Pharmaceutical gaps and unmet need in Europe - a workshop primer

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Lunch Symposium: “A fresh take on policy for pharmaceutical research: ensuring access to medical innovation and tackling medical gaps”

10th European Public Health Conference, November 3rd 2017, Stockholm
Outline

(1) Definitions: what is a pharmaceutical gap? What is unmet need?

(2) Pharmaceutical gaps in Europe?
   • Link between priority areas and burden of disease to the pharmaceutical pipeline and R&D spending
   • Pharmaceutical gaps for specific population groups

(3) What causes pharmaceutical gaps? And...

(4) What has been and can be done to tackle the issue?
What is a pharmaceutical gap?

(1) Treatment(s) exist, but are/will become ineffective (e.g. antibacterial drug resistance, pandemic influenza)

(2) Treatments exist but delivery mechanisms or formulations need to be more appropriate (e.g. CVD, HIV/AIDS, depression, certain cancers)

(3) Treatment does not exist or is not sufficiently effective (e.g. stroke, Alzheimer’s)
Relationship between unmet need and pharmaceutical gaps

- Unmet need
  - Medical/treatment gap
    - Pharmaceutical gap
Pharmaceutical unmet need – issues beyond R&D

(1) Slow or missing launches
(2) Market withdrawals
(3) Reimbursement issues
(4) Medicines shortages
(5) Prescribing practices / adherence
List of priorities in WHO's 2013 report

(1) Antibacterial drug resistance
(2) Pandemic influenza
(3) Ischaemic heart disease
(4) Diabetes
(5) Cancer
(6) Acute stroke
(7) HIV/AIDS
(8) Tuberculosis
(9) Neglected tropical diseases
(10) Malaria
(11) Alzheimer’s disease and other dementias
(12) Osteoarthritis
(13) COPD
(14) Alcohol use disorders and alcoholic liver disease
(15) Depression
(16) Postpartum haemorrhage
(17) Tobacco use
(18) Obesity
(19) Rare diseases
(20) Diarrhoea
(21) Hearing loss
(22) Pneumonia*
(23) Neonatal conditions*
(24) Low back pain
Global Burden of Disease Study 2016

Leading ten causes of all-age DALYs in 2016, Western Europe

1. Low back and neck pain (24)
2. Ischaemic Heart Disease (3)
3. Alzheimer’s and other dementias (11)
4. Sense organ diseases (21)
5. Cerebrovascular disease (6)
6. Lung, bronchus and trachea cancers (5)
7. Skin and subcutaneous diseases
8. Migraine
9. Depressive disorders (15)
10. Falls

“Worldwide, *ischaemic heart disease* and *stroke* remained the two leading causes of DALYs (...). In addition to being the most common leading causes of DALYs, *ischaemic heart disease* and *stroke* were sources of more DALYs than expected for most locations in central Europe, eastern Europe and central Asia.”
### Global Burden of Disease Study 2016

<table>
<thead>
<tr>
<th>Western Europe</th>
<th>Back+Neck (1.24)</th>
<th>IHD (0.63)</th>
<th>Alzheimer's (1.65)</th>
<th>Stroke (0.68)</th>
<th>Lung C (1.04)</th>
<th>Skin (1.06)</th>
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<td>Andorra</td>
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<td>Migraine (1.12)</td>
<td>Depression (1.11)</td>
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<td>Falls (0.73)</td>
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</tbody>
</table>
Global Burden of Disease Study 2016
Global Medicines in Late Stage Development in 2016

- Oncologics: 35% (259 out of 720.0x540.0)
- CNS: 30% (1981 out of 720.0x540.0)
- Anti-infectives and Antivirals: 6% (259 out of 720.0x540.0)
- Arthritis/Pain: 6% (1981 out of 720.0x540.0)
- Immune System: 6% (259 out of 720.0x540.0)
- Genito-urinary and Hormones: 12% (1981 out of 720.0x540.0)
- Others: 28% (1981 out of 720.0x540.0)

