DELAYED ACCESS FOR PATIENTS WITH RARE DISEASES IN ASIA PACIFIC: FINDING A SOLUTION THAT WORKS

ISPOR Asia Pacific 2018 – Workshop W14
Tuesday 11th September 10.45am

Discussion Leaders: Dr Annabel Griffiths (Head of Rare Diseases, Costello Medical, UK)
Prof Ming-Chin Yang (Professor, National Taiwan University, Public Health, Taiwan)
Prof Shanlian Hu (Professor and Senior Consultant, Fudan University and Shanghai Health Development Research Center, China)
Prof Bertram Häussler (Chairman of the Board, IGES Institut GmbH, Germany)

Disclosures

• This workshop was sponsored by Shire
• Annabel Griffiths is an employee of Costello Medical
The Discussion Leaders

Dr Annabel Griffiths
Head of Rare Diseases, Costello Medical, UK

Prof Ming-Chin Yang
Professor, National Taiwan University, Public Health, Taiwan

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Chairman of the Board, IGES Institut GmbH, Germany

Structure of the Workshop

• Each discussion leader will speak for ~10 minutes
• After all discussion leaders have presented there will be a ~20 minute discussion session

• This symbol indicates an audience vote
• Questions and comments from the audience will be taken during the discussion session
Introduction to Access Challenges for Orphan Drugs in Asia Pacific

Dr Annabel Griffiths
Head of Rare Diseases, Costello Medical, UK

What is a Rare Disease?

EU: <5 in 10,000 (≤250,000 patients, based on EU population of 514m)¹

Japan: <50,000 patients (<4 in 10,000, based on Japanese population of 128m)³

China: <1 in 500,000 people or <1 in 10,000 new borns²

Korea: <20,000 patients or diseases for which an appropriate treatment or alternative medicine has yet to be developed³

USA: <200,000 patients (<6.37 in 10,000, based on USA population of 314m)¹

EU: Ultra-rare diseases are defined as those affecting 1 in 50,000 patients²

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EU: European Union; USA: United States of America
# Examples of Rare Diseases

**Fabry Disease**
- A progressive, inherited, multisystemic lysosomal storage disease characterised by a range of neurological, cardiovascular and renal symptoms\(^1,2\)
- Prevalence: 1–5 in 10,000\(^3\)
- Available treatments: enzyme replacement therapies\(^2\)

**Haemophilia**
- Genetic disorder characterised by spontaneous haemorrhage or prolonged bleeding due to factor VIII (haemophilia A) or IX (haemophilia B) deficiency\(^3\)
- Prevalence: 1–9 in 100,000\(^3\)
- Available treatments: recombinant factor VIII and IX\(^4\)

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# What Makes Rare Diseases Different?

- Need for accelerated processes
- Lack of good quality evidence available
- Poor awareness and understanding of the condition
- Significant unmet need
**Time to Reimbursement**

![Bar chart showing time from regulatory approval to reimbursement (months) for various countries.](chart)

**Overview of Healthcare Systems**

<table>
<thead>
<tr>
<th></th>
<th>UK</th>
<th>Taiwan</th>
<th>China</th>
<th>Germany</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subsidised patient access system</strong></td>
<td>National Health Service¹</td>
<td>National Health Insurance system²</td>
<td>Basic Health Insurance Scheme (BHIS)—urban and rural schemes¹</td>
<td>Statutory Health Insurance system⁴</td>
</tr>
<tr>
<td><strong>Public healthcare coverage</strong></td>
<td>Universal healthcare²</td>
<td>Universal healthcare²</td>
<td>Universal healthcare³</td>
<td>Universal healthcare⁶</td>
</tr>
<tr>
<td><strong>Healthcare financing</strong></td>
<td>General tax revenue¹</td>
<td>Insurance premiums (99%), patient out-of-pocket payments²</td>
<td>Government funding (for urban non-employed residents and rural residents), payroll taxes (employed urban residents), patient out-of-pocket payments³</td>
<td>Statutory Health Insurance (SHI) premiums and private insurance premiums (from high-income holders who opt out of public SHI insurance)³</td>
</tr>
<tr>
<td><strong>2017 GDP per Capita (% spent on healthcare)</strong></td>
<td>42,514 USD⁴ (9.7%¹²)</td>
<td>24,318 USD¹⁷ (6.3%¹¹ [2016 data])</td>
<td>7,229 USD¹⁷ (5.5%¹¹ [2016 data])</td>
<td>46,747 USD¹⁷ (11.3%¹³)</td>
</tr>
<tr>
<td><strong>% of total drug spending accounted for by orphan drugs</strong></td>
<td>1.0%¹²</td>
<td>0.5%¹³</td>
<td>&lt;1%*</td>
<td>2.1%¹²</td>
</tr>
</tbody>
</table>

