Trends of the Pharmaceutical Industry Following the British Withdrawal

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Market Development Director

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Disclaimer

This presentation is a preliminary perspective on the potential implications, specially for the prescription medicines market, of the majority LEAVE vote. It takes no view on the wider implications of such a vote, for the UK or for Europe.

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Healthcare Systems, Pharma and Patient Needs Underpinned
The Merger Rationale

Improve clinical trial design and execution

Deliver higher commercial results more efficiently

Demonstrate value of medicine and measure outcomes
QuintilesIMS – UK Market Profile

A leading employer and contributor to the UK Life Sciences industry (Revenue: £650m Employees: 3,800)

- The UK’s leading Clinical Trial provider
- Leading global centre for Real World Evidence
- Over 1bn patient transactions processed per year
- #1 provider of cost-benchmarking to NHS England

**Technology**
- UK #1 in CRM & Market Reference data
- Master Data Management
- Multi Channel Marketing
- Social Media

**Real World Late Phase**
- >1,000 staff
- Salesforce Delivery
- Nursing and Home care services
- Medical Writing & remote support

**Integrated Engagement Solutions**
- Observational Studies
- Enriched Real World Insights
- PHE SACT Data (Simulacrum)

**Clinical Trials**
- c.180 RCT’s conducted every year
- >5,000 patients enrolled every year
- Over 90 Hospitals engaged at any one time
- 3 Prime Sites (UCLP, Peninsular, Scotland)

**Market Insight**
- 99% of all Hospitals contribute to the IMS audit
- 85% of Retail Pharmacies engaged to provide insight
- 1bn transactions per year captured and transformed

**Real World Evidence**
- >200 Real World Evidence scientists
- THIN 5.2m anonymised GP records
- Cancer Vanguard Medicines Optimisation Partner of Choice
- Oncology Data Collaborative
- Over 500m global patient records
- Research & Privacy Platforms

**Healthcare Services**
- Cost Benchmarking to over 90 NHS Trusts
- Market Leader in Patient Level Costing (46 Trusts)
- Care Pathway Analytics
- Mobile Health Prescribing

**Commercial Support**
- Market Access consulting
- Leading M&A advisory services
- Segmentation and targeting
- Primary Market research

• Over 90 Hospitals engaged at any one time
• 3 Prime Sites (UCLP, Peninsular, Scotland)
Trends of the Pharmaceutical Industry Following the British Withdrawal

Global and EU Trends in Pharmaceutical market

Brexit-9 months on

Concluding Thoughts
The economic future remains bright in Ireland

GDP 1.9% - 2017
GDP 2.8% - 2018
GDP 2.9% - 2019

In the next few years, Ireland’s domestic economy is expected to continue to expand at robust rates. But the risks have also increased, reflecting the referendum on the UK’s membership of the EU and the uncertainty surrounding future US tax policies.
Key Issues for Ireland Pharmaceuticals 2017-2021?

The operating environment facing manufacturers is increasingly complex. QI forecast a 1.6% CAGR to 2021 (£2.1bn IPHA agreements & overall affordability to the HSE limiting net revenues generated by most companies.

- **Business Environment**
  - GDP growing, but uncertainty about the future of Ireland's relationship with the UK free trade, border controls.

- **Healthcare Provision**
  - Healthcare reforms pursued against a background of financial challenge and in context of new IPHA agreement. Govt net funding to HSE lower than 2009.

- **Prescribing & Dispensing**
  - Payors using affordability and outcomes based evaluation to manage entry of tsunami of specialised medicines eg: High cost drugs have to replace existing medicine to gain NCPE approval, HSE decision authority over 20mn.

- **Pricing & Reimbursement**
  - IPHA savings 600mn
  - Rebates agreed +5% of sales
  - Biologics price cuts 30%
  - Small molecule LoE price cut 50%
  - Will UK stay in Irish price comparator basket post Brexit?

- **Regulatory Environment**
  - EMA HQ Dublin?
  - Regulatory alignment on joint UK&I packs?
  - Future of leading in corporate inversions in a Trump era?
  - ‘Free trade, free travel, no border controls with UK’-the lucky shamrock post Brexit?

Source: IMS Health Market Prognosis, 2016 *at ex-manufacturer price levels, excluding rebates & discounts
In the coming decades healthcare spending will outgrow the economy, creating a sustainability challenge for healthcare systems and new opportunities for life sciences industry growth.

**Projected GDP vs healthcare spend**
Compound annual growth rate, Percent

**OECD**
- Annual GDP growth over next 50 years: +1.3, 2.0
- Annual healthcare spend growth over next 50 years: 3.3

**BRICS**
- Annual GDP growth over next 50 years: +1.6, 3.9
- Annual healthcare spend growth over next 50 years: 5.5

- OECD predicts that **global healthcare spend growth will likely outpace economic growth** (3.3% vs 2.0% OECD; 5.5% vs 3.9% BRICS)
- Spend increases driven by tailwinds incl. changes in demand, macroeconomics, healthcare systems and innovation
- Healthcare systems globally are facing an **unprecedented sustainability challenge**, but also an opportunity for innovative life sciences companies to grow

Source: OECD GDP long-term forecasts 2009-2060; OECD public spending on health and long-term care: a new set of projections
# Forces shaping global healthcare

