Workshop outline

- Quick entry poll
- What are the costs of pharmaceutical R&D and are they rising?
- How is the cost of R&D being sustained and can this be maintained in the future?
- Are there other approaches to funding R&D that should be considered?
- Is the approach being considered for antimicrobial research a suitable model for other therapeutic areas?
Topics and moderators

Quick entry poll and introduction
**Monique Martin**

What are the costs of R&D and why are they rising - **Mike Drummond**

Sustainability of R&D
- New approaches
- Antimicrobial model suitable for other TAs?
  **Ali McGuire**

Quick exit poll
**Monique Martin**

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Quick entry poll 1

Who believes that there is a problem related to the sustainability of R&D?

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**Yes!**  **NO**
Quick entry poll 2

Who believes that it is increasingly difficult to obtain a high prices in the reimbursement of new products?

Yes! NO

Quick entry poll 3

Who believes that there is an issue related to the productivity of R&D research (meaning that there are fewer new compounds)?

Yes! NO
Quick entry poll 4

Who is of the opinion that R&D costs are increasing beyond what is sustainable?

Yes!  No

Quick entry poll 5

Which area has the highest rate of return in R&D?

- Oncology
- CNS
- Cardiology
Introduction

- Pharma industry is dependent on the discovery of new treatments and technology
- Lengthy process
  - 12-13 years and increasing due to pre-and post-marketing requirements
- R&D is associated with substantial uncertainty
  - 1-2/10,000 substances synthesised will become a marketable drug
- Patent duration unchanged since first conceived (20 years) but effective patent life is now around 11 years
- Return on investment is uncertain
  - Around 16 years of effective patent life is required for breakeven
  - 2 out of every 10 newly approved drugs will be profitable

EFPIA 2014: pharmaceutical industry in figures; Wall Street Journal Jan 23 2012

R&D Expenditure facts

- R&D expenditure is substantial
  - 2013: €30,630m EU
  - Continued increase 1990 – 2010
  - Levelling off from 2010
- R&D statistics:
  - 1-2 / 10,000 NMEs becomes a marketable medicine
  - 12-13 years between first synthesis to the market introduction

Pharmaceutical R&D Expenditure in Europe, USA and Japan (million of national units), 1990-2013

Note: Europe: € million; USA: $ million; Japan: ¥ million x 100; (e): estimate
Source: EFPIA member associations, phRMA, JpMA
Increase in R&D expenditure does not guarantee drug approval, highlighting the riskiness of R&D and underlining the failings of the old approach to R&D.

**Annual New Approvals by FDA with Industry R&D expenditure 1994-2013**

Source: Health Affairs, February 3, 2015.

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**Number of approvals by FDA increased in 2014**

Source: FDA [http://www.fda.gov/drugs/developmentapprovalprocess/druginnovation/default.htm](http://www.fda.gov/drugs/developmentapprovalprocess/druginnovation/default.htm)
Lack of sustainability in antimicrobial research

- Inadequate return from developing new antimicrobials which are typically held in reserve until antimicrobial resistance develops to older classes of drugs

- Consequently no new classes of antimicrobials developed for several years, leading to real concerns about consequences of formerly anodyne infections

- This has led to discussions of alternative funding models for antimicrobial research

Estimates of the cost of developing a drug

<table>
<thead>
<tr>
<th>Study</th>
<th>Period</th>
<th>Sample</th>
<th>Out of pocket costs ($-million)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young and Surrusco (2001)</td>
<td>1990-2000</td>
<td>84: average per annum of all drug approvals by the US FDA (PhRMA)</td>
<td>222</td>
</tr>
<tr>
<td>DiMasi and Grabowski (2007)</td>
<td>1990-2003</td>
<td>17 unspecified biotech compounds (CSDD)</td>
<td>660</td>
</tr>
<tr>
<td>Adams and Brantner (2010)</td>
<td>1989-2001</td>
<td>2245 unspecified drugs from 183 firms (PPJB)</td>
<td>551</td>
</tr>
<tr>
<td>Paul et al. (2010)</td>
<td>1997-2007</td>
<td>R&amp;D modelling to develop a single new molecular entity</td>
<td>956</td>
</tr>
<tr>
<td>Light and Warburton (2011)</td>
<td>1983-1994</td>
<td>68 unspecified compounds (Calculations based on DiMasi et al. (2003))</td>
<td>198</td>
</tr>
<tr>
<td>Mestre-Ferrandiz et al. OHE (2012)</td>
<td>1998-2002</td>
<td>209 unique molecules (unspecified compounds; CMRI)</td>
<td>949</td>
</tr>
<tr>
<td>DiMasi et al. (2014)</td>
<td>1995-2007</td>
<td>106 randomly selected new drugs from 10 firms (CSDD)</td>
<td>1,418</td>
</tr>
</tbody>
</table>

