Using Real-World Data/Evidence in Regulatory Decision Making

Chi-Hsun Chen, M.D.
Senior Team Leader/Medical Reviewer
Center for Drug Evaluation, Taiwan
Outlines

1. What are RWD & RWE? 
   From RWD to RWE

2. Applications of RWD/RWE 
   In Regulatory Decision Making 
   Taiwan Experiences

3. RWD Sources in Taiwan 
   Individual database and 
   HWDC in Taiwan
Evidentiary Standards for Drug Approval

Is there substantial evidence of drug safety and efficacy for the claimed indication?

Confirmatory randomized controlled trials (RCTs) – An ideal Setting

Eligible patients
- Strict inclusion and exclusion

Randomization
- Proper randomization
- Concealed allocation
- Appropriate blinding

Treatment

Control

Outcome

Artificially homogeneous

Minimize the chance of bias from patient selection, treatment assignment, patient evaluation and data analysis
Increasing use of real-world evidence to support decision making

Real World Data (RWD)

Data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources

Analytics

Real World Evidence (RWE)

Clinical evidence regarding the usage, and potential benefits or risks, of a medical product derived from analysis of RWD
Ability of RWD to generate RWE

RWD Relevant

Sufficient?
- enough drug exposure,
- meaningful endpoint,
- population.....

RWD Reliability/Quality

Sufficient & Assured?
- data accrual (protocol),
- source verification,
- minimizing missing data/outliers, sites monitoring/audit

Analytics

Adequate?
- appropriate methodology

Minimize source of bias?
How to Translate RWD into RWE

1. Define a meaningful question
2. Setup an appropriate design and/or choose an adequate RWD source
3. Protocol and Analysis Plan
4. Conduct study; Analyze RWD
5. Complete study report → RWE
Outline

1. What are RWD & RWE? From RWD to RWE
2. Applications of RWD/RWE in Regulatory Decision Making - Taiwan Experiences
3. RWD Sources in Taiwan - Individual database and HWDC in Taiwan
Taiwan regulatory experience with RWD/RWE

Change of approved product label
• Update label information of drug-drug interaction and safety

Post-market safety surveillance
• Phase IV safety study requested by regulatory
• Post-marketing pharmacovigilance

Pre-market safety assessment
• PSURs/PBRERs from other countries can be used as the sources of pre-marketing safety evaluation

Pre-market efficacy assessment
• Provide critical efficacy evidence (e.g. rare disease)
• As a historical control for single arm control
Case 1
The approval of Sapropterin Tablet for Hyperphenylalaninemia (HPA)

Case 2
Oral Ketoconazole, Hepatotoxicity
Case Study 1 – The approval of Sapropterin Tablet for Hyperphenylalaninemia (HPA)

- HPA is diagnosed as an abnormal elevation in blood phenylalanine level (>120 μmol/L)
- Caused by
  - Phenylalanine hydroxylase (PAH) deficiency: phenylketouria (PKU), or
  - Tetrahydrobiopterin (BH4) deficiency
- Incidence
  - Caucasian: ~ 1 in 10,000 & 1.5-2% of HPA are BH4 deficiency type
  - Taiwanese: ~ 1 in 34,000 & 30% of HPA are BH4 deficiency type
- In Taiwan, Sapropterin tablets (BH4) have been imported and used for the treatment of BH4 deficiency for many years without registration.
Case Study 1 – Sapropterin Tablets ("Excelsior" BH4)

✓ Well collected patient clinical data derived from two retrospective observational studies in patients with BH4 deficiency.

National Taiwan University Hospital
(14 patients; 3-20 years)

+ 

Taipei Veterans General Hospital
(21 patients; >10 years)

RWD
↓
RWE
The "Excelsior" BH4 Tablet (sapropterin) was approved for the treatment of hyperphenylalaninemia due to tetrahydrobiopterin (BH4) deficiency, based on following consideration:

- Claimed indication is a rare disease
- Clear mechanism of action
- Surrogate endpoint (blood Phenylalanine level)
- Well-collected patient clinical data (real world data)
Case Study 2 – Oral Ketoconazole / Hepatotoxicity

✓ In Taiwan, oral ketoconazole was indicated for the treatment of fungal infections.
✓ Concerns raised internationally on liver toxicity associated with oral ketoconazole

EMA: Suspended

FDA: Restriction of use & lots of warnings
Oral Ketoconazole / Hepatotoxicity

Taiwan National ADR Reporting Database

<table>
<thead>
<tr>
<th>Item</th>
<th>Hepatobiliary disorders</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>31</td>
<td>58</td>
</tr>
<tr>
<td>Age (year)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>45±15</td>
<td>51±20</td>
</tr>
<tr>
<td>Range</td>
<td>16-86</td>
<td>16-94</td>
</tr>
<tr>
<td>Gender (N)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>8</td>
<td>18</td>
</tr>
<tr>
<td>Female</td>
<td>23</td>
<td>40</td>
</tr>
<tr>
<td>Outcome of adverse reaction (N)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Life threatening</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td>Non-serious</td>
<td>6</td>
<td>26</td>
</tr>
</tbody>
</table>

ADR=Adverse drug reaction

- Some uses without prescription
- Use due to mild skin conditions
## Oral Ketoconazole / Hepatotoxicity