<table>
<thead>
<tr>
<th>Description</th>
<th>Illustrative data points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demand</strong></td>
<td></td>
</tr>
<tr>
<td>1 Population pyramids are inverting, and shifts in the old-age population[^1^] are often more extreme in emerging markets</td>
<td>▪ 1 billion more people on the planet, 90% of whom will be in emerging markets. Irish popn grown 12% in 10 years. Half a billion more people older than 50 and &gt;320m people older than 80 by 2030</td>
</tr>
<tr>
<td>2 Chronic diseases will dwarf other needs for healthcare</td>
<td>▪ Chronic diseases will account for over 80% of DALYs (Disability-Adjusted Life Years) in 2025 led by cancer, heart disease, and unipolar depressive disorders</td>
</tr>
<tr>
<td>3 Patient expectations are rapidly evolving in line with changing consumer habits – healthcare needs to be on demand and service focused</td>
<td></td>
</tr>
<tr>
<td><strong>Macro-economics</strong></td>
<td></td>
</tr>
<tr>
<td>4 Structural growth in emerging markets will drive the majority of the global growth within the life sciences market</td>
<td>▪ By 2025, the global economy will almost double compared to today in nominal terms led by Asia. Ireland GDP growing-2.8% 2018</td>
</tr>
<tr>
<td>5 Emerging markets will be a large driver of growth across all markets</td>
<td>▪ By 2023, emerging market pharma sales will account for ~45% (of the global total, up from 35% in 2016)</td>
</tr>
<tr>
<td><strong>Healthcare systems</strong></td>
<td></td>
</tr>
<tr>
<td>6 Sustained pressure on healthcare budgets from an aging population will force healthcare systems to refocus on productivity &amp; affordability</td>
<td>▪ Irish Gov’t spending to HSE now less than in 2009.</td>
</tr>
<tr>
<td>7 Health systems are shifting to integrated care and outcome-based payments from hospital-based care with activity-based payments</td>
<td>▪ Average share of GDP OECD countries spend on healthcare is forecast to fall from 9% in 2015 to 8.5% in 2020 as populations grow and age</td>
</tr>
<tr>
<td>8 Explosion of patient level healthcare data from research, clinical and real-world sources</td>
<td>▪ Volume of healthcare data could increase 120 times by 2030 if current trends of data capture are maintained</td>
</tr>
<tr>
<td><strong>Innovation</strong></td>
<td></td>
</tr>
<tr>
<td>9 Innovation is rapidly evolving life sciences towards “Industry 4.0” – the advance and convergence of key technologies including increasing data volumes, advanced robotics, data science, computational power and connected devices</td>
<td>▪ Delivery model is accelerating business model innovation, e.g., remote patient care, telemonitoring, outcomes based payments</td>
</tr>
<tr>
<td></td>
<td>▪ An estimated 50bn devices will be connected to the Internet by 2020, creating opportunities for real time patient monitoring and interventions</td>
</tr>
</tbody>
</table>

[^1^]: People aged over 65 per population of 100 aged between 18 and 65

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[^1^]: No Ordinary Disruption, United Nations Population Division, WHO (DALYs), Literature research (prevalence), The Conference Board’s Total Economy Database; United Nations Population Division; International Labour Organisation, Nuffield Trust The funding pressures facing the NHS from 2010/11 to 2021/22 A decade of austerity?; Better Procurement, Better Value, Better Care A Procurement Development Programme for the NHS, DH, 2013; OECD; Business Monitor International; The Heritage Foundation; press search
Ireland Cumulative Percentage Increase In Population Compared to the EU

Source: Eurostat.
Pharmaceutical market grows to $1.4 trillion by 2020, with a CAGR of 4-7%
Government net funding to HSE – spend is now less per head of population than in 2009

Source: HSE monthly performance reports. Available at: http://www.hse.ie/eng/services/Publications/corporate/performance reports/MonthlyPRs.html
There is increasing convergence between developed and emerging markets

Developed vs. Emerging pharmaceutical sales growth (list price, pre rebates and discounts)

**Developed** – Recovery from patent cliff, economic austerity

**Emerging** – Universal coverage expansion

**Developed** – Strong specialty launches

**Emerging** – Economic volatility, cost cutting measures

Notes: *Full Year PPG shown
Source: IMS MIDAS MAT Q2 2016; Rx-bound; Period Growth calculated using MAT LCUS$
EU5 is no longer a single bloc in the rankings—and Ireland sliding down the league table