Notes: Figures converted to year 2014 US dollars using the US Gross Domestic Product (GDP) deflator (Bureau of Economic Analysis); CSDD: Center for the Study of Drug Development; CMRI: Centre for Medicines Research; FDA: Food and Drug Administration; OHE: Office of Health Economics; PhRMA: Pharmaceutical Research and Manufacturers of America.
Out of pocket cost estimates in terms of preclinical and clinical research

**Cash estimates in $-million dollars**

![Cash estimates graph]

Note: Figures converted to year 2014 US dollars using the US Gross Domestic Product (GDP) deflator (Bureau of Economic Analysis)

**Capitalised cost estimates**

**Capitalised costs estimates in $-million dollars**

![Capitalised costs graph]

Notes: Figures converted to year 2014 US dollars using the US Gross Domestic Product (GDP) deflator (Bureau of Economic Analysis)
Capitalised clinical costs of drug development by therapeutic area

Notes: Figures converted to year 2014 US dollars using the US Gross Domestic Product (GDP) deflator (Bureau of Economic Analysis)

Success rates* by therapeutic area
(* Transition probability from phase I to HTA Approval)

Development time* in months by therapeutic area

(* time from the beginning of phase 1 to the end of phase 3)

![Development time chart]


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Estimates of the projected value of R&D projects

<table>
<thead>
<tr>
<th>Rank</th>
<th>Product</th>
<th>Company</th>
<th>Phase (Current)</th>
<th>Pharmacological class</th>
<th>Worldwide Product Sales ($m) 2020</th>
<th>Today’s NPV ($m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Nivolumab</td>
<td>Bristol-Myers Squibb</td>
<td>Phase III</td>
<td>Anti-programmed death-1 (PD-1) MAb</td>
<td>6,012</td>
<td>23,150</td>
</tr>
<tr>
<td>2</td>
<td>MK-375</td>
<td>Merck &amp; Co</td>
<td>Filed</td>
<td>Anti-programmed death-1 (PD-1) MAb</td>
<td>4,063</td>
<td>16,747</td>
</tr>
<tr>
<td>3</td>
<td>RG7446</td>
<td>Roche</td>
<td>Phase III</td>
<td>Anti-programmed death-1 ligand-1 (PD-L1) MAb</td>
<td>2,937</td>
<td>15,639</td>
</tr>
<tr>
<td>4</td>
<td>Obeticholic acid</td>
<td>Intercept Pharmaceuticals</td>
<td>Phase III</td>
<td>Farnesoid X receptor (FXR) agonist</td>
<td>2,992</td>
<td>11,426</td>
</tr>
<tr>
<td>5</td>
<td>Ledipasvir / Sofosbuvir</td>
<td>Gilead Sciences</td>
<td>Filed</td>
<td>Hepatitis C nucleoside NSSA &amp; NS5B polymerase inhibitor</td>
<td>2,818</td>
<td>9,876</td>
</tr>
<tr>
<td>6</td>
<td>Palbociclib</td>
<td>Pfizer</td>
<td>Phase III</td>
<td>Cyclin-dependent kinase (CDK) 4 &amp; 6 inhibitor</td>
<td>2,992</td>
<td>7,925</td>
</tr>
<tr>
<td>7</td>
<td>DCVax-L</td>
<td>Northwest Biotherapeutics</td>
<td>Phase III</td>
<td>Cancer vaccine</td>
<td>2,046</td>
<td>5,502</td>
</tr>
<tr>
<td>8</td>
<td>VX-809 + ivacaftor</td>
<td>Vertex Pharmaceuticals</td>
<td>Phase III</td>
<td>Cystic fibrosis transmembrane conductance regulator (CFTR)</td>
<td>1,900</td>
<td>5,011</td>
</tr>
<tr>
<td>9</td>
<td>MEDI4736</td>
<td>AstraZeneca</td>
<td>Phase III</td>
<td>Anti-programmed death-1 ligand-1 (PD-L1) MAb</td>
<td>967</td>
<td>4,711</td>
</tr>
<tr>
<td>10</td>
<td>Lampalizumab</td>
<td>Roche</td>
<td>Phase II</td>
<td>Anti-complement factor D MAb</td>
<td>1,122</td>
<td>4,520</td>
</tr>
</tbody>
</table>

Source: EvaluatePharma®, World Preview 2014, Outlook to 2020
Can the price increases in oncology drugs in the US be justified?

