The Cost-Effectiveness of Thorough QT/QTc (TQT) studies

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Background

- Dutch Top Institute Pharma’s Escher project
  - Public-Private Partnership of universities, industry, and Dutch government

- The Escher project:
  - Aimed at identifying, evaluating, and removing regulatory bottlenecks hampering pharmaceutical innovation:

  **Science-driven drug regulation**
“Innovations that improve the health of the public include not only the development of novel methods but also a lifecycle approach to the evaluation of approval methods and regulatory actions as a central element of regulatory science.”

Drug Regulation

- **Protect** Public Health
  - Keep unsafe, low-quality, inefficacious drugs from entering the market

- **Promote** Public Health
  - Facilitate needed drugs reaching the market without unnecessary delay
Drug Regulation

• Drug regulation serves a societal function
  ▪ Taxes
    • Medical expenses, regulatory authorities
  ▪ Health insurance
  ▪ Consumption of medicines

• Therefore, drug regulation should be subjected to social scrutiny

• If drug regulation not cost-effective:
  ▪ Opportunity costs for society
Value of Drug Regulation

- Each regulatory requirement, directly or indirectly, either protects or promotes public health

- Any intervention or policy aimed at increasing health can be subjected to a cost-effectiveness analysis
The cost-effectiveness of drug regulation:

- Could the same methods we use to assess whether medical interventions provide value for money (should we reimburse them?) be used to evaluate drug regulation?
Methods

- We assessed the cost-effectiveness of ICH E14

- A cost-effectiveness analysis is always comparative:

- Are the additional resources spent by implementing the regulation justified by the health gains resulting from implementing the regulation?
Methods

- We compared two regulatory scenarios:
  
  - **REGULATION** (ICH E14)
  
  - **NO REGULATION** (ICH E14 is not implemented)
Methods

• How does the implementation of ICH E14 result in health gains?
Clinical Development (without TQT study)

Drug does not prolong QT interval
- Market authorization
- Health effects: None
- Costs: None

QT-prolonging drug
- Market authorization
- Health effects: Drug-induced sudden cardiac deaths
- Costs: Healthcare costs related to sudden cardiac deaths
Clinical Development (with TQT study)

Positive TQT study
- Market authorization
  - Health effects: Drug-induced sudden cardiac deaths prevented
  - Costs: TQT study, ECG monitoring

Negative TQT study
- No market authorization
  - Health effects: (1) Drug-induced sudden cardiac deaths prevented (2) Effective treatment not reaching the market
  - Costs: TQT study

- Market authorization
  - Health effects: None
  - Costs: TQT study
Methods

• Health outcomes:
  • Drug-induced sudden cardiac deaths
  • Life years gained
  • Quality-adjusted life years (QALYs) gained

• Life years gained and QALYs gained:
  • Patient-specific characteristics

• Therefore health effects of the regulatory scenarios were assessed for a **specific patient population**
  • Users of antipsychotics

• Dynamic population model was constructed in Microsoft Excel
Regulatory Scenarios: Model

**REGULATION:** QT-prolonging antipsychotic enters the market

- TQT studies are routinely performed thus QT-prolonging potential is known at market entry

**Assumptions:**
- All starting users in EU and US will switch to this new antipsychotic;
- All starting users will undergo two ECGs (baseline + follow-up);
- Users with proarrhythmic QT prolongation (QTc>500 ms) will switch to other antipsychotic or dose will be lowered
- **No** drug-induced sudden cardiac deaths occur

**Costs:**
- 150 TQT studies (€1mil) 2003-2009
- ECG monitoring of all users (€20 p/ECG)

**NO REGULATION:** QT-prolonging antipsychotic enters the market

- TQT studies are **not** performed: QT-prolonging potential unknown at market entry

**Assumptions:**
- All starting users in EU and US will switch to this new antipsychotic;
- No routine ECG monitoring is performed
- Drug-induced sudden cardiac deaths occur.

