Opportunities for the use of regulatory data

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(BfArM and EMA Biostatistics Working Party)
Outline

• Key regulatory questions
• Challenges in CNS drug development
• Clinical trial effect
• Opportunities with analysis of individual patient data
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• Clinical trial effect
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Key regulatory questions

- What is of primary interest to regulators?
  - **Safe and effective** medicinal products available to patients
  - **Protecting patients from harm**
  - Thus facilitate efficient and robust drug development
  - More **efficient studies** allowing for **valid and robust conclusions** (e.g. design issues)
  - Increase understanding of data from clinical trials (regulatory assessment/review)
Recent positive developments in CNS

- Existing medicines represent a significant progress from a historical perspective
- Several EMA approvals in 2017 (including for rare diseases and/or conditions with high unmet medical need)

But

- Still unmet need with high economic and societal impact
- Phase III attrition rate higher in CNS than in other areas
- Need to develop drugs for early stages of disease / partial responders / benign safety profile
Outline

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• **Challenges in CNS drug development**
• Clinical trial effect
• Opportunities with analysis of individual patient data
Challenges in CNS drug development

https://www.nature.com/articles/nrd.2016.237.pdf


- Study conducted on evaluation files to understand the main determinants of the outcome of a regulatory application

- The evaluation of a dossier in Europe foresees that all issues identified as raised as Objections to Applicant.

- Major Objections are assumed to reflect the critical points of a medicinal product development.
Data

- All applications for **Initial Marketing Authorisation or Extension of Indication** for Neurological and Psychiatric Conditions
- *Ab urbe condita* up to December 2014

<table>
<thead>
<tr>
<th>By Indication</th>
<th>By procedure</th>
<th>By Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>46 Psychiatry</td>
<td>70 Initials</td>
<td>74 Positive</td>
</tr>
<tr>
<td>57 Neurology</td>
<td>33 Extensions</td>
<td>29 Negative</td>
</tr>
</tbody>
</table>

- Submitted dossier not a random sample of drug development programmes (EMA submissions, not at national level)
Outcome variable for the analysis

- Outcome of an application → three levels
  - 1) **Approval** of the **full indication** as applied for by the applicant
  - 2) **Approval** with **restricted indication** as compared to the one it was applied for
    - e.g. application for two conditions but only one approved
    - or restricted to a subset of the targeted population
  - 3) **Refusal**
Main exposure variable for the analysis

- Content analysis to classify objections in **18 categories**
- Across **5 domains**: early phase, planning of confirmatory studies, efficacy, safety, clinical relevance

### Examples

<table>
<thead>
<tr>
<th>Variable name</th>
<th>Description</th>
<th>Raised (Y/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insufficient justification of the dose</td>
<td>Dose finding for confirmatory studies missing or not properly performed</td>
<td></td>
</tr>
<tr>
<td>Choice of comparator</td>
<td>Objections concerning the choice, the dose or the lack of comparator</td>
<td></td>
</tr>
</tbody>
</table>
Method of the main analysis

• Main model: **Random Forest** (Breiman, 2002)
  • “Variable importance” of the categories of Objections as predictors of outcome as indicator of the “importance” of each pitfall identified in the clinical developments.
  • Average and variability from 1000 “random forests”.
  • Model chosen due to no overfitting despite many predictors and limited dataset.

• We also did **linear modelling** to confirm the analysis results.
## Results: % of objections by domain

<table>
<thead>
<tr>
<th>Neurology</th>
<th>Psychiatry</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rejected</strong>&lt;br&gt;(N = 17)</td>
<td><strong>Rejected</strong>&lt;br&gt;(N = 12)</td>
</tr>
<tr>
<td>Approved with restricted indication&lt;br&gt;(N = 27)</td>
<td>Approved with restricted indication&lt;br&gt;(N = 18)</td>
</tr>
<tr>
<td>Approved with the indication applied for&lt;br&gt;(N = 13)</td>
<td>Approved with the indication applied for&lt;br&gt;(N = 16)</td>
</tr>
</tbody>
</table>

Percentage of MOs by TA, domain and outcome shown as proportional to the colour darkness.

