Innovating in Orphan Diseases

Patrick Jordan
VP Global Distributor Markets
Rare diseases require a ‘Marshall Plan’

Approximately 7,000 rare disease are known today\(^1\)

350 million people suffer from rare diseases worldwide\(^1\)

Up to 80% have identified genetic origins\(^1\)

And affect between 3% and 4% of births\(^1\)

Only 5% of rare disease have an approved treatment in the US\(^1\)

Despite there being many rare diseases, there are very few treatments for patients suffering from these conditions\(^1\)
### Orphan drug legislation was a statement of intent

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Prevalence (/10,000)</td>
<td>7.5</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Estimated population</td>
<td>20 million</td>
<td>No info</td>
<td>25-30 million</td>
</tr>
<tr>
<td>Marketing exclusivity</td>
<td>7 years</td>
<td>10 years</td>
<td>10 years</td>
</tr>
<tr>
<td>Tax credit</td>
<td>Up to 50% for clinical studies, FDA fee exemption</td>
<td>6% for any type of study &lt;10% of the company’s corporation tax</td>
<td>Managed by member states</td>
</tr>
<tr>
<td>Grants for research</td>
<td>NIH and other government grants</td>
<td>Governmental funds</td>
<td>“FP7,8” + national measures</td>
</tr>
<tr>
<td>Reconsideration of ODD</td>
<td>No</td>
<td>Yes</td>
<td>Yes (every 6 years)</td>
</tr>
<tr>
<td>Technical assistance</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Legislation has been successful in stimulating R&D in rare diseases: US

Designated and approved orphans by FDA by year

Orphan designations by year  Approved orphan products by Year

http://www.fdalawblog.net/2015/02/the-2014-numbers-are-in-fdas-orphan-drug-program-shatters-records/
https://www.accessdata.fda.gov/scripts/opdlisting/oopd/listResult.cfm
Legislation has been successful in stimulating R&D in rare diseases: EU

Cumulative designated and approved orphans by EMA by year

- Cumulative Orphan Designations
- Cumulative Market Authorizations

EMA registry
https://www.eurordis.org/content/2016-marketing-authorisations
Legislation has been successful in stimulating R&D in rare diseases

Cumulative approved orphans by FDA and EMA by year

http://www.fdalawblog.net/2015/02/the-2014-numbers-are-in-fdas-orphan-drug-program-shatters-records/
https://www.accessdata.fda.gov/scripts/opdlisting/opd/listResult.cfm
EMA registry
https://www.eurordis.org/content/2016-marketing-authorisations
Orphan drugs policies have been successful as they incentivise the development of new therapies.

The FDA has approved more than **640 ORPHAN DRUGS**
Since the passage of the orphan drug act¹

The EMA has approved more than **158 ORPHAN DRUGS**
Since the passage of the orphan regulation²

The MHLW has approved more than **254 ORPHAN DRUGS**
Since the passage of the orphan regulation³
And we can afford it

Historical and forecast drug expenditure in EU5 at list and net prices

Drug expenditure €M

2010 - 2016
2017 - 2021

Net historical
Net forecast
List historical
List forecast

CAGR 3.4%
CAGR 2.0%
CAGR 2.9%
CAGR 1.5%

After accounting for discounts pharmaceutical expenditure is expected to grow only 1%-2% over the next 5 years

Incentives by governments and regulatory bodies encouraged greater investments in orphan drug R&D

WW orphan drug sales and share of prescription drug market (2008 – 2022; forecast)

The cost of orphan medicines accounts for a relatively small proportion of overall pharmaceutical spending.

Proportion of medicine expenditure spent on orphan medicines across EU5 in 2015

<table>
<thead>
<tr>
<th>Country</th>
<th>Proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spain</td>
<td>3.2%</td>
</tr>
<tr>
<td>Italy</td>
<td>3.5%</td>
</tr>
<tr>
<td>France</td>
<td>3.7%</td>
</tr>
<tr>
<td>UK</td>
<td>3.8%</td>
</tr>
<tr>
<td>Germany</td>
<td>4.4%</td>
</tr>
</tbody>
</table>

In 2015, OMPs accounted for approximately 4% of total medicine cost across the EU5

1. “IMS data (Sep 2015) (data on file)”
Orphan drug market access requires a different approach

- Complex and unique routes to access
- Low payer understanding of burden & benefit
- Value is interpreted differently
- Policy environment shapes decisions