<table>
<thead>
<tr>
<th>Rank</th>
<th>2010</th>
<th>Rank</th>
<th>2015</th>
<th>Rank</th>
<th>2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>USA</td>
<td>1</td>
<td>USA</td>
<td>1</td>
<td>USA</td>
</tr>
<tr>
<td>2</td>
<td>Japan</td>
<td>2</td>
<td>China</td>
<td>2</td>
<td>China</td>
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<tr>
<td>3</td>
<td>China</td>
<td>3</td>
<td>Japan</td>
<td>3</td>
<td>Japan</td>
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<tr>
<td>4</td>
<td>Germany</td>
<td>4</td>
<td>Germany</td>
<td>4</td>
<td>Germany</td>
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<tr>
<td>5</td>
<td>France</td>
<td>5</td>
<td>France</td>
<td>5</td>
<td>Brazil</td>
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<tr>
<td>6</td>
<td>Italy</td>
<td>6</td>
<td>Italy</td>
<td>6</td>
<td>UK</td>
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<tr>
<td>7</td>
<td>Spain</td>
<td>7</td>
<td>UK</td>
<td>7</td>
<td>France</td>
</tr>
<tr>
<td>8</td>
<td>UK</td>
<td>8</td>
<td>Brazil</td>
<td>8</td>
<td>Italy</td>
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<tr>
<td>9</td>
<td>Canada</td>
<td>9</td>
<td>Spain</td>
<td>9</td>
<td>India</td>
</tr>
<tr>
<td>10</td>
<td>Brazil</td>
<td>10</td>
<td>Canada</td>
<td>10</td>
<td>Spain</td>
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<td>11</td>
<td>South Korea</td>
<td>11</td>
<td>India</td>
<td>11</td>
<td>Canada</td>
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<tr>
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<td>Australia</td>
<td>12</td>
<td>South Korea</td>
<td>12</td>
<td>South Korea</td>
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<tr>
<td>13</td>
<td>India</td>
<td>13</td>
<td>Russia</td>
<td>13</td>
<td>Russia</td>
</tr>
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<td>14</td>
<td>Mexico</td>
<td>14</td>
<td>Australia</td>
<td>14</td>
<td>Australia</td>
</tr>
<tr>
<td>15</td>
<td>Russia</td>
<td>15</td>
<td>Mexico</td>
<td>15</td>
<td>Turkey</td>
</tr>
<tr>
<td>16</td>
<td>Poland</td>
<td>16</td>
<td>Argentina</td>
<td>16</td>
<td>Mexico</td>
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<tr>
<td>17</td>
<td>Netherlands</td>
<td>17</td>
<td>Turkey</td>
<td>17</td>
<td>Saudi Arabia</td>
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<tr>
<td>18</td>
<td>Belgium</td>
<td>18</td>
<td>Poland</td>
<td>18</td>
<td>Poland</td>
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<tr>
<td>19</td>
<td>Greece</td>
<td>19</td>
<td>Saudi Arabia</td>
<td>19</td>
<td>Argentina</td>
</tr>
<tr>
<td>20</td>
<td>Turkey</td>
<td>20</td>
<td>Belgium</td>
<td>20</td>
<td>Switzerland</td>
</tr>
<tr>
<td>40</td>
<td>Ireland</td>
<td>48</td>
<td>Ireland</td>
<td>54</td>
<td>Ireland</td>
</tr>
</tbody>
</table>

Notes: LCUS$ used for ranking; Pharmerging countries highlighted; Venezuela removed from pharmerging definition in 2016; at ex-manufacturer price levels, not including rebates and discounts. Contains Audited + Unaudited data.

Source: QuintilesIMS Market Prognosis Q3 2016
Over 60% of global growth comes from five TAs, four specialty

Global: Highest growth Therapy Areas
Absolute one year growth 2016 (LCUS$ Bn)

<table>
<thead>
<tr>
<th>Therapy Area</th>
<th>US</th>
<th>EU5</th>
<th>Japan</th>
<th>Pharmerging</th>
<th>All Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncologics</td>
<td>53%</td>
<td>21%</td>
<td>-</td>
<td>16%</td>
<td>11.3</td>
</tr>
<tr>
<td>Antidiabetics</td>
<td>81%</td>
<td>3%</td>
<td>-</td>
<td>15%</td>
<td>11.3</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>8%</td>
<td>36%</td>
<td>-</td>
<td>13%</td>
<td>9.7</td>
</tr>
<tr>
<td>Autoimmune</td>
<td>78%</td>
<td>10%</td>
<td>-</td>
<td>13%</td>
<td>9.6</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>53%</td>
<td>-</td>
<td>-</td>
<td>5%</td>
<td>3.5</td>
</tr>
<tr>
<td>Respiratory</td>
<td>78%</td>
<td>-</td>
<td>-</td>
<td>4%</td>
<td>3.1</td>
</tr>
<tr>
<td>HIV</td>
<td>84%</td>
<td>-</td>
<td>-</td>
<td>4%</td>
<td>2.7</td>
</tr>
<tr>
<td>MS</td>
<td>76%</td>
<td>-</td>
<td>-</td>
<td>3%</td>
<td>2.5</td>
</tr>
<tr>
<td>Nervous System</td>
<td>74%</td>
<td>-</td>
<td>-</td>
<td>3%</td>
<td>2.0</td>
</tr>
<tr>
<td>GI</td>
<td>1.8</td>
<td>-</td>
<td>-</td>
<td>2%</td>
<td></td>
</tr>
</tbody>
</table>

Share of global growth 2015

<table>
<thead>
<tr>
<th>Therapy Area</th>
<th>US</th>
<th>EU5</th>
<th>Japan</th>
<th>Pharmerging</th>
<th>All Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncologics</td>
<td>21%</td>
<td>-</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>Antidiabetics</td>
<td>3%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Autoimmune</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Respiratory</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HIV</td>
<td>-</td>
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<td>-</td>
<td>-</td>
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<tr>
<td>MS</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Nervous System</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>GI</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

62% of global growth

Concentration has reduced from the previous iteration (73% in top 5 TAs) because we have passed peak Hepatitis C

Source: QuintilesIMS MIDAS MAT Q2 2016
Specialty and biologics drive global growth

**Specialty vs. traditional sales**
*2010-2015 US$*

- **2010**
  - Specialty: 748 (23%)
  - Traditional: 77% (77%)
- **2015**
  - Specialty: 893 (30%)
  - Traditional: 70%

**Biologic vs. small molecule sales**
*2010-2015 US$*

- **2010**
  - Biologic: 748 (20%)
  - Small Molecule: 80%
- **2015**
  - Biologic: 893 (24%)
  - Small Molecule: 76%