**Domain**
- **Neurology**
- **Psychiatry**

**Outcomes**
- **Learning**
- **Planning**
- **Outcome**
- **Clinical relevance**

- Percentage of MOs by TA, domain and outcome shown as proportional to the colour darkness.
Results – Variable importance in **Neurology**

• Issues with strongest impact on the outcome of applications in neurology: **failure to reach the primary end point, safety** and lack of properly conducted specific **PK/PD studies**.
• Issues with strongest impact on the outcome of applications in neurology: **selection of the population, safety, clinical benefit** and lack of proper **justification of the dose.**
Main findings on challenges for CNS drug dev.

• The evaluation of dossiers in Psychiatry often detects issues in planning of confirmatory studies and clinical relevance of results.

• On the other hand, Neurology evaluations focus on outcome of confirmatory studies.

• For both Neurology and Psychiatry, the outcome of applications does not only depend on safety and efficacy results but also on elements of the learning phase (e.g. PK and dose finding).
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- **Clinical trial effect**
- Opportunities with analysis of individual patient data
Placebo effect in depression and schizophrenia

- High number of failed clinical developments over past 20 years in major depressive disorder and schizophrenia
- **Known factors**: lack of knowledge of the pathophysiology, lack of biomarkers, lack of well-validated preclinical models, and...

- **Response to placebo**
  - In the context of a randomised parallel placebo-controlled trial
  - What are the determinants of change in the placebo arm?
  - Investigational treatment may actually not be efficacious or trial may be inefficient
Placebo effect or clinical trial effect?

• **Positive expectancy** with regard to the non-specific effects of a treatment attributable to factors other than specific active components.
  
  • e.g., health care setting, medical rituals, and engagement with health care professionals
  
  • confirmed in a number of meta-analyses in psychiatry

• Effect occurs among **all patients** - randomly assigned to receive placebo and active treatment

• Magnitude of placebo effect so large that **trial fails to distinguish effect** of active treatment vs. placebo **OR effect is absent**
Data and outcome measure

- Parallel, short-term, randomised double-blind placebo-controlled clinical trials submitted to EMA for regulatory approval; major depressive disorder and schizophrenia
- Baseline and final values, or change from baseline
  - HAMD-17 for MDD and PANSS for SCZ
- Mean difference:
  - Not a standardised mean difference
  - Not a standardised scale
An additive effect?

- Difference between treatment and placebo vs. change from baseline in the placebo arm
- Decrease in the difference between treatment and placebo:
- Non-fully additive effect?
- Artefact of the data?
- Is the correlation between these two factors caused by other confounders?
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Access to individual-patient data: an obvious added value?

Main determinants of the outcome of a regulatory application

- IPD is not relevant to research based on regulatory data

Clinical trial effect

- In theory, it should help, but...
  - Data management issues (e.g. inconsistent data standards)
  - Meta-analysis based on aggregate data sometimes as useful as IPD meta-analysis
  - Added value is for specific questions only, e.g. missing data, effect driven in subgroups, individual baseline value vs. inclusion criterion.
IPD – further ideas for methodology research

- **Methodological research**: adequacy of the design, statistical analysis methods...
- **Typical factors to study**: baseline predictors, post-baseline predictors, item change in scales, variability in scales...
Caveat with regulatory databases

• Submitted dossier not a random sample of drug development programmes; EMA does not have access to data from failed programmes.

• EMA piloted an initiative in Alzheimer’s Disease inviting companies to discuss with the Agency developments that did not lead to a submission.

• Important learnings for the Agency – highlighting the value of sharing data from negative trials – with the Agencies but even better with the public.
Thank you for your attention

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