*Expt. opinion

| National HTA Body | National Institute for Health and Clinical Excellence - NICE¹ | National Health Insurance Administration - NHIA¹⁴ | Locally-adapted (China National Health Development Research Centre - CNHDRC)¹¹ | National (Institute for Quality and Efficiency in Health Care – IQWIG)¹⁵ |

References available in slide notes.
Key Considerations for Access to Orphan Drugs Over the Next 10 Years

- How do we ensure fair access for rare disease patients globally?
- Which approaches are most effectively reducing delays to access for rare disease patients?
- How and when could these approaches be used in other healthcare systems?
- How do we ensure the collection of "sufficient" clinical and economic evidence but allow rapid access to treatments?
- How do we manage reimbursement of orphan drugs considering the increasing numbers and development of advanced therapy medicinal products?

Do you think that the current reimbursement system in your own country is able to manage the increasing number of orphan drugs expected in the next 5 years?

Audience Vote – Raise Your Hand for No

Current Status and Challenges of Accessibility to Orphan Drugs in Taiwan

Ming-Chin Yang, Dr.PH
Professor
Institute of Health Policy and Management
National Taiwan University
General Overview of Taiwan
Population, Age, Life expectancy and Economy

TAIWAN FACT SHEET

Population
• Total population: 23.6 million
• 2014-2018 CAGR: 0.15%

Age Distribution
• 0-14 yrs: 13.0%
• 15-64 yrs: 72.8%
• > 65 yrs: 14.2%

Life Expectancy
• Total population: 80.0 years
• Female: 83.4 years
• Male: 76.8 years

Economy
• GDP: USD 565 bn (2017)
• GDP per capita: USD 24,318 (2017)

Source: 2014/2018 statistics, Dept. of Household Registration, MOI

Rare Disease Act in Taiwan

Jun, 1999 TFRD started to operate and advocate rare disease patients' rights

Jan, 2000, rare disease act legislation was introduced
Definition of Rare Disease in Taiwan

- Prevalent in fewer than 1/10,000 people,
- Has a genetic origin,
- And is difficult to diagnose and treat.
The Rare Disease and Orphan Drug Act was enacted for:

- preventing the occurrence of rare diseases;
- early diagnosis of rare diseases;
- intensive care of rare disease patients;
- assisting patients in gaining access to specific drugs and special nutritional foods essential for the maintenance of life; and for promoting and ensuring the supply, manufacturing, research and development of such drugs and foods.

### Taiwan Rare Disease Act Key Highlights

1. Rare disease prevention
2. New born screening
3. Assure early access
4. Orphan drug special funding (2005)
5. Free for health care service and nutrition supplement
6. Reward for innovation (10-yr data exclusivity)
Rare Disease Care Network within the Government

MOHW

HPA
Rare Disease Designation

TFDA
Orphan Drug Designation & Registration

NHIA
Orphan Drug Reimbursement

Rare Disease Care

Rare Disease Designation Process

Submission

Submission received by HPA/MOHW

Documents Completed

1. 5 medical reviewers will assemble within 1 week for document review (1W)
2. Review comments will be provided within 2 weeks
3. 1 reviewer consolidates all comments reply to HPA (1W)

Rare Disease Medical Sub-Committee meeting is held for review and discussion (every 3 months)

Rare Disease Committee meeting is held for review and discussion (every 3 months)

Recognized as rare disease
1. Estimated administration process is around 45 days
2. Official Notification by MOHW issued within 30 days

Not recognized as rare disease
NHP provides reason and result for the decline (around 1 month)

Documents Incomplete

Rejection, addendum resubmission within 2 weeks

Resubmission within 1 month

Need to submit supplement
Orphan Drug Registration Process

Manufacture, Academic or Hospital
- Submission
  - TFDA
  - Operational review
  - Orphan Drug Committee-Pharmaceutical Sub-Committees
  - Orphan Drug Committee
    - Not approved
    - Approved
      - Official Notification
      - Apply for NHI reimbursement
    - Provides reason and result

