Regulatory Challenges of Global Drug Development in Oncology

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Topics

- General global R&D issues
- Regulatory issues with global oncology drug development
- US FDA initiatives in oncology
- International comparisons
- Do emerging markets have a role in global drug development?
Pharmaceutical R&D Environment

- Industry (discovery, development, commercialization)
- Academia (discovery, some development)
- Government Agencies (NIH, NCI)
- Regulatory Authorities
- ICH
- Outsourcing industry (CRO, SMO, etc.)
- Patients, activists
- Others (press, analysts, investors, reimbursement authorities, etc.)
Consequences

Need to bring safe, efficacious, and high quality medicines to patients as fast as possible:

1. More study subjects
2. More trial providers
3. Higher R&D budgets
Specifics of Oncology Drug Development

- Life threatening condition
- Willingness to accept greater risks or side effects by patients, researchers, and authorities
- Important public health issue (especially in developed markets)
- Product may qualify for orphan status
- Huge R&D investments
- Scientific advances
- Few really effective treatment modalities
Access to Unapproved Drugs

- Non-life saving drugs
  - Participation in clinical trials
- Life saving drugs
  - Participation in clinical trials
  - Various country specific mechanisms
US FDA Initiatives With Oncology Drug Development

- **Shorten approval times** for cancer treatments by recognizing that tumor shrinkage is often an early indicator of a treatment's effectiveness.

- **Make promising cancer therapies available** to cancer patients in the US even before the product is approved in the United States.
US FDA Initiatives With Oncology Drug Development (Cont’d)

• Improve the therapy review process by ensuring that all FDA cancer-therapy advisory committee meetings include an ad hoc member who has personal experience with the illness for which a new product is being considered

• Make it easier for investigators to test new uses for cancer therapies already on the market
**Access to Unapproved Drugs - USA**

- Participation in clinical trials
- Special (compassionate) exemption (when patient does not meet protocol eligibility criteria)
- Emergency (single patient) IND
- Treatment IND (during NDA review)
Access to Unapproved Drugs - Europe

• No EU procedure
• Each member state defines its own rules (under Directive 89/341/EEC)
  – Compassionate use available in all member states, but processes, responsibilities, and other administrative details vary from state to state
Access to Unapproved Drugs – Europe
(Cont’d)

– France – (Temporary Authorization for Use)
  • Therapeutic Use Protocol required
  • No informed consent needed
  • Products reimbursed by the French Social Security
  • SPC and PIL issued
  • One year period (renewable)

– UK – Named Patient Access
– Germany – only through clinical trials
– Sweden – compassionate and named patient use
Canada - Special Access Programme (SAP)

- Formerly called the Emergency Drug Release Programme
- Access to non-marketed drugs to practitioners treating patients with serious or life-threatening conditions when conventional therapies have failed, are unsuitable, are unavailable or offer limited options
Australia – Special Access Scheme (SAS)

- Requested by the physician
- Notification of the TGA only (no approval for Category A: very seriously ill patients)
- Includes experimental and investigational products
- Informed consent required
- All responsibility lies with the physician
Japan – Named Patient Access

- Identify the patient(s)
- Physician assumes responsibility
- Drug should be approved in the exporting country
US – Fast Track Drug Development Program

- FDAMA, Section 506
  - Serious or life-threatening condition
  - Potential to address an unmet medical need
  - Development plan evaluates that potential

The fast track designation is given to the program (drug + condition + specific indication), not to the drug itself!
EMEA Position on Accelerated Reviews

- Exceptional cases defined by three cumulative criteria:
  - the seriousness of the disease to be treated (e.g. heavy disabling or life-threatening diseases such as AIDS, cancer...)
  - the absence or insufficiency of an appropriate alternative therapeutic approach
  - the anticipation of high therapeutic benefit