Requires specialist knowledge and experience
Several factors have an influence on pricing in major markets

Typical framework for P&R decisions. Cost effectiveness also used in some markets

<table>
<thead>
<tr>
<th>Lower Price</th>
<th>Higher Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rarity</td>
<td>5.0 to 0.2 in 10,000 (Between rare and ultra-rare*)</td>
</tr>
<tr>
<td>Alternative treatments</td>
<td>Effective unlicensed drug</td>
</tr>
<tr>
<td>Typical framework for P&amp;R decisions.</td>
<td>No alternatives</td>
</tr>
<tr>
<td>Treatment effect</td>
<td></td>
</tr>
<tr>
<td>Symptom modifying</td>
<td>Disease modifying</td>
</tr>
<tr>
<td>Replacement therapy</td>
<td>Curative</td>
</tr>
<tr>
<td>Age of onset</td>
<td></td>
</tr>
<tr>
<td>Elderly</td>
<td>Young adult</td>
</tr>
<tr>
<td>Type of disease</td>
<td></td>
</tr>
<tr>
<td>Lifestyle related</td>
<td>Genetic/congenital</td>
</tr>
<tr>
<td>Disease severity</td>
<td></td>
</tr>
<tr>
<td>Chronic, not life threatening</td>
<td>Loss of function</td>
</tr>
<tr>
<td>Chronic, not life threatening</td>
<td>Life threatening</td>
</tr>
</tbody>
</table>

**Ultra-rare definition: <1 cases out of 50,000 subjects (REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 April 2014).**
Despite challenges, orphan manufacturers are achieving commercial success in Europe

European sales as proportion of global revenue: selected orphan manufacturers

Celgene 2016

Alexion 2016

Biomarin 2016

Vertex 2016

EU ~30% of total sales

EU ~30% of total sales

EU ~25% of total sales

EU ~20% of total sales
Summary

- Rare diseases are severely underserved
- Orphan legislation has stimulated investment and output
- A key growth area in pharma but a small proportion of overall expenditure

- Capitalise on opportunities where others may not
- Depth of understanding and innovation are key to accessing opportunities
Alternative slides
P&R processes for ODs are challenging due to the inherent characteristics of rare diseases.

**Inherent characteristics of rare diseases**

- Small number of patients
- Heterogeneous patient populations
- Lack of existing approved treatments
- Lack of disease knowledge
- Complex, severe and life-threatening

**Challenges for evidence generation**

- Difficult to recruit many patients into trials
- Variability in outcomes across patients
- Lack of established clinical endpoints
- Lack of data on natural history
- Controlled-trials sometimes not ethical

**Challenges for P&R assessment**

- Small sample sizes / great heterogeneity
- Difficulty in interpreting clinical benefit
- What is appropriate comparator?
- What is magnitude of benefit vs SoC?
We can beat rare diseases

△ Haemophilia example:

- Sustained investment in a rare disease
- Incremental improvement in treatments over time
- Improvement in life expectancy and QoL (child born in Sweden with haemophilia has same life expectancy and QoL as healthy child)
- Cure in sight (gene therapy)
- Costs have fallen with competition and loss of patent (tenders)
Successful access for orphans requires…..

<table>
<thead>
<tr>
<th>Experience</th>
<th>need first hand understanding of complex P&amp;R systems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start early</td>
<td>get the P&amp;MA strategy and planning right</td>
</tr>
<tr>
<td>Stakeholder engagement</td>
<td>the less well established the disease, the more effort required</td>
</tr>
<tr>
<td>Establish value</td>
<td>align messaging with payer decision drivers in rare diseases</td>
</tr>
<tr>
<td>Prevalence and budget impact</td>
<td>get the best data possible and ‘play a straight bat’</td>
</tr>
<tr>
<td>Robust evidence generation plan</td>
<td>take post-marketing evidence seriously</td>
</tr>
<tr>
<td>Negotiation strategy and positioning</td>
<td>be proactive in preparing fall-back deal structures and managed entry agreements</td>
</tr>
<tr>
<td>Engage at payer level and above</td>
<td>establish the parameters for payer assessment</td>
</tr>
<tr>
<td>Build experience with treatment</td>
<td>devise early access programs to build physician experience and support</td>
</tr>
</tbody>
</table>
P&G assessment and evidence generation needs to be adaptive

- To be developed
Innovative contractual agreements balance risk between payers and manufacturers