Source: QuintilesIMS MIDAS Q4 2015
Primary care squeezed in Europe — and in Ireland speciality medicines grown by 420mn Euros in 10 years

Europe : Top 15 Therapy Areas sales and growth

<table>
<thead>
<tr>
<th>Therapy Area</th>
<th>Sales 2016 US$ Bn</th>
<th>Value CAGR 2011-16</th>
<th>Volume CAGR 2011-16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncologics</td>
<td>25.7</td>
<td>8%</td>
<td>3%</td>
</tr>
<tr>
<td>Autoimmune</td>
<td>11.5</td>
<td>13%</td>
<td>4%</td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>9.9</td>
<td>-6%</td>
<td>2%</td>
</tr>
<tr>
<td>Antidiabetics</td>
<td>9.7</td>
<td>6%</td>
<td>3%</td>
</tr>
<tr>
<td>Viral Hepatitis</td>
<td>9.5</td>
<td>56%</td>
<td>-1%</td>
</tr>
<tr>
<td>Pain</td>
<td>9.4</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Respiratory</td>
<td>8.6</td>
<td>0%</td>
<td>1%</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>8.0</td>
<td>9%</td>
<td>4%</td>
</tr>
<tr>
<td>Mental Health</td>
<td>6.5</td>
<td>-5%</td>
<td>3%</td>
</tr>
<tr>
<td>HIV</td>
<td>6.0</td>
<td>6%</td>
<td>-1%</td>
</tr>
<tr>
<td>Antibacterials</td>
<td>6.0</td>
<td>-2%</td>
<td>-1%</td>
</tr>
<tr>
<td>Nervous System</td>
<td>5.6</td>
<td>2%</td>
<td>4%</td>
</tr>
<tr>
<td>MS</td>
<td>5.0</td>
<td>11%</td>
<td>26%</td>
</tr>
<tr>
<td>Lipid Regulators</td>
<td>4.7</td>
<td>-6%</td>
<td>3%</td>
</tr>
<tr>
<td>Other CV</td>
<td>3.3</td>
<td>0%</td>
<td>-6%</td>
</tr>
<tr>
<td>Market</td>
<td>185.3</td>
<td>3%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Source: QuintilesIMS MIDAS Q2 2016, Rx only; Europe excludes Russia and Turkey
Infliximab: UK leads in EU5 with 60% penetration, Ireland 2\textsuperscript{nd} lowest uptake at 8.9% against a €785 IPHA target

Europe: Infliximab biosimilar market share in treatment days

Source: QuintilesIMS MIDAS MTH October 2016; Denmark data from MIDAS Monthly Restricted database; Latvia excluded because only biosimilar manufacturers present in market (treatment days)
The pipeline is rich with biologics…and orphan drugs

Over 25% of late stage pipeline is orphan designated

### Pharmaceutical Pipeline by product type 2015

<table>
<thead>
<tr>
<th>Stage</th>
<th>Small Molecule</th>
<th>Biologic</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preclinical</td>
<td>645</td>
<td>689</td>
<td>1334</td>
</tr>
<tr>
<td>Phase I</td>
<td>426</td>
<td>525</td>
<td>951</td>
</tr>
<tr>
<td>Phase II</td>
<td>731</td>
<td>731</td>
<td>1462</td>
</tr>
<tr>
<td>Phase III</td>
<td>192</td>
<td>300</td>
<td>492</td>
</tr>
<tr>
<td>Pre-Reg/Reg</td>
<td>72</td>
<td>134</td>
<td>206</td>
</tr>
</tbody>
</table>

### Phase III-Registered products split by orphan designation

- Non-orphan: 73%
- Orphan designated: 27%

Source: IMS Lifecycle R&D Focus, Dec 2015
Orphan drug (OD) approvals surge in Europe, making ~1/3 of all NCE’s launched in 2014

Vigorous patient advocacy, medical breakthroughs, legislative incentives, venture capital investment and industry collaboration, are dramatically changing the landscape of rare disease research

Number of ODs in Europe with European market authorization (MA) and orphan designation

- **Oncology** represents the largest category of products, including Revlimid, Tasigna, Sprycel and Nexavar
- ~15% are **Alimentary Tract and Metabolism** products, which include many of the most expensive ODs such as the enzyme replacement therapies
- **Cystic Fibrosis** treatments account for 7% of all approved ODs (TOBI Podhaler, Bronchitol, Kalydeco)

Source: European Medicines Agency Feb 2016
Brexit: Implications for Life Sciences, the Pharmaceutical Industry and Ireland Article 50: ‘T-Day’ 29th March 2017
Finding a Cure: Getting the Best deal for Britain’s Life Sciences
Report commissioned by QuintilesIMS

Finding a cure:
Getting the best Brexit deal for Britain’s life sciences
A report by Public Policy Projects | Supported by QuintilesIMS

Written by Luke Tryl
Introduction by Rt Hon Stephen Dorrell
The UK – a “great global nation”? Importance to global pharma is far greater than simple share suggests

Global pharma sales by region (2005-15) Billions of USD

- UK contributes up to 4.5% of global sales for top 20 companies
- For newly launched innovation and specialty growth, UK is a major contributor
- Third highest number of NCEs launched behind US and Germany between 2010-14
- Home to major global pharmaceutical HQs
- Highest pharmaceutical R&D expenditure in Europe
- Top five on pharma industry R&D investment and headcount
- Global leader in Health Technology Assessment and Real World Data collection and use

