Issues on Acceptance of Foreign Clinical Data in Europe from a Regulatory Perspective

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Outline of Presentation

- European regulatory system
- General considerations in the assessment of foreign data
- Examples from applications
- Conclusion
The European regulatory system
The European Union (EU)
The European Regulatory System

- Single EU market for pharmaceuticals

- EMEA (European Medicines Agency), London UK
  - Created in 1995
  - Permanent secretariat
  - Coordinate scientific resources at National Authorities

- EU Commission
The EMEA

- CHMP (Committee for Human Medicinal Products)
- CVMP (Committee for Veterinary Medicinal Products)
- COMP (Committee for Orphan Medicinal Products)
- HMPC (Herbal Medicines Products Committee)
- PDCO (Paediatric Committee)

Several Working Parties / Expert Groups
The CHMP

• 1 member/member state
• 1 alternate /member state
• 1 member from Iceland, Norway
• 5 coopted members
General considerations in the assessment of foreign data
Geographical Distribution of Pivotal Clinical Trials

2005

2007

Region

US
EU-Swiss
South-Central America
Canada
Australia-New Zealand
Asia Pacific
CIS
Africa
Eastern Europe
Japan

10226

CIS

Japan
Guidance for the Assessment of Foreign Data

- ICH E5; (1998), Q&A (2006)
  - Regulatory standards
  - Extrapolation issues

- ICH = International Conference of Harmonisation
  - 6 parties (FDA, EU, MHLW, PhRMA, EFPIA & JPMA)
ICH E 5; Fulfillment of regulatory standards

- Adequate characterisation of PD, PK, efficacy and safety
- Design and conduction of trials; choice of control, GCP, appropriate endpoints, accepted diagnostic definitions
- Characterisation of PK (PD) in a population relevant to the new region
Inspections by Region (1997-2008)

Inspection by region

- Rest of the world
- North America
- EU/EEA/AFTA

Year
- 2008
- 2007
- 2006
- 2005
- 2004
- 2003
- 2002
- 2001
- 2000
- 1999
- 1997

Values
- 19
- 13
- 10
- 21
- 3
- 10
- 7
- 8
- 1
- 1
- 21
- 1
- 3
- 3
- 7
- 4
- 1
- 3
- 4
- 3
- 1
ICH E 5;
Extrapolation of the data

• Properties of the drug;
  – PK and PD characteristics affect sensitivity to ethnic factors
• Clinical experience
• Type of study
• Intrinsic/extrinsic factors
# Intrinsic/Extrinsic Factors

<table>
<thead>
<tr>
<th>INTRINSIC</th>
<th>EXTRINSIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic</td>
<td>Environmental</td>
</tr>
<tr>
<td>Physiological and pathological conditions</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>Climate</td>
</tr>
<tr>
<td>Height</td>
<td>Sunlight</td>
</tr>
<tr>
<td>Bodyweight</td>
<td>Pollution</td>
</tr>
<tr>
<td>Liver</td>
<td>Culture</td>
</tr>
<tr>
<td>Kidney</td>
<td>Socio-economic factors</td>
</tr>
<tr>
<td>Cardiovascular functions</td>
<td>Educational status</td>
</tr>
<tr>
<td>ADME</td>
<td>Language</td>
</tr>
<tr>
<td>Receptor sensitivity</td>
<td>Medical practice</td>
</tr>
<tr>
<td>Race</td>
<td>Disease definition/Diagnostic</td>
</tr>
<tr>
<td>Genetic polymorphism of the drug metabolism</td>
<td>Therapeutic approach</td>
</tr>
<tr>
<td>Genetic disease</td>
<td>Drug compliance</td>
</tr>
<tr>
<td>Diseases</td>
<td>Regulatory practice/GCP</td>
</tr>
<tr>
<td></td>
<td>Methodology/Endpoints</td>
</tr>
</tbody>
</table>
Drafting of Reflection paper

- Extrinsic factors less well understood, sometimes not taken into account during drug development

- Reflection paper based on current experience to highlight extrapolation issues to industry and regulators

- Background research in a number of files (11) for which extrapolation issues had been identified
Examples from applications
Examples from Applications; Clopidogrel

• New indication sought for ST elevated MI (STEMI)
  – CLARITY; (6000 patients), 90 % Caucasian, surrogate endpoints
  – COMMIT; (46 000 patients), conducted in China, "hard" endpoints
Examples from Applications; Clopidogrel