<table>
<thead>
<tr>
<th>Managed Entry Agreements (MEAs)¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manage budget impact</td>
</tr>
<tr>
<td>Ensure value for money</td>
</tr>
<tr>
<td>Reduce evidence uncertainly</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manage budget impact</td>
<td></td>
</tr>
<tr>
<td>Patient level schemes</td>
<td>Patient utilisation cap, Patient cost cap, Free/ discounted treatment initiation</td>
</tr>
<tr>
<td>Population level schemes</td>
<td>Discount, Price volume agreement cap, Price volume agreement without cap</td>
</tr>
<tr>
<td>Performance linked reimbursement</td>
<td>Outcomes guaranteed, Money back guarantees, Conditional treatment continuation</td>
</tr>
<tr>
<td>Coverage with evidence</td>
<td>Only with research, Only in research</td>
</tr>
</tbody>
</table>

² Innovative managed entry agreements.
Value frameworks need to reflect all aspects of rare diseases: ORPH-VAL*

<table>
<thead>
<tr>
<th>Disease burden</th>
<th>Impact of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival/life expectancy</td>
<td></td>
</tr>
<tr>
<td>Morbidity</td>
<td></td>
</tr>
<tr>
<td>Patient experience and quality of life</td>
<td></td>
</tr>
<tr>
<td>Patient economic burden</td>
<td></td>
</tr>
<tr>
<td>Existing treatment options</td>
<td>Side effects</td>
</tr>
<tr>
<td>Resources and budget</td>
<td></td>
</tr>
<tr>
<td>System organisation</td>
<td></td>
</tr>
<tr>
<td>Societal level</td>
<td></td>
</tr>
<tr>
<td>Family/Carer quality of life</td>
<td></td>
</tr>
<tr>
<td>Societal economic burden</td>
<td></td>
</tr>
</tbody>
</table>

Considerations beyond OMP value
- Rarity
- Societal preferences

Uncertainty of OMP value
- Quality of evidence
- Uncertainty around value parameters
Rarity matters in OD pricing

Cost effectiveness threshold by level of rarity

Prevalence per 100,000

£22K
£43K
£538K
£1,076K

Drummond & Towse. Adjusting ICER thresholds for rarity + R&D expenditure. ISPOR 2017
EU launch prices of new orphans are not always that different to US

<table>
<thead>
<tr>
<th>Country</th>
<th>Kalydeco Annual Price</th>
<th>Vimizim Annual Price</th>
<th>Strensiq Annual Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>€270</td>
<td>€640</td>
<td>€354</td>
</tr>
<tr>
<td>DE</td>
<td>€230</td>
<td>€485</td>
<td>€505</td>
</tr>
<tr>
<td>IT</td>
<td>€230</td>
<td>€520</td>
<td>€505</td>
</tr>
<tr>
<td>FR</td>
<td>€230</td>
<td>€500</td>
<td>N/A</td>
</tr>
<tr>
<td>UK</td>
<td>€180</td>
<td>€550</td>
<td>N/A</td>
</tr>
</tbody>
</table>

-15% for Kalydeco in US and -14% for Vimizim in US. Strensiq has a +43% increase.

1. Does not include confidential discounts
2. Assumes average patient weight of 19kg.

MSP = manufacturer selling price

Source: see slide notes
US environment remains positive, but payers are increasingly managing orphan drugs

US payer decisions for 151 out-patient orphan drugs approved by FDA between 1983 and 2012¹

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Payer coverage</td>
<td>97%</td>
</tr>
<tr>
<td>Average percentage of drugs with restrictions</td>
<td>84%</td>
</tr>
<tr>
<td>Average coinsurance for physician-administered drugs</td>
<td>20%</td>
</tr>
<tr>
<td>Average coinsurance for outpatient drugs</td>
<td>31%</td>
</tr>
</tbody>
</table>

¹. Cohen 2014
US environment remains positive, but payers are increasingly managing orphan drugs

Percentage of insurers using strategies for managing specialty drug use*

- Prior Authorisation Pharmacy Benefit: 84%
- Require Use of Specialty Pharmacy: 76%
- Clinical Care Management Programs: 76%
- Preferred Products Formulary: 74%
- Step Therapy under Pharmacy Benefit: 69%
- Limit Specialty Drugs to 30-day Supply: 68%
- Move Drugs to Pharmacy Benefit: 54%
- Prior Authorisation Medical Benefit: 50%
- Separate Cost Tier for Specialty Drugs: 45%
- Restrict Medical Benefit Coverage: 41%
- First Fill Limit of 1-2 Weeks: 26%