Source: IMS Health MIDAS MAT Q4 2005-Q4 2015; Constant currency
The UK is currently one of the leading countries for NCE launch numbers

Top 8 vs. BRICTM: number of NCE launches
2005-2009 & 2010-2014
n=150 and 170 respectively

<table>
<thead>
<tr>
<th>Top 8 mature</th>
<th>NCE's launched 2005-2009</th>
<th>NCE's launched 2010-2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>93</td>
<td>121</td>
</tr>
<tr>
<td>GERMANY</td>
<td>88</td>
<td>92</td>
</tr>
<tr>
<td>UK</td>
<td>82</td>
<td>83</td>
</tr>
<tr>
<td>JAPAN</td>
<td>41</td>
<td>67</td>
</tr>
<tr>
<td>ITALY</td>
<td>59</td>
<td>62</td>
</tr>
<tr>
<td>CANADA</td>
<td>48</td>
<td>60</td>
</tr>
<tr>
<td>SPAIN</td>
<td>70</td>
<td>59</td>
</tr>
<tr>
<td>FRANCE</td>
<td>57</td>
<td>58</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BRICTM</th>
<th>NCE's launched 2005-2009</th>
<th>NCE's launched 2010-2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>RUSSIA</td>
<td>35</td>
<td>33</td>
</tr>
<tr>
<td>BRAZIL</td>
<td>36</td>
<td>28</td>
</tr>
<tr>
<td>CHINA</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>INDIA</td>
<td>28</td>
<td>12</td>
</tr>
<tr>
<td>TURKEY</td>
<td>23</td>
<td>15</td>
</tr>
<tr>
<td>MEXICO</td>
<td>35</td>
<td>44</td>
</tr>
</tbody>
</table>

Source: IMS Health MIDAS 2014; *Analysis negates the impact of later launches outside of the US, NCE launches between 2004-2013 considered

UK third highest after Germany
The UK currently matters for launching innovative new pharmaceutical treatments, but needs to improve uptake

Proportion of cumulative 1- and 5-year sales of new launches 2005-2015 by country

<table>
<thead>
<tr>
<th>Country</th>
<th>1 Year</th>
<th>5 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germany</td>
<td>6.5%</td>
<td>5.5%</td>
</tr>
<tr>
<td>Italy</td>
<td>5.1%</td>
<td>4.5%</td>
</tr>
<tr>
<td>Spain</td>
<td>5.1%</td>
<td>2.6%</td>
</tr>
<tr>
<td>France</td>
<td>3.9%</td>
<td>2.5%</td>
</tr>
<tr>
<td>UK</td>
<td>0.9%</td>
<td>2.2%</td>
</tr>
</tbody>
</table>

Four key areas of uncertainty for the UK pharmaceutical industry

**Regulatory**
- Future location of the EMA and the future relation of the MHRA to it
- Distribution, Pharmacovigilance and Clinical trials regulation are among many areas which could be impacted
- European Patent system; Pharma Branch of the Unified Patents Court will be sited in London as planned

**Trade**
- Sterling devaluation shifts balance of pharmaceutical trade, although UK remains a net pharmaceutical importer
- Impact of creeping regulatory dissonance on trade?

**Commercial**
- Concerns about location and freedom of movement of highly international pharmaceutical industry employees
- Increased divergence / complexity in harmonised structures supporting pharmaceutical business
- Possible impact on launch sequence across Europe for novel drugs

**Scientific**
- Uncertainty on post-2020 position with respect to key EU scientific funding; Theresa May announces £2bn of extra funding for science by 2020 much of which will go to biotech
- Barriers to movement of highly skilled labour
- Barriers to international cooperation on policy, research and other crucial scientific areas
The £350mn lie - the money will never get back to the NHS - today, tomorrow, ever...
Drs and nurses aren’t waiting to be asked to leave the UK—they are leaving now…

57,000 EU nationals work for the NHS—including 10,000 doctors and 20,000 nurses

- The number of EU nationals registering as nurses in England has dropped by 92% since Brexit referendum
- 80 of the 136 NHS acute trusts showed a 68% increase in EU nurses leaving the NHS in 2016
- 60% of Drs polled said they were considering leaving the UK - and, of those doctors, 91% said the UK’s decision to leave the EU was a factor in their considerations.

Source: The Guardian March 2017
We are currently in a situation where there are multiple regulatory scenarios

<table>
<thead>
<tr>
<th>Positives/opportunities</th>
<th>Negatives/challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK forms entirely separate regulatory agency to EMA, the new UK agency aligns more closely to the FDA</td>
<td>Disruption to both UK and EMA approvals rate likely, given movement of EMA staff FDA will likely be undergoing its own Trump transformation - uncertainty How will it work if UK regulation is aligned to FDA but UK standard of care is not in key therapy areas? UK has no influence on the future direction of the EMA</td>
</tr>
<tr>
<td>Potential to shape all aspects of regulation to make UK more attractive as a clinical development environment: faster trials set up, earlier approvals</td>
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</tr>
<tr>
<td>Potential to shape some aspects of regulation to make UK more attractive as a clinical development environment</td>
<td>Would require out of box thinking and political will to make it happen UK misses out on any opportunities created by freedom from EMA</td>
</tr>
<tr>
<td>No disruption of approvals or other regulatory work for EU or UK Dependent on nature of compromise, UK could retain significant influence on future direction of EMA</td>
<td>Unlikely, given “hard BREXIT” rhetoric and need for EMA to be in EU country UK misses out on any opportunities created by freedom from EMA</td>
</tr>
</tbody>
</table>