- Four times increase in R&D cost per patient in clinical trials between 2000 and 2012 ($25,000 to $100,000) [1]
- Ten to twenty times increase in average price of cancer drugs between 2000 and 2012 ($5000 - $10,000 to > $100,000) [2].

<table>
<thead>
<tr>
<th>Increase in R&amp;D costs</th>
<th>Increase in average price</th>
</tr>
</thead>
<tbody>
<tr>
<td>➢ Increasing regulatory burden imposed by health agencies including NIH, NCI, FDA and Office human protection</td>
<td>➢ Price generally based on what the market will bear</td>
</tr>
<tr>
<td>➢ A total of 300 to 600 regulatory steps to initiate a trial (half of them judged unnecessary).</td>
<td>➢ No clear relationship between price and added clinical value</td>
</tr>
<tr>
<td></td>
<td>➢ A ‘fair drug price must also reflect the reality of its true benefit and social and personal costs’</td>
</tr>
</tbody>
</table>


Can the current rate of price increases be sustained?

- Price reductions and restrictions in reimbursement have occurred in many European markets
- Future clinical guidelines from the American Heart Association and American College of Clinical Cardiology will incorporate an assessment of cost-effectiveness
- American clinical oncologists have openly questioned the rising cost of cancer drugs (Walker J The Wall Street Journal, June 1, 2015)
- The American Society of Clinical Oncology (ASCO) scorecard has ‘patient cost’ as one of its dimensions
- The Institute for Clinical and Economic Review (ICER) is planning to publish ‘value assessments’ of 15-20 ‘high impact’ drugs per annum
- The initial reports suggest that ‘value-based prices’ may be much lower than current list prices in the US
Summary on R&D costs

- Although there is debate about the methodologies for estimating the cost of developing a drug, these costs are substantial and are rising.

- The average cost estimates mask the fact that costs vary by therapeutic area, owing to differences in success rates and development times.

- Despite the increases in the cost of research, the projected returns on the research investment remain high, mainly because of the ability to raise drug prices, particularly in the US.

- The main question for the future is whether raising drug prices will be sustainable in the long run.

Changes in R&D costs over time

- Development costs vary across different TAs — High costs for neurology, respiratory vs. lower costs for HIV/AIDS and anti-parasitics.

- Development costs increased nearly 600% from the 1970s to the 2000s:
  - Success rates fell from 1 in 5 in the 1980s to 1 in 10 in the 2000s.
  - May be picking up again.

- Science underlying drug development has become more complex and regulatory barriers have risen: Market access slowed from 6 to 13.5 years between the 1970s and 2000s.
Is sustainability sustainable?

- If ever increasing prices are not sustainable what is the future?
  - Answer depends on the problems

- R&D Problems:
  - Falling/Small revenue base: Antibiotics/Orphan drugs
  - High/differential cost of R&D: General/different cost basis

- Large uncertainty

- Increasing length to market/increasing regulation
  - USA – focus on safety/efficacy
  - Europe safety/efficacy & reimbursement

Responses to rising R&D costs

- Improve R&D returns by:
  - Increasing Product revenue
  - Reducing R&D costs
  - Reducing R&D cycle times
**Problem: Falling revenue base**

- **Example: Antibiotics**
    - “Pull” mechanism
      - Global authority with resources to award lump sum payments to successful drug development
      - Objective of 15 new antibiotics per decade with 2 new classes of drug
      - Estimated cost of $16bn - $37bn per decade, i.e. $1bn-$2.5bn per drug
    - $2bn “push” AMR innovation fund paid for by industry

**Problem: Falling revenue base**

- Will this be the case for new targeted products?
- Oncology, high R&D costs, increasingly targeted population (increasing orphan drug status), sometimes dual-therapies
- Not everything can be an orphan drug!
- Revenue base shrinkage for each product?
- Public response (as with antibiotics which can be seen as an extreme case)
  - Cancer Drugs Fund could be seen in this light
  - Weak empirical evidence on cancer premia
  - Not sustainable...
  - Patient Access Schemes, risk-sharing generally...
Reducing R&D Costs

- Companies focus on less therapeutic areas to give higher return through:
  - Improved scientific knowledge (reduces uncertainty)
  - Better understanding of disease management (reduces uncertainty)
  - Better negotiation over price, reimbursement and market access (better information leads to an improved bargaining position)
  - Examples
    - Teva re-shaping therapeutic focus
    - Deloitte study 4 or less therapeutic areas optimal

