr Timothy Nash

Retired, formerly Assistant Vice-President, Clinical Research, Asia Pacific, Wyeth Research



Wyeth CR&D Asia Pacific History



What's it about?

- Past experience in clinical research in Australia and Asia
- Impressions regarding Australian CR
- Information regarding Asian quality and costs
- A personal view from a pharma viewpoint

The Competition

In the 90's Australia had advantages for big pharma

- Streamlined Regulatory Process (CTN)
- Quality & Commitment to research commitment to numbers, timing and quality
- Relatively inexpensive compared to USA and EU

Clinical Research in Australia

- Regulatory process was a big advantage
 - CTN acknowledgement in 10days
 Compared to:
- Taiwan, 2-3 month assessment (6 weeks if IND)
- Korea 3 months assessment
- Hong Kong, 6 weeks, almost a CTN

BUT - Ethics approvals

- Submit June deadline for July approval, 4 sites, one protocol
- Often, no EC objections

BUT:

- Lawyer from each EC raises an objection, e.g. insurance level, indemnity wording, other.
In Victoria, one legal firm covers all hospitals for CT approvals, but each hospital has a different lawyer in the firm and, for one protocol, 4 different objections each taking months to answer
- Actual approval September to October, depending on lawyer



Clinical Research in Australia

- Regulatory process has been a big advantage
 - CTN acknowledgement in 10 days

BUT

- Taiwan, 2-3 month assessment 6 weeks if IND
- Korea 3 months assessment
- Hong Kong, 6 weeks, almost a CTN



Clinical Research in Australia

RESULT:

- Previous advantage diminished



An Australian National Research Ethics approval process has been discussed:

- Could it ever happen?
- Limited to multi-centre clinical trials?
- Can the assembled company influence such a move?



Clinical Research Issues

- **QUALITY & COMMITMENT TO RESEARCH**

commitment to numbers, timing and quality

- **NUMBERS:** pharma absolutely, must, enrol on time

To enrol on time, one needs to start on time

- **QUALITY** is not just good data,

it is certified, training to auditing, good data



Clinical Research Issues

NUMBERS: post menopausal breast cancer study
premature closure for fertility after 20 months

Australia, 14 sites 8 patients committed	China, 10 sites 20 patients committed
11 sites, 0, 1, patients	0 sites <5 patients
1 site, 3 patients	7 sites 5-12 patients
2 sites, 7, 9 patients	3 sites 13-20+ patients
Total commitment =80	Total commitment =140
Total enrolled = 26	Total enrolled = 110



Clinical Research Issues

TIMING/COMMITMENT

- Date of Ethics approval: 08 December 2004
- Requests for SIVs
 - December 14th 04
 - January, any date 05
 - February any date 05
- Date of Site Initiation: 09 March 2005
- Date Screening started: April 2005
- Date of Study Termination: April 2005



Clinical Research Issues

CHINA START UP (SAME STUDY AS PREVIOUS)

- Regulatory approval February
- EC approval 2 weeks later
- SIV 1 week later
- 14 enrolments, 2 sites



Clinical Research Issues

COSTS:

- Per patient payments "grants": actual costs have increased to around dollar equivalence (USD:AUD),
- Monitoring: actual costs have risen enormously because of success in the 90's, our CRA costs now are comparable to US
- Administrative: ICH guidelines clearly state that investigator is responsible for investigation.



Clinical Research Issues

QUALITY

- Pharmaceutical research is the most regulated industry on earth
- For a study to be used for new drug approval the clinical research group needs to demonstrate:
 - Every person contributing has the qualifications to do his job
 - Every person has the training to do the job
 - Training is demonstrated by attendance at training sessions incl. GCP
 - 25 minutes to review the molecule is not enough to satisfy authorities.



Clinical Research in Australia

- The investigator is responsible for carrying out the investigation. (See recent FDA guidance.)
- Company/CRO is responsible for monitoring investigator compliance



Clinical Research in Asia

CHINA INVESTIGATORS

- Many post graduate education overseas, (includes US, UK, Germany, Australia)
- Most Senior Medical people speak English
- Huge Clinics 2-3,000 beds; daily outpatient clinics numbering 100s per specialty. (7-9,000 OPs/day)
- Concentration of suitable patients in few hands
- Infrastructure - coordinators, pharmacists, records
- Almost Universally EVERYONE attends all the SIV, AND it lasts 4+hours