* Based on survey of insurers and other plan sponsors covering 17.6 million enrollees
EU P&R environment is getting tougher

- Price limits
- ICER thresholds
- Risk sharing/pay for performance
- Political challenges – e.g. EU incentives review
- Payer trends in Europe for ODs
- Revenue caps
There is variation in access and time to decisions for ODs across European markets

![Graph showing variation in orphan medicines reimbursement across European markets. Germany, France, Italy, Spain, England are marked with different colored flags. Germany and England show quick access and high willingness to pay. France, Italy, and Spain show slow decision making but willingness to reimburse. Scotland is also marked with a different flag. Despite long lead times to price and reimbursement, some markets offer opportunity for early access funding (e.g., Italy, France, Spain).]

Source: Zamora et al. 2017
P&R decisions in rare diseases are especially political

Stakeholder engagement is essential and must start early

**Example: Orkambi in Ireland**

"Orkambi price is unacceptably high [...] making it inaccessible for Ireland’s CF patients”

Minister for Health, Ireland

![Pan-franchise funding agreement]

**Policy**

Shape the reimbursement pathway

**Stakeholder engagement**

**P&R success**

**Tactical P&R excellence**

**Strategic P&R excellence**

**Product**

Jan 2016

June 2017
Orphan drug prices in Europe have been largely static

Annual cost of therapy of all orphan drugs in Germany by MA, €mn

![Graph showing annual cost of therapy of all orphan drugs in Germany by MA, €mn with a point labeled Glybera.](image)
Payers are concerned about the aggregate cost of orphan medicines

Forecast budget impact of orphan drugs in EU5, €Bn

Source: IMSCG 2016
Payers try to minimise Financial uncertainty

Uncertain prevalence / diagnosis / uptake

High per-patient price

Uncertain DoT (prognosis)

Uncertain dose (e.g. weight-based)

High uncertainty around potential budget impact

Payers seeking to minimise their financial risk

Restrictions on prescribing to specialist centres

Reimbursement restrictions to specific patient characteristics

Start – stop criteria

Price-volume agreements / caps

Need accurate patient number estimates in each market – don’t low/high-ball it
Develop negotiation strategy to manage payer concerns about budget impact
Pricing and reimbursement pathways are different for orphan drugs in Europe

HST process for drugs with ~500 patients or less in England & Wales ICER threshold (£100K - £300K)

Higher degrees of uncertainty accepted in the case of ODs

ODs automatically granted added benefit (sales <€50m; 1 year only)

ATU provides early access for drugs without alternatives

Funded importation scheme

Funded importation scheme

CZ SK

TK

HU SL

648 Law provides early access for drugs without alternatives (e.g. ODs) Innovative drugs exempt from national rebate repayments

Early and effective planning is necessary to maximise likelihood of benefitting from orphan exemptions
Patient access to orphan medicines is inconsistent across Europe

Share of positive and conditional HTA recommendations, by country

- Wales
- Scotland
- Poland
- England
- Netherlands
- France
- Sweden
- Germany

- Fixed ICER thresholds
- Adjusted ICER thresholds
- Non-ICER based decisions

Source: Kawalec et al. 2016
Orphan drug P&R future

Political pressure on drug prices

"The industry is getting away with murder...you know why? Campaign contributions [...] somebody’s getting very rich"

"He’s right. And I’ve been saying that for years. Pharma does get away with murder"

Media scrutiny on orphan incentives

One Pharma Fix: Limit the ‘Orphan Drug’ Incentives

Don’t Ignore Politicians’ Ire Over Orphan Drugs

High prices make ‘orphan’ drugs a booming business
Trends shaping the future P&R environment in Europe

**Assessment changes**
- Possible reduction of threshold for automatic additional benefit
- QALY assessment may change and new review process implemented
- Potential cost-effectiveness studies for ODs

**Agreements with MNFs**
- Further establishment of registries
- Continued use of Outcomes-based agreements
- Creation of funds for specific ODs

**Joint procurement**
- Official announcement of potential joint commissioning of orphan drugs

They will keep the special status, but in real life the benefit will decrease slowly – Spanish payer

We will need a European solution for this – German payer

Payers across EU all agree that OD prioritisation will have to occur in order to manage budget impact
Payers try to minimise product **Value** uncertainty

<table>
<thead>
<tr>
<th>High uncertainty around likely clinical benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small trial sample</td>
</tr>
</tbody>
</table>

Adaptive payer processes will become increasingly common

**Example: Germany**

Strensiq, Kanuma

- Non-quantifiable benefit
- Price > €300K ppy

> The G-BA considers more evidence to be urgently needed .....orphan drugs should be evaluated the same as other drugs if they fail to produce the requested data.