Source: IMS R&D Focus, Sept 2016; QuintilesIMS Institute, Oct 2016

Note: Drugs included are beyond Phase II development. Cardiovascular includes antihypertensives, anticoagulants, lipid regulators, and other cardiovascular therapies. Genito-urinary and Hormones includes women's and men's health, osteoporosis, urological and hormonal therapies. CNS is central nervous system.
Figure 2 Bubble plot representing disability-adjusted life years (DALYs) for EU-25 and active ingredients (NCEs). The areas of the bubbles are DALYs' weighted contribution of each disease condition(s) to the total burden of disease. 1: Other neoplasms; 2: Unintentional injuries (poisoning); 3: Congenital anomalies; 4: Digestive diseases; 5: Respiratory diseases; 6: Skin diseases; 7: Respiratory infections; 8: Maternal conditions; 9: Perinatal conditions.

Catalá-López et al. 2010
Disease-specific research funding, USA

Moses et al. 2015
Trends for specific conditions

Hwang et al. 2016
Gaps for special population groups

WHO 2013 report:
- Children
- Women
- Elderly

Bourgeois et al. 2014:
- Background: Fewer clinical trials are performed in children, unclear how well aligned with needs
- Findings: Only moderate correlation between trial activity and paediatric burden of disease, certain conditions clearly underrepresented

**TABLE 1** Number of Pediatric Trials and Participants and Pediatric Burden of Disease by Country Income Level

<table>
<thead>
<tr>
<th></th>
<th>All Trials (N = 5373)</th>
<th>RCTs (n = 3771)</th>
<th>Drug RCTs (n = 1526)</th>
<th>Randomized Participants (n = 1,466,689)</th>
<th>Burden of Disease in DALYs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>High-income countries</td>
<td>4261</td>
<td>79</td>
<td>2882</td>
<td>76</td>
<td>1176</td>
</tr>
<tr>
<td>Middle-income countries</td>
<td>746</td>
<td>14</td>
<td>568</td>
<td>15</td>
<td>225</td>
</tr>
<tr>
<td>Low-income countries</td>
<td>366</td>
<td>7</td>
<td>321</td>
<td>8</td>
<td>125</td>
</tr>
</tbody>
</table>
Gaps for special population groups

WHO 2013 report:
• Children
• Women
• Elderly

| Table 2. Comparison of the Obstetric Drug Pipeline with that of a Mainstream Area (Cardiovascular) and that of a Neglected Disease (Amyotrophic Lateral Sclerosis) |
|---------------------------------|---------------|---------------|-------------|
| Indication                     | Obstetric     | Cardiovascular| ALS         |
| Pre-clinical                   | 3             | 303           | 16          |
| Phase I                        | 5             | 104           | 7           |
| Phase II                       | 5             | 163           | 7           |
| Phase III                      | 3             | 73            | 4           |
| Pre-registration               | 1             | 17            | 0           |
| Total                          | 17            | 660           | 34          |

ALS, amyotrophic lateral sclerosis
doi:10.1371/journal.pmed.0050022.t002

Fisk & Atun 2008

• Only one new class of drug licensed between 1988 and 2008
• Drugs for maternal health indications under active investigation (less than 3% of the pipeline for cardiovascular health, less than some rare diseases)
• Reasons for lack of activity include risk aversion, cost of reproductive toxicology studies, small market size, widespread off-label use
Gaps for special population groups

WHO 2013 report:
- Children
- Women
- Elderly

*Bourgeois et al. 2016*

- Among > 80000 interventional trials conducted in high-income countries, 1.4% focused exclusively on elderly.
- 81% of those were mostly funded by non-profit organizations
- 33% of interventions were drugs
- Very few and mostly small studies are conducted exclusively in elderly, even for conditions affecting almost exclusively the elderly

