Pharmacovigilance in Asia: The China Perspectives

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Agenda

• China regulatory agency
• Overview of pharmacovigilance regulations in China
• Pre-approval safety assessment
• Post-marketing safety monitoring
• Challenges facing China State Food & Drug Administration (SFDA) & global pharmaceutical companies in China
• Future directions

China regulatory agency

SFDA
(State Food and Drug Administration)

Technical supporting institutes

Dept. of Drug Registration
Dept. of Medical Device Supervision
Dept. Drug Safety & Inspection
Bureau of Investigation & Enforcement
Dept. of Policy & Regulations
Dept. of Food License
Dept. of Food Safety Supervision
Dept. of International Cooperation

CDE
(Center for Drug Evaluation)

SPC
(State Pharmacopoeia Commission)

NICPB
(National Institute for the Control of Pharmaceutical and Biological Products)

CDR
(Center for Drug Re-evaluation)

CCD
(Certification Committee for Drugs)

CMDE
(Center for Medical Device Evaluation)
Overview of Pharmacovigilance practice in China

• Still evolving
• Pre-approval safety assessment conducted by Center of Drug Evaluation (CDE)
  – Emphasis on Chinese patient safety data
  – Risk Management Plan (RMP) requirement for both clinical development and for New Drug Approval
• Post-approval safety monitoring conducted by Center of Drug Re-evaluation (CDR), National & Regional Centers of Adverse Drug Reaction Monitoring

China Registration Trial

<table>
<thead>
<tr>
<th>Category 1</th>
<th>Requirements</th>
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<td>(New chemical entity never marketed in any country)</td>
<td>• Cases of patients should meet the statistical requirement and the minimal cases required.</td>
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<td></td>
<td>• The minimal cases (trial group) are:</td>
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<tr>
<td></td>
<td>20-30 for Ph 1</td>
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<tr>
<td></td>
<td>100 for Ph 2</td>
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<td>300 for Ph 3</td>
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<table>
<thead>
<tr>
<th>Category 3</th>
<th>Drug marketed outside of China</th>
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<tr>
<td></td>
<td>• human PK study</td>
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<td>• randomized comparative clinical trial on at least 100 pairs of subjects (chemical drug)</td>
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Pre-approval safety assessment

• Chinese patient safety data from SFDA certified or accredited centers required
• Minimum 300-patient requirement on biologic treatment
• Cumulative review of all safety data of the investigational product in China useful in our experience
• China label usually follows US label (Black box warning) rather than EU Label

Clinical trial SAE Submission

• Sponsor should report Serious Adverse Events (SAEs) to the Registration Department of State Food Drug Administration (SFDA) in a timely manner
• Sponsor may have reporting requirement to regional center of ADR monitoring for marketed products
• For an international multi-center clinical study, foreign Suspected Unexpected Serious Adverse Reactions (SUSARs) associated with the study drug should be submitted to SFDA in a timely manner
• Emphasis on China SAE reports and therefore different from expedited reporting of all SUSARs to FDA and EU
Risk Management Plan

• Regulations of Special Examination and Approval in New Drug Registration issued in January 2009
  – A risk control and implementation plan (or risk management plan) required for both clinical trials (Clinical trial application or CTA) and production (new drug application or NDA).
  – Risk control plan mainly refers to precaution and prevention measures established against those potential risks during the clinical use of the new drug.