Prof. Josef Hecken, G-BA’s chairman

**Example: Elaprase France**

ASMR

- 2007
  - I
  - II
  - III
  - IV
  - V

> Given the long-term results in real life, one may question....the long-term efficacy of idursulfase treatment

- 2015
  - I
  - II
  - III
  - IV
  - V

Post-approval data collection has to be taken seriously
Regulatory agencies use specialised approaches to evaluate the value of new medicines

In 2015, US FDA designated special categories to 27 drugs; EMA approved 8 novel drugs under early access routes

- Fast Track: 31%
- Priority Review: 53%
- Breakthrough: 22%
- Accelerated Approval: 13%
- Accelerated Assessments: 13%
- Conditional Marketing Authorisation: 8%

Intensive guidance on drug development that have potential to address unmet medical needs
Early approval of drugs for serious or life-threatening illness

Limited government incentives can potentially challenge the viability of the business model.

Factors responsible for underinvestment in antibiotic research:

- Low profitability
- Lack of P&R policies
- Antibiotic resistance
- Short drug life span due to resistance
- Generic erosion

According to a 2009 EMA report, only 2 novel antibiotic drugs with a new mechanism of action were in development.

Rare diseases are a major public health issue for which new policies are drafted.

<table>
<thead>
<tr>
<th>POLICY CHALLENGES FOR RARE DISEASES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improving diagnosis, prevention and treatment of rare diseases</td>
</tr>
<tr>
<td>Facilitating the regulatory pathway for potential treatments</td>
</tr>
<tr>
<td>Effective and equal provision of health care for patients with rare diseases</td>
</tr>
<tr>
<td>Effective management and pooling of research and medical data to benefit all patients</td>
</tr>
<tr>
<td>Contributing to and benefiting from global collaboration</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EUROPEAN POLITICAL PRIORITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jobs, Growth and Investment</td>
</tr>
<tr>
<td>Digital Single Market</td>
</tr>
<tr>
<td>A Stronger Global Actor</td>
</tr>
</tbody>
</table>
Incentives should encourage interventions that deliver most value, regardless of historical budget silos.

**Silo Budget**
- Disintegrated care pathway
- Redundancies
- Inefficient allocation of resources
- Rationing
- Lengthy waiting time

**Global Budget**
- Integrated care pathway
- Cooperation
- Collaboration
- Reduce expenses
- High efficiency

**Value for money**
- Utilisation

**Foster innovation**
- Improve health

Garrison and Towse, Value in Health 2003:6 Suppl 1
Ensuring that patients have timely access to promising medicines is also an important goal for public health agencies

EMA is piloting the development of support and early access tools for medicines addressing unmet need
Adaptive licensing seeks to maximize the positive impact of new drugs on public health by balancing timely access for patients with the need to provide adequate evolving information on benefits and harms.
Proposal for ICER’s adjustment for orphan drugs

Normative ACETs for orphan and ultra-orphan drugs calculated as per new formula

<table>
<thead>
<tr>
<th>Description</th>
<th>Non-orphan population (100/50,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orphan (cut-off: 25/50,000)</td>
<td>£21,520</td>
</tr>
<tr>
<td>Orphan (midpoint: 12.5/50,000)</td>
<td>£43,040</td>
</tr>
<tr>
<td>Ultra-orphan (cut-off: 1/50,000)</td>
<td>£538,000</td>
</tr>
<tr>
<td>Ultra-orphan (midpoint: 0.5/50,000)</td>
<td>£1,076,000</td>
</tr>
</tbody>
</table>
## Incentives and special channels for OD in France