Manufacture
- Orphan drug registration application
  - TFDA
  - Operational review
  - Review report
  - Drug Committee
  - Orphan Drug Committee
    - Not approved
    - Approved
      - Issue Orphan Drug Certification

Orphan Drug Designation Process

Manufacture, Academic or Hospital
- Submission
  - TFDA
  - Operational review
  - Orphan Drug Committee-Pharmaceutical Sub-Committees
  - Orphan Drug Committee
    - Not approved
    - Approved
      - Official Notification
      - Apply for NHI reimbursement
    - Provides reason and result

Reimbursement Review Process (since 2013)

Applicant
- NHIA
  - Patient Opinion sharing
- Applicant response to HTA
- NHIA expert meeting
  - No consensus
    - Two proposals
      - Minister of MOHW decision
- PBRS discuss
  - Consensus
    - Reimburse
  - Not reimburse
- PBRS agenda and HTA report published
- PBRS: Pharmaceutical Benefit and Reimbursement Scheme Joint Committee
Reimbursement Challenges

• Prompt access to orphan drug became harder after the new review process started in 2013

98 ODD granted items only 57 items received reimbursement approval (58%)

<table>
<thead>
<tr>
<th>From 1995-2012 NHI</th>
<th>Since 2013 NHI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ODD granted</td>
<td>ODD granted</td>
</tr>
<tr>
<td>Reimbursement approval</td>
<td>Reimbursement approval</td>
</tr>
<tr>
<td>80</td>
<td>18</td>
</tr>
<tr>
<td>52</td>
<td>5</td>
</tr>
</tbody>
</table>

Reasons for PBRS Reject to Reimburse -Since 2013 NHI

• Major reasons for PBRS reject to reimburse:

- Not cost-effective: 45%
- Not licensed: 22%
- Insufficient evidence of efficacy: 33%

NHIA new drug pricing methodology (A-10 lowest)

International reference pricing (IRP), A-10 country pricing
- Annual sales ≤ €0.17m, upper limited: A10-median mark-up 20%
- €0.17m < annual sales ≤ €0.34m, upper limited: A10-median mark-up 10%
- €0.34 < annual sales, upper limited: A10-median

Cost-plus pricing
- Imported products: Import cost (including shipment, insurance, storage etc.) mark-up 30% management and marketing expense
- Domestically manufactured products: manufacturing cost (excluding R&D) mark-up 30% management and marketing expense

A-10 lowest price is the norm, yet the orphan drug pricing rule is much more generous than the rest

Delayed Access to Orphan Drugs
-Since 2013 NHI

<table>
<thead>
<tr>
<th>ODD granted</th>
<th>Licensed</th>
<th>Reimbursement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opsumit (Macitentan)</td>
<td>2013/10</td>
<td>2015/04</td>
</tr>
<tr>
<td>Vimizim (Elgosulfase alfa)</td>
<td>2014/12</td>
<td>2016/01</td>
</tr>
<tr>
<td>Aubagio (Teriflunomide)</td>
<td>2015/04</td>
<td>2016/05</td>
</tr>
<tr>
<td>Eleyso (Taliglucerase alfa)</td>
<td>2016/05</td>
<td>2017/04</td>
</tr>
<tr>
<td>Repatha (Evolocumab)</td>
<td>2016/10</td>
<td>2017/01</td>
</tr>
</tbody>
</table>
Orphan Drug Special Funding From 2005

- High growth rate in the past decade from 11% to 25%. In 2017, the total orphan drug expenditure was around USD 179M.
- Multiple stakeholders are challenging the spending and asking for appropriate adjustment in orphan drug pricing.

Hemophilia Drug Special Funding From 2005

- Hemophilia is classified as a catastrophic illness by the NHI, exempting patients from a co-payment and assuring them to obtain sufficient clotting factor concentrates for suitable replacement therapy.
- NHIA introduced new reimbursement guideline in 2014 for patients with hemophilia to get prophylaxis therapy.
Reimbursement Challenges

Conclusions

1. Policy decisions and legitimization of the Rare Disease Act provides clear authorization to various government agencies to implement the Act.

2. Transparency in TFDA, NHIA, and HPA improves the control, monitoring and management in related domains.

3. Well-organized patient advocate group (TFRD) provides public scrutiny and support.

4. New approval process introduced by NHIA in 2013 making orphan drugs reimbursement more challenging.
Taiwan NHI allows ODs to apply for reimbursement before receiving TwFDA license, do you think this is feasible in your country or region?