**Potential to shape all aspects of regulation to make UK more attractive as a clinical development environment:**
- Faster trials set up
- Earlier approvals

**Positives/opportunities:**
- UK forms entirely separate regulatory agency to EMA, the new UK agency aligns more closely to the FDA
- Potential to shape all aspects of regulation to make UK more attractive as a clinical development environment: faster trials set up, earlier approvals
- Potential to shape some aspects of regulation to make UK more attractive as a clinical development environment

**Negatives/challenges:**
- Disruption to both UK and EMA approvals rate likely, given movement of EMA staff FDA will likely be undergoing its own Trump transformation - uncertainty How will it work if UK regulation is aligned to FDA but UK standard of care is not in key therapy areas? UK has no influence on the future direction of the EMA
- Disruption to both UK and EMA approvals rate likely, given movement of EMA staff
- UK loses influence on the EMA’s direction, whilst remaining constrained by it
- UK misses out on any opportunities created by freedom from EMA
- Would require out of box thinking and political will to make it happen
- UK misses out on any opportunities created by freedom from EMA

**UK remains regulated by EMA, which retains significant activity within the UK whilst moving an oversight office to an EU country:**
- No disruption of approvals or other regulatory work for EU or UK
- Dependent on nature of compromise, UK could retain significant influence on future direction of EMA

**UK remains regulated by EMA, which remains located in UK:**
- No disruption of approvals or other regulatory work for EU or UK

**FDA will likely be undergoing its own Trump transformation - uncertainty:**
- How will it work if UK regulation is aligned to FDA but UK standard of care is not in key therapy areas? UK has no influence on the future direction of the EMA

**UK misses out on any opportunities created by freedom from EMA:**
- Possible disruption to both UK and EMA approvals rate
- Potential to shape all aspects of regulation to make UK more attractive as a clinical development environment
- Faster trials set up
- Earlier approvals

**Unlikely, given “hard BREXIT” rhetoric and need for EMA to be in EU country:**
- UK misses out on any opportunities created by freedom from EMA

**Potential to shape all aspects of regulation to make UK more attractive as a clinical development environment:**
- Faster trials set up
- Earlier approvals
The EMA is hot property – many countries want to take it on if it leaves the UK-Dublin & Paris hot favourites

- It is not known at this point when the decision for relocation would be made (immediately after triggering article 50 or later on in the process) and there is no established process for assignment.

- Staff: 900 full and part time experts – Guido Rasi, Executive EMA director, has said since Brexit the agency has lost an unprecedented number of senior staff, morale is low and capacity is under threat.

- Future host will need to be able to attract and retain talent and have excellent inter-EU connections

<table>
<thead>
<tr>
<th>Interested host</th>
<th>Rapporteurs (2015)</th>
<th>Proportion of staff (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(UK)</td>
<td>40</td>
<td>6.7</td>
</tr>
<tr>
<td>Sweden</td>
<td>34</td>
<td>2.1</td>
</tr>
<tr>
<td>Germany</td>
<td>26</td>
<td>6.4</td>
</tr>
<tr>
<td>Spain</td>
<td>16</td>
<td>10.7</td>
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<tr>
<td>France</td>
<td>12</td>
<td>12.6</td>
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<tr>
<td>Italy</td>
<td>11</td>
<td>12.4</td>
</tr>
<tr>
<td>Ireland</td>
<td>8</td>
<td>2.3</td>
</tr>
<tr>
<td>Denmark</td>
<td>7</td>
<td>1.4</td>
</tr>
</tbody>
</table>

“I would like to think it [the EMA] could stay. The reason for that is that the disruption would be harmful for everybody and we have got to remember this agency is responsible for the safety of 400 million people across Europe. We hear they are losing people through the anxiety of the potential move and it will take time to rebuild that whole capability.” Sir Andrew Witty, Davos 2017 (from the UK Times)

“Irish Minister for Health Simon Harris urged the pharmaceutical industry to back his efforts to tempt the EMA, which regulates all drugs in the EU, to relocate to Dublin from London post-Brexit. He said such a move would provide 900 jobs and up to 30,000 professional visitors a year. Moving to Dublin would benefit industry by ensuring there was no slowdown in the work of the agency, he said” (Irish Times, Wednesday, February 8th 2017)
BREXIT could bring opportunities to fully realise the potential of the UK for clinical trials

**Positives/opportunities**

- UK becomes a world-leading country in terms of clinical trial and RWI friendliness, with state of the art use of patient and other data to speed patient recruitment, and the go-to place for pioneering technologies, including drug/device combinations, gene therapy, gene editing, cell therapies.
- UK clinical trials regulations and processes re-written, with a focus on increasing speed and ease of set up, and also to become world-leading on regulatory approaches to novel technologies such as cell and gene therapies. NHS encouraged to share data and change working practices so that NHS data can be used to very effectively identify where patients and investigators are for clinical trials.
- Including the UK in European wide clinical trials may be easier, if an agreement is reached which allows alignment and a single access point, but the UK could position itself as a place where patients and investigators can be rapidly and cost effectively identified, so the UK could be the go-to country in Europe for clinical trial activity.

**Negatives/challenges**

- The effort to make UK RWI friendly is undermined by the UK frequently having a standard of care that is different to the US and/or Europe in key diseases, such as cancers, because of HTA decisions or slow innovation uptake- this could especially compromise highly innovative and expensive therapies. This could also have impact on clinical trial activity.
- UK seen as separate to Europe in clinical trials, not included within European arms of international clinical trials.
- Any differences in standard of care treatments between UK and the EU start to become a factor in deciding between the UK and r-EU sites.