| Authorisation for Temporary Use (ATU) | Access to drugs that do not have market authorisation in France is possible through the Authorisation for Temporary Use (ATU) granted by the ANSM and fully covered, criteria include: Treatment of a serious or rare disease, No therapeutic alternative available, Positive risk/benefit ratio expected, Therapeutic aim of use of treatment in hospital setting (i.e. not research), Treatment cannot be postponed, The aim is therapeutic Decisions made by ANMS and the cost is reimbursed from a special national budget. 70% of ODs were available through ATU prior to marketing authorisation on average 35 months before their approval |
| Compassionate use | Compassionate use is only reimbursed if HAS has received a Temporary Treatment Protocol. |
| Fast-track price notification | ODs can also benefit from an earlier start of P&R procedure if deemed “a priori innovative” drugs, assessment period is reduced from 90 days to 15 |
| Other incentives | There are a number of incentives provided for pharmaceutical companies marketing ODs in France: • ODs costing less than €50,000/patient/year are exempt from therapeutic class repayment (in case of health expenditure exceeded, these ODs will not be subject to cuts or rebates) • For ODs with total annual sales below €30 million (public prices), tax waivers apply • During OD development, free scientific advice is provided by the ANSM to answer specific questions pertaining to quality, safety and efficacy |
Incentives and exemptions in Germany

Exemptions in Germany

ODs have some special dispensation in the AMNOG process. The AMNOG law assumes an additional benefit for authorised ODs with an annual out-of-hospital turnover less than EUR 50 million. Manufacturer can submit a lean dossier (no need to submit data on appropriate comparators, international MA status; Module 4, section 4.4 on additional benefit still needs to be completed).

According the General Methods report published by IQWiG, ‘for small sample sizes, it is reasonable to accept a higher than 5% p-value (e.g. 10%) to prove statistical significance and to accept evidence from surrogate endpoints’

Compassionate use

Compassionate use of ODs is reimbursed by the statutory health insurance (GKV) under the following conditions:

- Drug for the treatment of fatal or life-threatening disease
- No approved drug available in Germany for this indication
- Scientific evidence for its clinical benefit
- Drug added to an exemption list by the G-BA

Access to OD prior market authorisation
## Incentives and special channels for OD in Italy

| Law 648/96 | The Italian NHS reimburses medicines when there is not another valid treatment and for which results of Phase II trials are available and meet one of the following criteria:
|            | • Medicine authorised in other countries
|            | • Tested in phase III trial
|            | • Marketed for another indication in Italy with documented evidence of efficacy and safety |

| Compassionate use | Under a Ministerial Decree of 8 May 2003 compassionate use is possible for drugs not yet authorised but subjected to phase II or III clinical trials for the same therapeutic indication for which a favourable evaluation in terms of safety and efficacy is expected; the physician takes responsibility and the patient gives informed consent |

| Individual patient use | The Ministerial Decree 11/2/1997 also allows the import of unauthorised orphan on a case-by-case basis if the attending physician believes that the medicine is necessary for the patient and the payer is the Region or the NHS in the case of hospital or reference centre |

| Fast-track approval | Products for rare diseases may obtain faster market access, due to the severity and rarity of the condition, however products are closely monitored by the specialty centres |

| 5% AIFA Fund | A contribution paid by the pharmaceutical company (5% of their total promotional expenditure) to a special fund for the promotion of clinical research of ODs and the reimbursement of ODs awaiting market entry |

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Access to OD prior market authorisation

Incentives for ODs
Special channels for OD in England

NHS Specialised Commissioning

- An OD may be covered through the NHS Commissioning Board (CB) within NHS England, aiming to ensure the same level and standards of care for patients requiring specialised treatment.
- Treatment protocols must be established with reference centres and agreed by Clinical Reference Groups within NHSE
- Specialised services are funded through capped budgets determined by NHS England.

Individual Funding Request (IFR)

For ODs that are not recommended by NICE or covered by specialised commissioning, an Independent Funding Request may be submitted. Management of IFRs are also the responsibility of the CB.

Alternative mechanism of drug reimbursement
The pharma model is based on a collaboration between the public sector and private enterprises.

While basic science is often initiated in academia, it is biopharmaceutical firms that provide the necessary critical mass, expertise, and experience needed to develop new medicines.