The COMMIT study; design

<table>
<thead>
<tr>
<th>Metoprolol</th>
<th>Clopidogrel plus aspirin</th>
<th>Aspirin alone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(i) 11500 patients</td>
<td>(iii) 11500 patients</td>
</tr>
<tr>
<td></td>
<td>Active-clopidogrel</td>
<td>Placebo-clopidogrel</td>
</tr>
<tr>
<td></td>
<td>plus aspirin</td>
<td>plus aspirin</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Active-metoprolol</td>
<td>Active-metoprolol</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No metoprolol</th>
<th>11500 patients</th>
<th>11500 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Active-clopidogrel</td>
<td>Placebo-clopidogrel</td>
</tr>
<tr>
<td></td>
<td>plus aspirin</td>
<td>plus aspirin</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Placebo-metoprolol</td>
<td>Placebo-metoprolol</td>
</tr>
</tbody>
</table>

Subtotal 1: 23 000 allocated active metoprolol
Subtotal 2: 23 000 allocated placebo metoprolol

Subtotal A: 23 000 allocated active-clopidogrel plus aspirin
Subtotal B: 23 000 allocated placebo-clopidogrel plus aspirin

Figure (9.1) 1 - Factorial design among 46 000 patients
Examples from Applications; Clopidogrel

The COMMIT study; results

<table>
<thead>
<tr>
<th>Event</th>
<th>No. (%) With Event</th>
<th>Odds Ratio (95% CI)</th>
<th>Absolute Benefit /1000 (SE)</th>
<th>Two-sided p-value$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite endpoint: Death, re-MI, or Stroke$^b$</td>
<td>Clopidogrel 75 mg* (N = 22961)</td>
<td>2121 (9.2%)</td>
<td>0.91 (0.86, 0.97)</td>
<td>8.5 (2.8)</td>
</tr>
<tr>
<td></td>
<td>Placebo* (N = 22891)</td>
<td>2310 (10.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>Clopidogrel 75 mg* (N = 22961)</td>
<td>1726 (7.5%)</td>
<td>0.93 (0.87, 0.99)</td>
<td>5.4 (2.5)</td>
</tr>
<tr>
<td></td>
<td>Placebo* (N = 22891)</td>
<td>1845 (8.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal re-MI$^c$</td>
<td>Clopidogrel 75 mg* (N = 22961)</td>
<td>270 (1.2%)</td>
<td>0.81 (0.69, 0.95)</td>
<td>2.7 (1.1)</td>
</tr>
<tr>
<td></td>
<td>Placebo* (N = 22891)</td>
<td>330 (1.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal stroke$^c$</td>
<td>Clopidogrel 75 mg* (N = 22961)</td>
<td>127 (0.6%)</td>
<td>0.89 (0.70, 1.13)</td>
<td>0.7 (0.7)</td>
</tr>
<tr>
<td></td>
<td>Placebo* (N = 22891)</td>
<td>142 (0.6%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* All treated patients received daily ASA (162 mg).

$^a$ Based on log-rank test.

$^b$ The difference between the composite endpoint and the sum of death + nonfatal re-MI + nonfatal stroke indicates that 9 patients (2 clopidogrel and 7 placebo) suffered both a nonfatal stroke and a nonfatal re-MI.

$^c$ Nonfatal re-MI and nonfatal stroke exclude patients who died (of any cause).

SE = standard error; re-MI = reinfarction.
Examples from Applications; Clopidogrel