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Trials studying exclusively elderly persons, N = 1,112</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention type, N (%)</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>368 (33.1)</td>
</tr>
<tr>
<td>Device</td>
<td>87 (7.8)</td>
</tr>
<tr>
<td>Behavioral</td>
<td>195 (17.5)</td>
</tr>
<tr>
<td>Procedure</td>
<td>70 (6.3)</td>
</tr>
<tr>
<td>Biologic</td>
<td>78 (7.0)</td>
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<tr>
<td>Dietary supplement</td>
<td>108 (9.7)</td>
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<tr>
<td>Radiation</td>
<td>7 (0.6)</td>
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<tr>
<td>Genetic</td>
<td>1 (0.1)</td>
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<tr>
<td>Other</td>
<td>198 (17.8)</td>
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</table>
Asymmetry within indications – liver diseases

Table 3: Attention to Burden Index

<table>
<thead>
<tr>
<th></th>
<th>HBV</th>
<th>HCV</th>
<th>NAFLD</th>
<th>ALD</th>
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<tr>
<td>Mean research attention</td>
<td>29%</td>
<td>51%</td>
<td>15%</td>
<td>5%</td>
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<tr>
<td>Mean disease burden</td>
<td>5%</td>
<td>28%</td>
<td>17%</td>
<td>50%</td>
</tr>
<tr>
<td>Ratio</td>
<td>6.71</td>
<td>1.67</td>
<td>0.93</td>
<td>0.10</td>
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<tr>
<td>Fold-over ratio</td>
<td>6.71</td>
<td>1.67</td>
<td>-1.08</td>
<td>-9.68</td>
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<tr>
<td>Attention-to-Burden Score</td>
<td>6.71</td>
<td>1.7</td>
<td>-1.1</td>
<td>-9.7</td>
</tr>
</tbody>
</table>

The Attention-to-Burden score is bolded to highlight it. It is the final score that was calculated that informed the Attention Burden Index.

ALD, alcoholic liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus; NAFLD, non-alcoholic fatty liver disease.
Pharmaceutical gaps – lack of incentive?

(1) Small target populations (e.g. rare diseases, specific population groups)

(2) Short courses of curative treatment (e.g. antibiotics)

(3) Factors complicating study design (e.g. research in vulnerable populations)
Examples of related developments so far

• EU Paediatric Regulation (2007)
• Antimicrobial resistance: G20 focus on AMR (“Berlin Declaration” 2017)
• WHO R&D blueprint & Priority Pathogen list
• WHO R&D Observatory
• Conclusions of the Dutch Presidency of the European Council 2016

⇒ Need for a comprehensive, evidence-based strategy
The way forward? Some ideas for zooming in on pharmaceutical gaps and related unmet need:

- Better EU Member State cooperation to identify needs based on burden of disease
  - Increased transparency
  - Structured information exchange
  - Coordination with WHO R&D Observatory
- Better alignment of national and EU funding to priorities
  - Clear communication to public and private funders
- Pooled financing mechanism at EU level to support
  - New R&D models
  - Clinical trial networks (e.g. EU PREPARE) in conducting studies in challenging populations
  - SMEs and non-entrepreneurial investigators
- Public-Private Partnerships
- Global R&D Collaboration Hub on AMR (G20)
- Horizon scanning linked to the documentation of persisting pharmaceutical gaps/unmet need?
Aligning priorities – a national example

Ideas to tackle unmet need beyond pharmaceutical gaps and R&D

• Increased focus on strategic procurement, including joint initiatives
• Medicine shortage reporting systems
• Use of national compassionate use programmes if products do not launch
• Public health waivers of data and market exclusivities (at least for publicly funded knowledge)
• Reduction of waste through
  ❖ Strengthening post-launch data collection
  ❖ Increased clarity and rigor in delisting pathways for medicines failing safety/effectiveness goals
  ❖ Enhanced collaboration in horizon scanning and HTA to enable
    ✓ Awarding premium prices only to medicines providing actual added value for patients
    ✓ Optimizing the design and implementation of MEAs
Literature