Payers manage uncertainty with MEA

<table>
<thead>
<tr>
<th>Financial schemes</th>
<th>Performance-based agreements</th>
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<tbody>
<tr>
<td><strong>Population-level</strong></td>
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<tr>
<td>Discounts</td>
<td>Patient registries with money back guarantees</td>
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<tr>
<td>Price/volume agreements with or without cap</td>
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<tr>
<td><strong>Patient-level</strong></td>
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<tr>
<td>Patient/dose dependent discount</td>
<td>Coverage with evidence</td>
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<tr>
<td>Utilisation/price capping</td>
<td>Outcome guarantees / Conditional treatment</td>
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<tr>
<td>Free/discounted treatment initiation</td>
<td>continuation</td>
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Despite gaining regulatory approval, biopharmaceutical companies are confronting commercial barriers

Drugs fail to be recommended for market access for a number of reasons:

- Non-robust economics
- Uncertain clinical benefit
- Inappropriate trial design, comparator, or patient population
- Increased drug cost
- Safety concerns

Since 2004, IQWiG have classified 70% of drugs as “benefit not proven”

Between 2000-2014, NICE conducted 313 appraisals, of which only 61% were recommended

Express scripts declined to cover 48 drugs in 2014

By definition, a rare disease affects very few patients:

- <200,000 patients in Europe
- <50,000 patients in Japan
- <250,000 patients in Europe
Incentives by governments and regulatory bodies encouraged greater investments in orphan drug R&D

Investment into specific disease areas is determined by assessing risk-weighted profitability. Government incentives influence these decisions.

- **Orphan Drug Act**
  - *Incentivises companies to develop drugs for rare diseases (affecting <200,000 people in the U.S.)*

- **1967 - 1983**
  - ~58 drugs approved
  - *Could qualify for orphan drug status*

- **1983**
  - 12 – 15 grants awarded annually to academic researchers/companies
  - Establishment of 50% tax credit for expenditures incurred during clinical testing phase for orphan drugs
  - 7 year market exclusivity provision granted for FDA-designated orphan drug indications

- **1983 - 2007**
  - FDA lists 1,793 orphan designations and approves 322 orphan drugs

Seoane-Vazquez E et al. Orphanet J Rare Diseases 2008;3:33;
Frameworks aligned with needs encourage development of innovation that society requires for a healthier population.

Pharmaceutical innovations have improved the quality and quantity of life for generations of patients.

AED=anti-epilepsy drug; DPP=dipeptidyl peptidase; PPI=proton pump inhibitor

Innovation and introduction of new medicines has helped reduce overall cancer mortality over time.

Change in all cancer mortality rates for both gender, 1990–2011 (or nearest year)

Between 1990 and 2011, overall cancer mortality decreased considerably in many developed countries.

US is still driving development investment

The private sector invests considerably more into R&D compared with the public sector (US data, 2005-2014)\textsuperscript{1,2}

Note: data are from separate sources and are for demonstrative purposes only
Profits from successful medicines are re-invested in research and development of new medicines

Determinants of pharmaceutical innovation

- Profits from past R&D investment
- Expected return on new investment
- Health needs (Willingness and ability to pay)
- Sales revenue (expenditure – distribution costs and VAT)
- R&D investment in new products
- Public and private pharmaceutical expenditure

GAAP: Generally Accepted Accounting Principles
Payers assess the value of the drugs considering all important factors, including innovation

Value elements considered as evaluation criteria among countries and their intensity of use

<table>
<thead>
<tr>
<th>Burden of disease</th>
<th>Disease severity</th>
<th>Unmet need/availability of treatments</th>
<th>Disease prevalence</th>
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<th>Therapeutic</th>
<th>Direct endpoints</th>
<th>Surrogate endpoint</th>
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<th>Safety</th>
<th>Adverse events</th>
<th>Tolerability</th>
<th>Contraindications</th>
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<tr>
<th>Innovation</th>
<th>Clinical novelty</th>
<th>Nature of treatment</th>
<th>Ease of use &amp; comfort</th>
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<th>Socioeconomic</th>
<th>Public health</th>
<th>Budget impact</th>
<th>Social productivity</th>
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</table>

(***): Highest intensity of use, i.e. “mandatory/formal/explicit/planned/directly measured grading system available” (**): Medium intensity of use, i.e. “recommended, informal/implicit but planned, formal/explicit but ad-hoc/indirectly measured” etc. (*): Lowest intensity of use, i.e. “optional/informal/implicit/ad-hoc/indirectly measured/no grading system available” (x) the value dimension is not considered in any way as an evaluation criterion

Rare diseases are an important public health issue

There are more than 6,000 different rare diseases affecting ~30 million patients in Europe.

To date, the EMA has authorised 128 OMPs and there are 1418 unapproved products that have an OMP designation.

EU regulation on OMPs has been successful in stimulating R&D in rare diseases, but much remains to be done.

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