Audience Vote – Raise Your Hand for Yes

The Recognition of Rare Disease Importance in China

Shanlian Hu. MD. MSc. Professor

W14. Delayed Access for Patients with Rare Diseases in Asia Pacific: Finding to Solution that Works

ISPOR Asia Pacific, Sept. 10, 2018, Tokyo Japan
The Definition of Rare Disease Prevalence Rate in Mainland China

- In May 2010, the Medical Genetics of the Chinese Medical Association proposed the definition of rare diseases to be <1/500,000 population or <1/10,000 newborns
- It is estimated that the number of patients with each rare disease in China is about 2,800. The total number of rare diseases in China is about 16.8 million
- Mainland China has a 1.34 billion population, and there is a large number of rare diseases with low prevalence

The Publication of a List of Rare Diseases in China

- In 2016, 56 rare diseases were published in Shanghai, which can be prevented and cured
- In May 2018, five Ministries, including the National Health Committee, jointly formulated the first national list of rare diseases and published 121 rare diseases, which will be on the Chinese national registry
- However, only 44 diseases (36.4%) have orphan drugs globally, while less than half of them have been launched in the Chinese market
Pattern of Rare Diseases in Beijing

- An eMR study conducted in tertiary hospitals in Beijing for five years (2015)
- 1,423 rare disease cases were found in 400,000 medical records
- The top 6 diseases were congenital malformations, diseases of the nervous system, endocrine and metabolic disorders, and diseases of the circulatory system, skeletal muscle and connective tissue

- Another eMR study of 405,000 medical records in 93 tertiary hospitals in 7 provinces
- 2.27% cases suffered from 952 rare diseases
- More than half of the rare diseases were congenital diseases

A Synergistic Study of RD in China

<table>
<thead>
<tr>
<th>RD Epidemiological Survey</th>
<th>Establishing Registry System</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hemophilia</td>
<td>• Establishing National and regional registry system platform registered &gt;50 RD</td>
</tr>
<tr>
<td>• Kawasaki disease</td>
<td>• Establishing national RD research network</td>
</tr>
<tr>
<td>• Down’s syndrome</td>
<td>• In 2016, National Health and Family Planning established a National Advisory Committee of RD diagnosis &amp; treatment</td>
</tr>
<tr>
<td>• Paroxysmal nocturnal hemoglobinuria</td>
<td></td>
</tr>
<tr>
<td>• Hepatolenticular degeneration</td>
<td></td>
</tr>
<tr>
<td>• Myasthenia gravis</td>
<td></td>
</tr>
<tr>
<td>• Chronic thromboembolic pulmonary hypertension (CTEPH)</td>
<td></td>
</tr>
<tr>
<td>• Hereditary cerebellar atonic atune (SCA)</td>
<td></td>
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</tbody>
</table>

Research Report on Rare Diseases in China 2018
In 2016, SHI, medical aid & catastrophic covered Gaucher’s disease, phenylketonuria & amyotrophic lateral sclerosis.

Reimbursement by SHI + Children’s mutual aid, No deductible & ceiling CNY 100,000 per year.

Special subsidies by major diseases medical insurance scheme.

Cost of Gaucher disease supported by SHI, civil affairs, health emergency and PAP.

Potential Models to Accelerate Patient Access of Orphan Drugs

• Doctor training, and prescribing orphan drugs by designated medical institutions and experts, & fixed distributors to supply

• Priority setting on some rare diseases that are expected to significantly improve patients’ access to care

• Listing some orphan drugs in the basic insurance reimbursement drug formulary through price negotiations

• Drug companies & Red Cross jointly conducted PAP for charitable donations

• Multi-party fund-raising, including civil affairs’ medical assistance
The Legislation Environment for Rare Disease is Getting Better

Key Market Events

1. NHC released first batch of rare disease in China
2. CDE Granted expedited approval to urgently-needed orphan drugs marketed overseas
3. CNDA issued the Technical Guidelines for Acceptance of Foreign drug clinical trial data
4. Chinese government waived import tariffs on import oncology drugs
5. SMIA intended to regularly hold nationwide price negotiation for high cost drugs in China