- Savings of 2-3 months
Canada – Accelerated Review

• Priority Review Process
  – allows for a faster review to make available promising drug products for life-threatening or severely debilitating conditions, such as cancer, AIDS, or Parkinson's Disease
  – a ten page summary of the application needed to submit for qualification
  – 6 months review anticipated, but usually comes closer to 12 months
Australia – Priority Review Process

- Not a true fast-track
- They will review each info as it arrives to the TGA
- No guarantee for a faster review
- 5-10 pages product summary to be submitted for the TGA decision
- Occasionally, very fast reviews
- A new (real) priority system is currently under consideration
Japan – Priority Review

- Orphan drugs may get priority attention
- Drugs with the following characteristics:
  - Target indication is severe
  - Definitely superior efficacy and safety
  - Different and innovative mode of action
- Also products in high public demand and under severe external pressures
  - Patients – Viagra
  - KOLs - old oncology products not available in Japan but marketed for years elsewhere
- Review time: 9-12 months
Practical Difficulties in Conducting NCE Clinical Trials in the Emerging Markets

• Regulatory
  – US FDA specific requirements not easily accepted abroad (Form 1572)
  – IND versus non-IND
  – Export waivers
  – Detailed and complicated CTA requirements in some markets
Practical Difficulties in Conducting NCE Clinical Trials in the Emerging Markets (Cont’d)

- **Regulatory** (Cont’d)
  - CMC requirements
  - Need for a CFS from one or more countries
  - Frequent changes of regulations
  - Regulations often non-transparent
Practical Difficulties in Conducting Clinical Trials in the Emerging Markets (Cont’d)

- General
  - Translations
  - Comparators
  - Adverse event reporting
  - Cultural (patient-physician relationship)
Practical Difficulties in Conducting Clinical Trials in the Emerging Markets (Cont’d)

- General (Cont’d)
  - availability of experienced local staff
  - distance from sponsor’s main office
  - patent protection issues
  - political instability in some markets
International Regulatory Issues With Oncology Drug Development

• Diverse regulatory sophistication
  – Various mechanisms for access to unapproved drugs
  – More regulatory obstacles for early access with few data in emerging than in the major markets
  – CFS often still required for CTA approvals
  – Limited (or non-existent) availability of written regulations in a number of countries
  – Non-transparency of the regulatory systems
International Regulatory Issues With Oncology Drug Development (Cont’d)

• Cultural difficulties
  – Cancer diagnosis not always shared with patients (which complicates Informed Consents)
  – Different treatment philosophy:
    • West: highest effective dose that can be tolerated
    • Japan: tolerated dose with resultant effect
    • Consequence: potential for lower doses in Japan
    • Role of traditional Chinese and other herbal medicine (Asia in general)
  – Requirement for ethnical data (bridging studies?)
Why Are the Emerging Markets Important for Clinical Cancer Research?

• New patient pools
• Large number of available study subjects
• Highly motivated research teams
• Presence of certain cancer types
• Treatment naïve patients
• Ability to collect data on ethnical differences
Pre-trial Study Site Assessments

- Standards of local medical practice
- Availability of diagnostic methods and equipment for:
  - Initial cancer diagnosis
  - Assessment of changes in tumor size
- On-site availability of all concomitant medications as per the trial protocol (example: standard pre-medication)
Pre-trial Study Site Assessments

- Local regulations on export of biological samples to the sponsor or central lab facility
- Ability to participate in trials based on scientifically advanced areas:
  - Gene therapy
  - Tumor vaccines
  - Molecularly targeted agents
Conclusions

- US institutions (FDA, NIH, NCI) lead and define novel developments in cancer research
- Various mechanisms for early access, followed with post-marketing obligations
- International markets offer a number of opportunities in cancer clinical research
- Careful assessment of each site required before decision can be taken
Conclusions

- Investigators around the world are eager to participate in global oncology trials
- Good access to motivated patients
- Industry experience excellent if proper steps taken in advance and during the trials
- Country specific expertise mandatory
- Need to continue helping local authorities adjust their regulatory environment to allow high quality clinical research in international markets