**Taiwan National Health Insurance (NHI) Claim Database**

<table>
<thead>
<tr>
<th>Medical care institute</th>
<th>No. of prescription (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical centers</td>
<td>280 (1.1%)</td>
</tr>
<tr>
<td>Regional hospitals</td>
<td>354 (1.4%)</td>
</tr>
<tr>
<td>District hospitals</td>
<td>1,103 (4.5%)</td>
</tr>
<tr>
<td>Primary care clinics</td>
<td>19,103 (77.3%)</td>
</tr>
<tr>
<td>Pharmacy</td>
<td>3,864 (15.6%)</td>
</tr>
<tr>
<td>Total</td>
<td>24,704 (100.0%)</td>
</tr>
</tbody>
</table>

- Difficulty in providing intense liver function monitoring
- Liver function test within 30 days before treatment: 2.7%
Literatures

- Within the recommended dosage, the incidence and severity of liver injury caused by oral ketoconazole are higher than those of other azoles.
- Liver injury occurs mostly between 1 and 6 months, but there are still many case reports occurring within 1 month (including few days).

Cannot reduce the risk by limiting the dosage/duration.

There are other available medicines in the market.

Taiwan: withdrawal.
Outlines

1. What are RWD & RWE?
   From RWD to RWE

2. Applications of RWD/RWE
   In Regulatory Decision Making and HTA

3. RWD Sources in Taiwan
   Individual database and HWDC in Taiwan
# RWD Sources in Taiwan

<table>
<thead>
<tr>
<th><strong>Patient-level data of nation-wide population</strong></th>
<th><strong>Summary data of national health statistics</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• National Health Insurance (NHI) Claim Database</td>
<td>• Population Projections (Taiwan)¹</td>
</tr>
<tr>
<td>• Disease Registry: Cancer Registry Database</td>
<td>• Healthcare statistics annual reports³</td>
</tr>
<tr>
<td>• Cause of Death Mortality Database¹</td>
<td>• Cancer registry annual reports⁴</td>
</tr>
<tr>
<td>✓ De-identification and encryption</td>
<td>• NHI healthcare quality public disclosure</td>
</tr>
<tr>
<td>✓ Limited access with IRB approval</td>
<td>✓ Aggregate data by age and gender</td>
</tr>
<tr>
<td></td>
<td>✓ Open access on official website</td>
</tr>
</tbody>
</table>

Data Linkage among Various Databases

Fundamental Databases

Health Promotion Administration

Taiwan Centers for Disease Control

National Health Insurance Administration

Social and Family Affairs Administration

ISO27001 Certification (information security standard)

HWDC

Sub-centers (10)

University affiliate medical centers and Research Institutes

Ministry of Health and Welfare, MOHW

Department of Statistics

Department of Information Management

Health and Welfare Data Statistics Application Review Committee

Encryption and Data Verification

Value-added Platform

Health and Welfare Databases

Application & Review

Query Interface

Requestors

One-stop Window

Statistics development

Information Security

Regulatory Analysis

Center For Drug Evaluation
✓ Health and Welfare Data Science Center (HWDC)
  – Manage all databases relevant to health and social welfare from birth to death
  – NHI claim database (2-millions sampling database)
  – Cancer registry, rare disease, catastrophic illness, disability
  – Health Survey: birth cohort, women, elderly, adolescent
  – Disease-specific database: diabetes, hypertension, chronic kidney disease

✓ Research proposal and IRB approval is required before submission
  – Preparation process from application to data access: 6 months

✓ Encrypted personal ID for de-identification
  – Researchers have to analyze data on-site (main- and sub-centers)
  – Statistical output will be carefully reviewed by HWDC to ascertain data security
10 HWDC Sub-centers for Research in Taiwan

- Chang Gung Univ. (Taoyuan)
- National Health Research Institute (Miaoli)
- China Medical University (Taichung)
- National Cheng Kung Univ. (Tainan)
- KaoHsiung Medical Univ. (Kaohsiung)
- National Taiwan Univ.
- National Yang Ming Univ.
- Taipei Medical Univ.
- Academia Sinica
- Tzu Chi University
- National Health Research Institute

Established since 2012 in university affiliate medical centers and research institutes
Facts and Opportunities

Data Value

-Ask right questions
  - Collect high-quality data
  - Conduct proper analyses
  - Generate reliable and robustness evidence

Regulatory
- Pharmacovigilance
- Safety label changes
- Drug-drug interactions
- Conditional approval requiring collection of on-market data
- Extension of indication

Industry
- Discover drug pathways
- Identify unmet clinical need, profile target populations
- Uncover new indication
- Profile patient compliance/adherence
Challenges of Using RWD in Taiwan

- Comprehensive RWD access is limited to some stakeholders
  - Databases in HWDC are not available for non-academic use, ex. pharmaceutical company
  - Collaboration between stakeholders is a possible solution

- RWD is not collected for research purposes
  - Inherent bias: selection bias, information bias, confounding bias
  - Development of statistical methods and pharmacoepidemiology design

- Data linkage between electronic health records (EHRs) and other RWD is still difficult
  - Ethical issue and informed consents of patients
  - Some medical centers establish data warehouse of EHRs for further application
Acknowledgements

Dr. Churn-Shiouh Gau, Executive Director, Taiwan Center for Drug Evaluation

Division of New Drug, Taiwan Center for Drug Evaluation

Division of Drug Safety, Taiwan Drug Relief Foundation
Question!!