- UK continues to be in a clinical environment that can be perceived as sub-optimal, possibly at a time when the FDA is seeing a radical loosening/change in regulations pushed through by the Trump administration.

- Including the UK in European wide clinical trials may be easier, if an agreement is reached which allows alignment and a single access point.

- UK clinical trials regulations continue to be aligned with Europe, including Clinical trials directive post 2018.

- Clinical trials regulations continue to be aligned to Europe, **NHS encouraged to share data and change working practices so that NHS data can be used to very effectively identify where patients and investigators are for clinical trials**.
The rare diseases community feels particularly at risk from Brexit

- **International trials and startup support**
  - Risk of loss of EU funding via Horizon 2020, which is a key support for rare diseases; EU funding supports startups

- **Rare disease specialists are few and need freedom of movement to create centres**
  - Risk of loss of free movement for scarce specialists

- **Loss of EMA and EMA influence for UK rare disease research**
  - Almost certain loss of EMA, risk of loss of important UK influence as researchers and companies leave

Rare disease research is especially dependent upon EU level collaboration

EMA is particularly supportive of orphan drug clinical development; UK leaving EMA could create significant challenge

Smaller companies could be especially vulnerable

Europe is second key market for many US biotechs: will this be at risk?
BREXIT could be an inflexion point in terms of the UK’s position in global pharma investment

**Positives/opportunities**

**A world beating pharmaceutical industry centre**
The UK manages to retain enough harmonisation and links to the EU to continue to be attractive as an entry point to EU, but a combination of a new regulatory environment, an NHS that is open to leveraging patient data and cooperation with pharma and adequately funded so that standard of care is aligned to US and EU trigger a new era of discovery and clinical investment in the UK.

**Negatives/challenges**

**A regional/global pharmaceutical centre, but at a price**
Unable to secure a favourable deal with the EU, the UK reverts to WTO rules, cutting itself off from cooperation on pharmaceutical and scientific matters. Significant corporation tax cuts encourage pharma to stay, but as regulatory and research diverge and lack of funding impacts both UK healthcare provision and research funding, the focus shifts to manufacturing and corporate HQs rather than R&D.

**Stasis, then decline**
UK fails to retain the elements of EU cooperation that will continue to be attractive, and fails to implement any measures to grow the attractiveness of the UK, whether those be in research funding, attractive regulatory environment, world beating clinical development, or industry friendly tax policies: companies gradually drift away.

With no position as an attractive access point to the EU and no distinctive regulatory, business or clinical trial proposition, the fact that the UK is only 3% of the global market and 2.1% of early innovative launch sales becomes the key point in pharmaceutical investment decisions.

Low corporate taxation impacts funding for the NHS and an austere medicines environment which routinely denies the newest treatments. The NHS’s potential as a world leading RWI environment cannot be realised as standard of care in UK drops behind the US and r-EU; NICE loses its reputation as an independent world leading HTA authority. Low tax means low research funding: discovery research falters.

The UK competes with Ireland as a low cost manufacturing and corporate HQ centre
UK continues to attract industry whilst keeping medicine spend severely controlled.
The introduction of a NICE budget impact test at £20M
Two government U-Turns in 1 month
What has been agreed 15th March 2017?

- It has been confirmed that a net budget impact threshold (now called ‘Budget Impact Test’) will be set at £20M in any of the first three years after launch.
- The test will trigger a ‘commercial negotiation’ between the company and NHS England. - and access would normally commence at 90 days
- Medicines covered by this proposal have proven to be cost effective by NICE
- Slowing down access to patients in this way, for NICE-approved medicines is a breach of:
  - The Conservative Manifesto, which promised to “speed up access to new medicines”; and
  - The NHS Constitution, which gives NHS patients in England the right to “drugs and treatments that have been recommended by NICE”
Three immediate questions for UK healthcare system

Currency and supply chain impact
- Devaluation of GBP will increase exports in the near term
- Potential impact on attractiveness of sterling as reporting currency, possibly of UK as business base

UK position as a launch country going forward?
- Traditionally high priority for UK launches will be re-assessed
- EMA - uncertainty on future relationship between MHRA and EMA. Administrative and legal preparations should be considered immediately
- March 2017 - Introduction of £20mn threshold budget impact assessment plus new CDF arrangements making England very unattractive launch market

Staff retention and hiring
- Uncertainty over immigration and weaker GBP may make it challenging for UK pharma to recruit and retain talent. Companies should have strong strategy/communication plans
Supply Chain
Importance of Biopharmaceuticals in Ireland

Regulatory and financial effect for Irish manufactured stock

GLOBAL IMPORTANCE

The Biopharmaceutical industry has made a capital investment of approximately $8 billion in new facilities in Ireland, most of which has come in the last 10 years. This represents close to the biggest wave of investment in new BioTech facilities anywhere in the world.

- 9 OF THE TOP 10
  world's pharmaceutical companies

- 7TH LARGEST EXPORTER
  of medicinal and pharmaceutical products in the world in 2014

- €39BN IN ANNUAL EXPORTS
  of pharma, bio and chemistry produce

- 75+ PHARMACEUTICAL COMPANIES
  operate in Ireland

- 33 FDA APPROVED
  pharma & biopharma plants
### Supply chain implications of Brexit for Ireland?