Clinical Research in Australia/Asia

QUALITY

- ICH E6 – GCP set the minimum standard for global drug development
- Many Asian countries have ICH based national GCP guidelines
- Emphasis on quality by governments in the regions:
 - China – GCP courses sponsored by the SFDA and Ministry of Science and Technology (investigators actually attend these courses)
 - Thailand – Annual GCP workshops sponsored by the Thai FDA



Regulatory Timelines

Significant reduction in IND timelines in many Asian countries over the past 5 years:

- Hong Kong, SAR	4 – 6 weeks
- Korea	30 working days
-Taiwan	18 working days
- Singapore	30 working days
- China	145 working days



China Regulatory

- Clinical Trial Certificate is necessary
- 4 changes in CTC regulations in last 10 years
- Currently considering further change
- Currently "IND" system, submitted in Chinese
 - CMC (inc GMP certificate for site of manufacture)
 - Toxicology
 - Pre-clinical
 - Phase 1, 2, data and sample protocols
 - SAMPLES! Reference Standard & analytical methods
- Approval for molecule/formulation, multiple trials approved for synopses submitted



Evaluation & Approval Timelines - China

SFDA Dossier Receiving Office: 30 days
(assesses completeness of dossier)

Simultaneously submit samples for testing, same lot as for study

CDE technical evaluation for CTA: 60-90 days

SFDA approval: 20 days

Total = approx. 145 days



Quality in Asia

Evaluability in Antibiotic Registration study

Evaluability	Overall (global)	India	China
By country			
Clinically evaluable	83%	87%	90%
Microbiologically evaluable	60%	50%	70%

Cost, country	Overall (global)	India	China
Per monitored patient			
Total USD monitoring & grants	US\$14000	US\$3500	US\$1800
Per Monitored micro evaluable patient	US\$23000	US\$7000	US\$2600



China Costs per subject

- Global Studies • US\$1800
- Local Studies • US\$1200
- Phase I/BE • US\$3500
- Phase II/III • US\$1100



Asian Cost per Patient

in USD	Bowel function	Bowel function	Calcium metab	Kinase inhib	Abdo infectn	Kinase inhib	Kinase inhib
Australia	9,641	10,094		16,069	14,232		
China	1,361		1,274	2,736	2,592	7,125	7,364
Hong Kong	3,704			8,973			
Korea	7,178	7,178	3,732	17,226	6,699		
Taiwan	5,884		2,615	13,403	4,904		
United States	13,940	13,871		21,658	23,612	19,087	20,465

Asian Patients Enrolled

USD	bowel	bowel	Osteoporosis	kinase	Anti-biotic	kinase	kinase
Australia	13	2		9	8		
China	3		253	40	52	28	20
Hong Kong	3			5			
Korea	82	3	134	28	40		
Taiwan	5		103	1	22		

China Studies

- Average 27 days for EC approval
- Review fees average US\$500
- 69% EC approvals are individual sites
- 31% EC approvals are central

Therapeutic Areas

- Cardiovascular
- Diabetes
- Oncology
- Neuroscience
- Infectious disease

Consent in Asia

- "family" affair, often requires 48 hours or more to involve the whole family.
- Almost invariably handled by investigator personally or sub-investigator
- Ph 2 serious UTI study in taiwan

Why consent?

- Element of trust (big clinics, important professors)
- Element of "free treatment"
- Availability of investigator to personally supervise participants

Having Alluded to the bad bits:

- There have been many excellent Wyeth experiences in Australia.
- Renal transplant formed the basis for Wyeth Research in Australia
- Vaccines phase 1 and 2 studies have been highly successful
- Perhaps it's all about only doing studies where researchers are keenly committed?
(not a local study for the 6th PPI)

The Opportunity

Co-operative Research Agreements

- Many institutions have signed agreements to contribute to early phase global studies
- Key universities e.g. Hong Kong
- Key clinics e.g. Siriraj, 301 PLA hospital
- Agree to have investigator evaluate protocol within 2-3 weeks
--- default is participation

Cooperation with China

- For your regimens where you think you can make a difference:
- If you have 40 patients in, say, RA; there will be clinics that have 100 suitable patients a week
- If you are committed, there may be opportunities for collaboration

Some local problems

Multi-centre Clinical Research in Australia

- Increasing costs of research staff
- Infrastructure costs
- Ability to keep on experienced staff between studies
- EC requests – indemnity, insurance

- Increasing costs/Ability of investigator to deliver?

Early Phase Pharma Clinical Research in Australia

- It is a mutually beneficial relationship that requires mutual respect for each other's objectives
- There is no commercial or other benefit in the relationship – just data, timing and quality – without this there is less advantage in conducting studies in Australia.