Innovation, risk and regulation in postmarket settings

Jarno Hoekman, PhD
Innovation Studies Group, Faculty of Geosciences; Utrecht-WHO Collaboration Centre for Pharmaceutical Policy & Regulation, Faculty of Sciences

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This talk

1) What is innovation

2) Innovation process and detection of ADRs

3) Empirics on market extensions and ADR detection
Innovation is not only novelty
A learning process

Select solution(s) guided by causal knowledge

Test against requirements and constraints

Learn about (un)foreseen outcome(s)

Make decision about moving solution forward

Refine solution and/or increase test complexity

Feedback

Product life-cycle dynamic
Learning and confirming

- Select solution(s)
- Test against requirements and constraints
- Learn about (un)foreseen outcome(s)
- Make decision about moving solution forward
- Refine solution and/or increase test complexity
- Test against requirements and constraints
- Confirm outcome
- Market introduction

Feedback
Learning does not stop at market entry

- Post-innovation innovation
- Different learning environment
  - Learning mechanisms
  - Learning scope
- Role of feedback
Innovation as a configuration

- Regulatory system
- Healthcare delivery system
- Human biology
- Performs function at interface
- Clinical practice

Inner environment

Outer environment
Why is this useful for learning about drug risks?
Learning about adverse drug reactions

- Innovation (solution) creates new problems
- Market does not sufficiently incentivise learning
- Problems are uncertain and fragmented
  - Divergent learning dynamic
  - Parallel learn-confirm cycles
- Risk of inner environment and safety of configuration
Regulation guides learning

**Market**
- Market entry

**Pharmacovigilance**
- Risk reporting
- Risk assessment
- Risk management
- Risk minimisation
- Risk communication

**Insufficient**

**Additional**
Innovation as a process

- Market
  - Market entry
  - Market entry conditions
  - Market extensions
  - Market exclusivity
  - Pre-market investment

- Pharmacovigilance
  - Risk reporting
  - Risk assessment
  - Risk management
  - Risk minimisation
  - Risk communication

Coupling and complementarities
(Potential) complementarities

- Market extensions (staggered approval)
- Conditional marketing authorisation
- Paediatric regulation
- Signal confirmation
- Risk management and minimisation
- Real-world evidence
- Emphasis on safety in innovation ecosystem
Empirical illustration: How do market extensions contribute to ADR detection?
Data

- All centrally authorised new active substances (NAS) by the European Commission (n = 460) in the period 01-01-1995 until 31-12-2016

- PDF versions of Annex 1 of Summary of Product Characteristics (SPC) extracted from European Commission (EC) Community Register of medicinal products for human use¹ on 01-01-2018

Extracting market extensions

1. Extract text from section 4.1 “Therapeutic indications”
2. Compare text of date consecutive versions to assess whether section is identical
3. Map all indications on MeSH classification as used by EMA on their website
4. Determine whether indication is new indication or extension within indication
Extracting Adverse Drug Reactions (ADRs)

1. Extract text of section 4.8 on “Undesirable effects”
2. Compare date consecutive versions to determine whether sections are identical
3. If not identical, map terms from MedDRA¹ on both sections
4. Identify new terms in the latest drug label

¹ Medical Dictionary for Regulatory Activities version 19.1
Exposure and events

- Follow-up until 01-01-2018 or withdrawal of marketing authorisation
- Median [IQR] follow-up time is 9.00 [4.27 – 14.89] years

<table>
<thead>
<tr>
<th>Median number of ADRs added</th>
<th>10 [2 – 30]</th>
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<td>% of all known ADRs at end of follow-up added after market entry</td>
<td>34.7%</td>
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Number of ADRs added postmarket

Proportion of ADRs added postmarket
Number of postmarket detected ADRs in market extensions

Proportion of postmarket detected ADRs in market extensions
Implications of innovation perspective

1) Learning about risks constitutive of innovation process
   - Moving further upstream...

2) Complementarity of market and risk regulation
   - Coupling in internal organisational operations

3) Need for population-specific drug safety profiles
   - Potential knowledge and method deficits
   - Variation in reporting practices
   - Need for regulatory innovation
Thanks for your attention

j.hoekman@uu.nl