The COMMIT study; results in subgroups

<table>
<thead>
<tr>
<th>Baseline Categorisation</th>
<th>Events (%)</th>
<th>Odds ratio &amp; C.I.</th>
<th>Heterogeneity or trend test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clopidogrel (22 891)</td>
<td>Placebo (22 891)</td>
<td>Clopidogrel better</td>
</tr>
<tr>
<td><strong>Sex:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1224 (7.5%)</td>
<td>1416 (9.9%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>847 (13.3%)</td>
<td>804 (14.9%)</td>
<td></td>
</tr>
<tr>
<td><strong>Age at entry (years):</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 60</td>
<td>465 (5.9%)</td>
<td>512 (5.4%)</td>
<td></td>
</tr>
<tr>
<td>60-69</td>
<td>746 (10.1%)</td>
<td>1006 (11.5%)</td>
<td></td>
</tr>
<tr>
<td>70+</td>
<td>801 (14.0%)</td>
<td>963 (16.2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Hours since onset:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 6</td>
<td>709 (9.2%)</td>
<td>830 (10.8%)</td>
<td></td>
</tr>
<tr>
<td>6-10.9</td>
<td>738 (9.8%)</td>
<td>808 (10.6%)</td>
<td></td>
</tr>
<tr>
<td>11-24</td>
<td>674 (9.5%)</td>
<td>702 (9.2%)</td>
<td></td>
</tr>
<tr>
<td><strong>SBP (mmHg):</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 120</td>
<td>762 (10.4%)</td>
<td>862 (11.6%)</td>
<td></td>
</tr>
<tr>
<td>120-159</td>
<td>609 (9.5%)</td>
<td>770 (9.9%)</td>
<td></td>
</tr>
<tr>
<td>160-199</td>
<td>398 (8.5%)</td>
<td>399 (9.0%)</td>
<td></td>
</tr>
<tr>
<td><strong>Heart rate (bpm):</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 70</td>
<td>229 (5.2%)</td>
<td>315 (9.2%)</td>
<td></td>
</tr>
<tr>
<td>70-89</td>
<td>868 (8.9%)</td>
<td>932 (9.8%)</td>
<td></td>
</tr>
<tr>
<td>90-109</td>
<td>632 (9.3%)</td>
<td>603 (10.5%)</td>
<td></td>
</tr>
<tr>
<td>110+</td>
<td>926 (16.9%)</td>
<td>910 (17.2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Fibrinolytic agent given:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1001 (4.8%)</td>
<td>1122 (9.9%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1116 (9.7%)</td>
<td>1100 (10.2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Prognostic Index (3 equal groups):</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>239 (3.5%)</td>
<td>292 (3.7%)</td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>674 (7.5%)</td>
<td>635 (9.3%)</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>1319 (17.3%)</td>
<td>1362 (16.2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Metoprolol allocation:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1051 (9.7%)</td>
<td>1110 (9.7%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1058 (9.2%)</td>
<td>1200 (10.5%)</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>2121 (9.2%)</td>
<td>2310 (10.1%)</td>
<td></td>
</tr>
</tbody>
</table>

Global Heterogeneity Test: \( \chi^2 = 16.4; \ p = 0.4 \)

Figure (1.) 2 - Proportional effects of adding clopidogrel to aspirin on the combined coprimary endpoint (death, reinfarction, stroke) by the protocol-specified subgroups of baseline characteristics - EFC7018 (COMMIT/CCS-2)
Examples from Applications; Clopidogrel

- Concerns regarding relevance of the clinical setting to EU clinical practice;
  - Background therapy; most European patients get beta-blockers
  - Results may not be relevant to European population
- CHMP considered COMMIT trial as supportive rather than pivotal
Examples from Applications; Gefitinib

- **Indication**
  - Non-small cell lung cancer refractory to other therapies
- **Two pivotal trial in initial application;**
  - One mainly in Caucasians, one in a mixed Asian and Caucasian population
  - Data suggested a difference between populations (higher response in Asian patients)
- **Following the above one large study, ISEL, was conducted**
  - (75% Caucasians)
Examples from Applications; Gefitinib

Survival Data by Ethnicity

Asian
HR=0.66
(0.48, 0.91)

Non-Asian
HR=0.93
(0.81, 1.08)
Examples from Applications; Gefitinib

- Survival effect only seen in Asian patients
- No obvious explanation for the lack of survival effect in Caucasian patients
  - tumor genetics?
- Gefitinib approved in Japan but not in the EU
Examples from Applications; Gefitinib

• Further studies
  • Gefitinib efficient mainly in mutation positive tumors
  • Asian patients; higher prevalence of mutations (40 versus 10%)
  • Caucasians; satisfactory effect in patients with mutations
Examples from Applications; Antipsychotic

• Indication;
  – Treatment of acute manic episodes associated with bipolar disorder

• One fixed dose study and one flexible dose study;
  – Dominated by US patients, 71% and 54%, respectively.
Examples from Applications

• Significant effects in favour of test drug compared to placebo

• No effect in US patients
  – Fixed dose study; large effect in Asian, primarily Indian patients (15% of the total study population)
  – Flexible dose study; large effect in Russian and Ukrainian patients (29%)
Examples from Applications

Results fixed dose study
Examples from Applications

Results flexible dose study
Examples from Applications

• CHMP conclusion;
  - Questionable whether positive findings are representative for the major part of European patients suffering from an acute episode of mania because of the differences in race and/or medical and social environment

• Application withdrawn
Main Findings

• Medical practice
  – Differences in co-medications and invasive procedures

• Disease definition
  – Heterogeneous medical conditions (fibromyalgia)
  – Insufficient standardization and understanding of scores and scales (psychiatric diseases)

• Study population
  – Life style, medical and social environment
Overall Conclusion

Extrapolation or Bridging Studies?

• Differences in intrinsic/extrinsic factors and study conditions exist both within and between regions

• Important to identify and control relevant factors

• Unknown factors
  • Some data in target population needed
  • Case-by-case basis (type of study, drug etc)

• More experience, less need for bridging studies
Thank you for your attention