**Costs:**
- Healthcare costs per sudden cardiac death (€2,500)
Risk of a drug-induced sudden cardiac death in users of the prototype antipsychotic

- Proarrhythmic (>500ms) QTc prolongation: 1% of users
  - Most potent QTc prolonging antipsychotics
  - Titier et al. (2005): TdP incidence of 1 in 10,000 users (irrespective of QT prolongation)
  - Titier et al. (2005), Shah & Hondeghem (2005), Abdelmawla & Mitchell (2006)

- Risk of Torsade de pointes in patients with proarrhythmic QTc prolongation: 1%

- Risk of developing ventricular fibrillation in patients with torsade: 20%

- Probability of death after ventricular fibrillation: 85%
REGULATION:
QT-prolonging antipsychotic enters the market

Risk of drug-induced sudden cardiac death:
Zero
(As all starting users will be subjected to ECG monitoring)

NO REGULATION:
QT-prolonging antipsychotic enters the market

Risk of drug-induced sudden cardiac death:
17 in 1 million starting users
Model specifications

- 150 TQT studies performed 2003-2009

- Prototype antipsychotic enters the market today

- Health effects (measured by sudden cardiac deaths occurring) are measured over the course of the next 20 years the antipsychotic will remain on the market

- 1 million starting users in the EU and US per year
Model specifications

- The model calculates the maximum effectiveness of ICH E14:
  - All starting users EU + US will switch to the prototype antipsychotic;
  - ECG monitoring of starting users is 100% predictive and effective
Incremental cost-effectiveness ratio (ICER): Resources required to gain one unit of health

Costs
REGULATION

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Costs
NO REGULATION

Health Effects
REGULATION

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Health Effects
NO REGULATION
Results

- Quality-adjusted life year (QALY):
- Measure of disease burden consisting of two components:
  - Remaining life years
  - Health-related quality of life during life years
    - (scaled between 0 and 1: health utility)
- One QALY equals one year of life lived in perfect health

Life years gains by preventing one drug-induced sudden cardiac death: 17.9

Mean QALYs gains: 12.9
Results

- Incremental cost-effectiveness ratios:
  - €2.4 million per drug-induced sudden cardiac death prevented;
  - €134,000 per life year gained;
  - €187,175 per QALY gained.

- UK threshold: ~£30,000 per QALY gained
- Dutch threshold: €20,000 to €80,000 per QALY gained
- US threshold: $50,000 to $100,000 per QALY gained is commonly cited
Results

• Sensitivity analyses: to investigate (considerable!) uncertainty surrounding our estimates

• Incremental costs per QALY gained: €187,000
  • 6% probability <€80,000
  • 13% probability <€100,000
  • 30% probability >€250,000

• All sensitivity analyses indicate it is highly unlikely this regulation is cost-effective
  • Only if proarrhythmic QTc prolongation is >2% of users
Limitations

• Incidence of drug-induced sudden cardiac deaths in antipsychotic users not known

• Model calculates maximum expected health gains
  • ECG monitoring 100% predictive and effective

• Did not study effect of ICH E14 on attrition rate clinical development

• Did not take any limitations of TQT study design into account
Considerations

- We believe the ICH E14 should be evaluated by means of its ability to increase patient safety
- Given our current knowledge of post-marketing risks of QTc-prolonging drugs, **even under ideal circumstances** ICH E14 will not be cost-effective
- Routine ECG monitoring of QT-prolonging drug users is not cost-effective:
  - A sensitivity analysis demonstrated that monitoring 30% of users which would prevent 80% of sudden cardiac deaths is still not cost-effective
Considerations

• If ICH E14 would be removed from the regulatory framework, it is highly unlikely this would result in any significantly increased patient risks

• Only require a TQT study when nonclinical evidence suggest QT prolongation, or substitute TQT with adequate PK/PD monitoring in early phase clinical pharmacology studies

  • Phase I studies registered in ClinicalTrials.gov often have change in QTc interval as a secondary endpoint
Considerations

- Only reason for concern:
  - A highly potent QT-prolonging drug entering the market without its QT-prolonging potential being known

- What is the probability this will happen given the current standards in place (but with no ICH E14)?
  - Current standards:
    - ICH S7B
    - Early phase clinical pharmacology studies
Conclusion

From an economic point-of-view, ICH E14 does not provide value for money