• The submission of developmental risk management plan is not required for clinical trial application in US and EU, reflecting a more open approach to IND application

Post-marketing safety surveillance

• Challenging because of lack of active post-marketing safety surveillance program - epidemiology/pharmaco-epidemiology data/large safety studies

• Relative short history of spontaneous Adverse Drug Reaction (ADR) reporting compared to US and EU
  – The establishment of the CDR in 1999
Laws & Regulations (1)

- The Drug Administration Law issued in 1984 (Article 71):
- Drug manufacturer, distributor & medical institutes to monitor & report ADR to the relevant regional ADR monitoring center
- For serious ADRs, SFDA may suspend production, distribution & use of the drug and SFDA will arrange assessment in 5 days & make final decision within 15 days

Laws and Regulations (2)

- Regulation for the Administration of Adverse Drug Reaction Reporting and Monitoring Issued by SFDA with Ministry Of Health (MOH) in 1999.
- Provided further details on the reporting requirements with online reporting using
  - ADR/ADE reporting form
  - Cluster ADR/ADE reporting form
  - ADR/ADE periodic reporting form
CDR & NCADRM

- In 1999, CDR was established and merged with the National Center for ADR Monitoring (NCADRM)
- CDR: providing technical support to nationwide pharmacovigilance of drug and device, formulating & revising National essential drug list, Over the Counter drug use, public education and training
- NCADRM: collecting, collating, evaluating and analyzing ADR reports nationwide, providing support to the regional ADR monitoring centers, publishing safety bulletins and journals and working with WHO Collaborating Center for International Drug Monitoring
Spontaneous ADR reporting process

- Manufacturers
- Distributors
- Healthcare Institutions

New / serious 15 days
Death timely ≤15 days
Other each quarter

Regional centers

New /serious 3 days
Other each quarter

Local FDA/Health Bureaus

National Center

WHO

Number of ADR reports (1999-2009)

- 1999: 0
- 2000: 0
- 2001: 0
- 2002: 0
- 2003: 0
- 2004: 0
- 2005: 0
- 2006: 2000
- 2007: 20000
- 2008: 40000
- 2009: 70000
Spontaneous ADR reporting

- Submission of spontaneous reports to regional ADR center
  - Death cases should be submitted in a timely manner
  - Serious and / or Unexpected AEs should be reported within 15 calendar days
  - Non-serious expected AEs should be reported within 3 months (Within 5 years of Import Drug Permit for imported product & New Drug Monitoring Period and for Locally Manufactured Products)
- Submission of foreign Serious and / or Unexpected ADRs associated with imported drugs in China to NCADRM

Challenges for China Regulatory Agency

- Improving post-marketing safety monitoring but signal detection still challenging
- Limited resources
  - <100 staff in CDR/NCADRM
  - >3,500 drug companies (domestic and global companies)
  - Approx. 190,000 domestic drugs & 8000 foreign drugs with >100 new drugs approved each year (imported drugs, locally manufactured drugs & Chinese traditional Medicine)
- Lack of a centralized national safety data bases for all AE reports with no automatic data mining tools
- Although rapid increase in reports, yet mostly from medical institutions and mostly non-serious/expected ADRs, often with incomplete information
Challenges for global pharmaceutical companies

- Lack of CIOMS/ICH harmonization with different reporting forms and timeline
- Lower awareness of public regarding AE reporting
- Misconceptions of the public requiring further educational effort
  - Interpretation of spontaneous AEs as definite ADR
  - Causality assessment appears to be based on only temporal relationship and other factors may not be considered (confounding factors or more likely alternative causes)
  - Focus on absolute number of AEs rather than reporting frequency and the benefit:risk profile of the drug

Future Directions

- SFDA published 2009 Annual Report for National ADR Monitoring for the first time, confirming the commitment to strengthen postmarketing safety surveillance
- New regulations are being drafted to require industry to conduct post-marketing safety surveillance program, specify reporting timeline of spontaneous ADR and Clinical trial SAE reporting
- Ongoing considerations of improving risk communication with dissemination of new safety information, modernizing the National safety database, initiation of PV inspection and adoption of MedDRA
- Harmonization with CIOMS/ICH will take some time for the domestic companies to catch up with global standard
References (in Chinese)

- The Drug Administration Law
- Regulation for the Administration of Adverse Drug Reaction Reporting and Monitoring
- 2009 Annual Report of for National ADR Monitoring
- Rules governing the registration and clinical trial of foreign drug(s) in china
- GCP

Thanks for your attention!

Q & A?