<table>
<thead>
<tr>
<th>Parallel Trade</th>
<th>• 2015: The UK bought €36.4bn worth of pharmaceuticals, €3.5bn of this coming from Ireland.</th>
</tr>
</thead>
</table>
| Legislation    | • Pharmaceutical supply chain regulation is predominantly at EU level  
• Need for regulatory alignment on joint UK&I packs?  
• Need for trade agreement on sale of medicines to UK from EU-Ireland |
| Single market  | • There could be supply shortages if importing medicines into the UK becomes more difficult due to UK leaving the single market |
| Storage of Irish Exports | • Irish manufactured Pharma companies ship finished products to mainland Europe through temporary storage facilities in the UK. Post Brexit, manufacturers may be forced to build specialist pharmaceutical storage facilities for exports and ship directly from Ireland. |
| Supply chain disruption | • Of most concern for pharmaceutical manufacturers is disruption to the supply chain to hospitals, pharmacies and sub-supply between their manufacturing plants across the Irish Sea and the English Channel which will inevitably arise when the UK exits the EU |
Parallel Trade: The £:€ exchange rate correlates with imports / exports

- In May-12 sterling is at a three and a half high vs the euro
- Trade trend correlates to exchange rate ~3 months lag
- Acceleration of implied exports from Q1/09 was exacerbated by PPRS
- Recent increase in exchange rate has resulted in an increase in Imports
- What happens post Brexit?
For some time the UK has primarily been an import market and this has been growing

- **In the short term parallel imports have grown**
- **Some therapy classes are more exposed than others**

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**Source:** IMS MIDAS and internal database. All sales at ex-MNF level.
Already we have seen an increase in trading activity

- The value of the pound dropped to its lowest level in three decades
- An increase has been observed in the proportion of pharmaceutical products being purchased by pharmacies known to parallel export
Conclusion: There’s major uncertainty; Plan out all scenarios

- Pharma manufacturing to Ireland is 25% of GDP (IDA) –most of it destined for export, via UK-new cross border regulation

- Ireland could benefit and relocation of the EMA to Ireland, if UK fails to reach an accommodation, would have the least disruption on medicines approvals

- Japanese Pharma have opted to base their European operations in London for proximity to the EMA, and because the U.K. capital serves as the largest clearing centre for Euro transactions in Europe.
  - A massive win for Ireland if Dublin wins the bid

- Shifting the EMA would mean the "appeal of London as an environment for the development of pharmaceuticals would be lost, which could possibly lead to a shift in the flow of R&D funds and personnel to Continental Europe.”
What are the implications for Ireland?

- Ireland as a possible location for EMA: Japanese companies with UK based R&D have stated they will relocate to country with EMA HQ (18 companies)

- EU as a single pharmaceutical market could lose 13%* of its value - what are the implications for relative commercial attractiveness of EU compared to US and Japan?

- EU as a bloc could lose a substantial contributor to global pharma R&D - are the knock-on implications for Irish life sciences base positive or negative?

*Based on MAT Q2 2016
• The bulk of Irish pharmaceutical manufacturing is earmarked for export and Pharma companies based in Ireland currently ship finished products to mainland Europe through temporary storage facilities in the UK.

• Post Brexit, manufacturers may be forced to build specialist pharmaceutical storage facilities for exports and ship directly from Ireland.

• Ireland is a base for nine of the 10 biggest pharma firms.
Trump promising Corporate Tax reform to keep manufacturing and R&D in US

• “We’ve got to get our drug industry back. Our drug industry has been disastrous. They’re leaving left and right. They supply our drugs, but they don’t make them here, to a large extent.”

• The Republic has been among the most successful countries in persuading US pharmaceutical and medical device companies to establish manufacturing and research operations outside the US.

• More than 50,000 people are employed in these areas in Ireland, according to IDA Ireland, and US companies are the largest employers.

• Ireland is now a base for nine out of 10 of the biggest pharma firms.
### Five key challenges for Pharma in Ireland for the next five years?

<table>
<thead>
<tr>
<th>Category</th>
<th>Challenges</th>
</tr>
</thead>
</table>
| **Finance**                    | • There is no more money. Access will be determined not by cost-effectiveness, nor innovation, but by overall affordability for the health system.  
                                 | • Industry will be urged to price its innovations ‘responsibly’  
                                 | • Ireland attractiveness as manufacturing base if Trump has his way?                                                                                                                                       |
| **Patients & Pharma Reputation**| • Patients will, through multichannel media, become informed of the affordability issue with medicines, and why they cannot access life-changing medicines.  
                                 | • Who will be the ‘good cop’ and who will be the ‘bad cop’ in the access debate - industry or the payor?                                                                                                     |
| **Proving Value and Rol**       | • Pharma must seize the moment to lead and educate payors on how mobilising industry expertise in clinical research, RWE and technology can harvest the data-rich fields of anonymised patient level data to improve outcomes, reduce variation, improve patient experience and demonstrate Rol |
| **Brexit**                     | • Ensuring through full engagement free trade, open borders and freedom of movement between Ireland and the UK.  
                                 | • Prepare for worst case scenario-and hope for the best.                                                                                                                                                   |
| **Remaining Relevant**         | • Industry needs to ensure it continues to provide value and that it not only really recognises the pressures in health systems, but develops innovative strategies to work together with those making difficult decisions to ‘find a way’ improve patient life chances |
Trends of the Pharmaceutical Industry Following the British Withdrawal

Angela McFarlane
Market Development Director

March 23rd 2017