Addressing the
Efficacy-Effectiveness gap

London, EMA, December 2010
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Efficacy versus effectiveness

**Efficacy** is the extent to which an intervention does more good than harm under **ideal circumstances**

**Effectiveness** is the extent to which an intervention does more good than harm when provided under the usual circumstances of **health care practice**

Definitions by the EU High Level Pharmaceutical Forum (Oct 2008)

**Efficacy >> Effectiveness**
What does, and what does not change?

before  ⇐  licensing  ⇒  after

?
Case study: Acomplia
(rimonabant 20 mg)

Jun 2006: approved for obesity and over-weight patients.
(“effect was moderate and of clinical relevance for 20-30% of patients”)
Case study: Acomplia (rimonabant 20 mg)

Jan 2009: marketing authorisation withdrawn in light of post-approval data

(“new data indicated a shorter duration of treatment in real life and a reduced beneficial effect... risk of experiencing the adverse mental effects are higher in patients with comorbidity”)
The efficacy - effectiveness gap: examples

- Mibefradil (Posicor)
- Cerivastatin (Lipobay, Baycol)
- Rimonabant (Acomplia)
- Varenicline (Champix/Chantix)
- Metoclopramide (Maxolon et al)
- ...
Can we conceptualise the efficacy - effectiveness gap?

A problem of variability
<table>
<thead>
<tr>
<th>Sources of variability in drug response</th>
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<tbody>
<tr>
<td><strong>Biology</strong></td>
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<tr>
<td>Genomics</td>
</tr>
<tr>
<td>Co-morbidity, baseline severity of disease, altered physiological states, external factors</td>
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<td>Inappropriate prescribing, prescr. to non-responders, medication errors</td>
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<tr>
<td>PD: Trastuzumab Abacavir Abacavir PK: Codeine: resistance / tox. (CYP2D6)</td>
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<tr>
<td>Cerivastatin; Gemfibrozil; Mibefradil; Anti-hypertensive, anti-infective drugs</td>
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When expectations (efficacy) don’t match reality (effectiveness)…

…there are two ways to bridge the gap:

• (a) lower the expectations to the level of reality:

“regulators should request industry to conduct studies with higher external validity” (pragmatic-/effectiveness trials)
“Clean”, explanatory or efficacy trial

“Noisy”, pragmatic or effectiveness trial
“Clean”, explanatory or efficacy trial

“Noisy”, pragmatic or effectiveness trial
When expectations (efficacy) don’t match reality (effectiveness)...

...there are two ways to bridge the gap:

- (b) bring up reality to the level of expectations

... a drug-problem or a healthcare delivery problem?
Addressing the efficacy - effectiveness gap:
An area for regulatory sciences

Which patient for this drug?

Which drug for this patient?
Which patient for this drug?

Biomarker-guided benefit-risk stratification

• Guidance for co-development of drugs and companion diagnostics
• Qualification procedure for (stratification) biomarkers
• Staggered approval, progressive authorisation ?
Which patient for this drug?

Biomarker-guided benefit-risk stratification

• Focus on “optimised” treatment-eligible population
• Departure from “last-line first” development / regulatory approach?
• Needs alignment of regulators and post-regulatory decision makers (payers, prescribers)
Addressing the efficacy - effectiveness gap: An area for regulatory sciences

Which patient for this drug?

Which drug for this patient?

- Quality of prescribing
- Patient adherence
Quality of prescribing, the regulators’ contribution?

• “The right drug, at the right dose, at the right time, to the right patient”
• RMP’s/REMS’s (“management” = evaluation and mitigation/minimisation)
• Present information in a useful format to guide drug prescribing
Information in a useful format

e-Label

Electronic Healthcare Record → Structured Drug Information → Computerised Physician Order Entry

e-HC databases

Post-marketing research and monitoring

Decision Support System

Appropriate prescribing
Patient adherence, the regulators’ contribution?

Is technology available?

Lester RT. Effects of a mobile phone short message service on antiretroviral treatment adherence in Kenya. Lancet 2010; 376: 144

Intelligent pill caps use light and sound, phone calls or text messages to remind people to adhere to drug regimen.
Patient adherence, the regulators’ contribution?

Is technology available?

Yes, but underutilised - should regulators encourage adherence-promoting technology?
Conclusions

• Observational studies of treatment outcomes will likely put the efficacy-effectiveness gap under the spotlight

• Pharmacogenomics and, perhaps, new licensing approaches are expected to reduce but will not eliminate the gap

• Improving drug effectiveness may represent an opportunity for low-hanging fruits (prescriber and patient-adherence directed interventions)

• In this space, regulatory science could have a major positive impact on public health
Give credit where credit is due

“You know, we are so focused on a pill, and industry is only about patenting a molecule - that alone cannot be successful …”

EMA Road Map to 2015:
Strategic Area 3: “Optimising the Safe and Rational Use of Medicines”