Implications

1. China may start to legislate on rare disease related field
2. The launch time of pipeline orphan drug will be significantly brought forward
3. It is possible that OD may also enjoy 0 tariffs in the near future due to similarity in high cost
4. The reimbursement review cycle can be significantly shortened, and in future, BMI inclusion may be quicker

In Line with the Recent Acceleration in Rare Disease Legislation, Rare Disease in China is Gaining Awareness

Type distribution of 36 NRDL listing negotiation high-cost drug (2017)

<table>
<thead>
<tr>
<th>Type Distribution</th>
<th>2016</th>
<th>2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>36</td>
<td>48</td>
</tr>
<tr>
<td>TCM</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Oncology drug</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Western chronic disease therapy</td>
<td>14</td>
<td>38%</td>
</tr>
<tr>
<td>Rare disease</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Therapy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Type distribution of 48 list of urgently-needed new drugs marketed overseas published by CDE (2018)

- Rare disease: 38%
- Other life threatening diseases: 63%
Policy Recommendations

- Formulating master plan
- Promoting government role & social security
- Strengthening register & monitoring system
- Establishing rare disease clinical center & referral
- Clinical pathway & guidelines
- Integrating social forces

Audience Vote

Do you agree that the most practical and fastest way to achieve national reimbursement coverage for rare disease therapy is through national price negotiation?

Audience Vote – Raise Your Hand for Yes
Thank You For Your Attention

The German Solution: Immediate Access and Data Collection
Bertram Häussler, IGES Institut
ISPOR Asia Pacific 2018 – Workshop W14
Tokyo, September 11th, 2018
Overview

Every new drug (including OD) can be marketed after
- EU marketing authorization &
- German licencing

Immediate market access for OD
- no further delay by decision process

Reimbursement for new drugs subject to
demonstration of additional benefit

For Ods „additional clinical benefit“ is automatically demonstrated
- if expenditure < 50 €m p.a.
- > 50 m → full clinical assessment

No patient-specific second opinion needed

Speciality drugs (including OD) may be
- restricted to specialized physicians or centers
- charged with requirements for data collection

Legal situation: Germany complies with EU regulation

EU law
- Orphan drug designation
- Marketing authorization

EU 141/2000
... the Member States shall not, for a period of 10 years, accept another application for a marketing authorization ... for the same therapeutic indication

German law
- Early benefit appraisal
- Price negotiation

SGB V § 35a (1) 9
Marketing authorization according to EU 141/2000 automatically means statement of additional benefit

Rahmenvereinbarung §6 (2) acc. SGB V § 130b (9)
Mark-up on costs of appropriate comparator therapy can be negotiated for drugs with additional benefit
Assessment / appraisal in detail

Appraisals all positive for orphan drugs
Germany market is attractive and permissive as well

Orphan drugs account for appr. 30% of all new drugs in the German market
Prices higher for orphan drugs (within oncology indication)

Orphans (oncology)

Non-Orphans (oncology)

Only 1 “opt out” since 2011

Re-assessment for exceeding 50 €m p.a. threshold

- Full assessment against comparator

4 / > 120

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Assessment</th>
<th>Reassessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruxolitinib</td>
<td>Small</td>
<td>Substantial</td>
</tr>
<tr>
<td>Pomali-domid</td>
<td>Substantial</td>
<td>Substantial/ not dem.</td>
</tr>
<tr>
<td>Ibrutinib</td>
<td>Not quant.</td>
<td>Not quant. / not dem.</td>
</tr>
<tr>
<td>Macitentan</td>
<td>Small</td>
<td>Not dem.</td>
</tr>
</tbody>
</table>

Source: IGES calculations based on Lauer-Taxe® and IGES

1/G/O = Tegafur/ Gimeracil/ Oteracil

September 11, 2018

Häussler: W14, ISPOR Asia Pacific 2018
Budget impact of Orphan Drugs growing relatively - "explosion" of health expenditures did not occur

Audience Vote

Do you believe that the expiration of the OD status does substantially contribute to contain the OD budget?

Audience Vote – Raise Your Hand for Yes
Discussion
Summary and Close

Dr Annabel Griffiths
Head of Rare Diseases, Costello Medical, UK

Summary

- Unmet need
- Define rare diseases
- Introduce policies and incentives
- Increased numbers of treatments
- Delays in access
- Pricing challenges
- Re-evaluation of reimbursement processes

AIM
Sustainable, timely and equitable access
Acknowledgements

Thank you for your attention

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