Reducing R&D cost

- Strategic alliances
  - Eli Lilly claims to have been first in forming strategic alliance
  - c25% of US-based Pharma R&D takes place in collaborative agreements (Robinson & Stuart J of Law and Economics, 2007)

- Development arrangements
  - Economies of scale in selling product reduces the D component
  - (Novartis/Vertex $600 million + $200 million over 5 years
  - Bayer/CuraGen $1.3 billion in obesity and diabetes
  - BMS/ImClone $2 billion for co-commercialization of anti-cancer therapy
  - Wyeth/Santaris Pharma $10 million + milestone target payments up to $83 million for 10 potential targets

- Mergers & acquisitions
  - $221 billion M&A activity in first half of 2015
  - Cheaper to acquire than develop
Reducing R&D costs

- Outsourcing: spreading risks
  - CRO growth
  - Reduces in-house costs
  - May even shift outcome risk to CROs

Reducing R&D costs: New style R&D collaborations (to increase R&D subsidies and spread risk):

- Scientific partnership between: government research institutions, academic laboratories, firms and small biotech companies, clinical research centres and contract manufacturing organisations:
  - IAVI, International Aids Vaccine Initiative;
  - MMV, Medicines for Malaria Venture;
  - SGC, Structural genomics consortium.

- Financing systems:
  - Donors: Government agencies, foundations, international organisations, corporations, and private individuals
  - Private sector: Biotech and Pharma
  - Public sector: Research and academic institutions, Governments, International organisations.
  - Non Governmental Organisations
  - Clinical centres

- Extending to other areas? Cancer research collaborations
SGC funding

- SGC is funded by: Canada Foundation for Innovation, Genome Canada, GlaxoSmithKline, Janssen, Merck & Co., Novartis, Ontario Ministry of Research and Innovation, Pfizer, Takeda, and the Wellcome Trust.

- November 29, 2011: Structural Genomics Consortium announces $49m new funding to sustain 4 years of research from: Eli Lilly Canada, Pfizer Inc., the Canadian Institutes for Health Research, GlaxoSmithKline, the Novartis Research Foundation, the Ontario Ministry of Research and Innovation and the Wellcome Trust.

- March 4, 2015: Merck has contributed a total of $7.5 million to the Structural Genomics Consortium (SGC) Toronto and its network, thereby becoming a member of the consortium.

Solutions to reduce R&D costs

- March 20, 2013: Mr. Sanders introduced the bill S. 627 referred to the Committee on Health, Education, Labor, and Pensions in the Senate of the US:
  
  The Medical Innovation Prize Fund Act Proposal
  
  - Price setting based on severity of the condition and the size of the patient population
  - Abolishment of patent system ➔ Prices would fall sharply. It would avoid the “me-too” market, preventing innovation
  - Project left out of his proposal for the US presidential elections 2016
  
  NOT MUCH ON GOING POLITICAL SUPPORT FOR THESE SCHEMES

Source: Overview of the Medical Innovation Prize Fund (2006)

https://www.govtrack.us/congress/bills/113/s627/text
Reducing Product Cycle times

- Various changes to regulation
  - Various proposals
    - EMA Conditional Marketing Approval
    - Adaptive Pathways Pilot
  - Working with different levels of efficacy
  - No clear agreement on different routes
  - Regulatory authorities reacting to increasing regulation...
  - Incrementalism in regulation...

Conclusions

- Clear that R&D costs rising and productivity (so far) falling
- Various solutions offered
  - Industry responses
  - De-coupling responses
  - Regulatory responses
- Not clear that there is a single golden solution
- Why is the anti-microbial solution important?
  - Falling revenue problem
  - Consistent with the future?
    - More targeting/more orphan drug status
Conclusions contd.

- Antibiotics characterize one dimension (flaying revenue base) of a larger problem (increasing R&D cost recovery)

- Although only one part of the issue it provided an impetus to a radical re-think of payment and R&D funding structures

- Currently regulators are responding to these issues incrementally

- But...
  - Not every product can be an orphan
  - Not every product can be fast tracked
  - Not every product can be opened to risk-sharing agreements

- Given the larger picture is it time to think about grander solutions?

- Or is the current regulatory environment able to adapt...?

Exit poll 1

Do you believe that problems related to R&D are different by therapeutic area

![Yes!](image1.png) ![No](image2.png)
Exit poll 2

Do we expect R&D costs to continue to rise?

Yes! NO

Exit poll 3

Do you expect R&D costs in cancer to continue to rise?

Yes! NO
Exit poll 4

Do you feel that any of the suggested solutions could make a difference?

Thank you