Real-world Data and Real-world Evidence in Support of Drug Development: Will China Soon be Leading the Way?
Conflict of Interest Statement

- Amanda Pulfer, Dimitra Lambrelli, and Lu Ban are paid employees of Evidera, a business unit of PPD, a Thermo Fisher Scientific company.
Real-world Evidence and Regulatory Environment in China
Lu Ban, Evidera
- To provide an overview of the regulatory environment and use of RWE to support development of pharmaceutical products in China

Real-world Evidence Generation Ecosystem in China: An Innovator’s Perspective
Sunil Garg, Astellas
- To provide an innovator’s perspective on RWE generation in China

Challenges and Opportunities in Conducting Real-world Studies in China
Haijun Cao, Happy Life Technology
- To provide practical guidance on conducting studies using RWD in China from a local company perspective

Questions and Answers

Abbreviations: RWD = real-world data; RWE = real-world evidence
Real-world Evidence and Regulatory Environment in China

Lu Ban, PhD, Associate Director, RWE, Evidera

21 September 2022 11:30 a.m. to 12:30 p.m. (KST/GMT+9)
RWE Regulatory Frameworks and Policies

<table>
<thead>
<tr>
<th>Year</th>
<th>US</th>
<th>Europe</th>
<th>China</th>
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<tbody>
<tr>
<td>2015</td>
<td>The 21st Century Cures Act</td>
<td>EMA Adaptive Pathways Pilot</td>
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<tr>
<td>2016</td>
<td>“Using Real-World Evidence to Support Regulatory Decision-Making of Medical Devices”</td>
<td>Big Data Task Force established</td>
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<td>2017</td>
<td>FDA Real-World Evidence program launched</td>
<td>Framework for RWE</td>
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<td>2018</td>
<td>“Guidelines for Use of RWD for Clinical Evaluation of Pediatric Drugs &amp; Medical Devices (interim)”</td>
<td>“Guidelines for Use of Single Arm Clinical Trials for Marketing Applications for Oncology Drugs”</td>
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<td>2019</td>
<td>“Guidelines for RWE Supporting Drug Development and Review (interim)”</td>
<td>“Guidelines for Communication of RWE Supporting Drug Registration Applications (for Comment)”</td>
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<td>2020</td>
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Abbreviations: EMA = European Medicines Agency; FDA = Food and Drug Administration; HMA = Headquarters of the European Medicines Agency; RWD = real-world data; RWE = real-world evidence.
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<thead>
<tr>
<th>Year</th>
<th>US</th>
<th>Europe</th>
<th>China</th>
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<tbody>
<tr>
<td>2011</td>
<td>Framework and guidelines for RWD from initiatives/collaboratives</td>
<td>ENCePP Guide on Methodological Standards in Pharmaco-epidemiology</td>
<td>China Real World Evidence Alliance (ChinaREAL) established</td>
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<td>2012</td>
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<td>2017</td>
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<tr>
<td>2018</td>
<td>RWE program describe high-level principles &amp; key questions</td>
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<td>2019</td>
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<tr>
<td>2020</td>
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<tr>
<td>2021</td>
<td>FDA issues series of guidance on RWD and RWE</td>
<td>Hainan RWD Research Institute &amp; Drug and Medical Device Regulatory Scientific Research Base established</td>
<td>“Guidelines for Real-World Data Used to Generate Real-World Evidence (interim)”</td>
</tr>
</tbody>
</table>

Abbreviations: EMA = European Medicines Agency; FDA = Food and Drug Administration; HMA = Headquarters of the European Medicines Agency; NMPA = National Medical Products Administration; RWD = real-world data; RWE = real-world evidence; US = United States

# RWE to Support Drug Approval in China and US

<table>
<thead>
<tr>
<th>Year</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2017</strong></td>
<td><strong>US</strong>&lt;br&gt;First Drug Approval&lt;br&gt;FDA granted accelerated approval to avelumab for patients ≥12 years of age with metastatic MCC.</td>
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<td><strong>China</strong>&lt;br&gt;First Drug Approval&lt;br&gt;NMPA granted approval for Pujihua® for adults with LA/m NSCLC previously received platinum-based chemotherapy.</td>
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<td><strong>2018</strong></td>
<td><strong>US</strong>&lt;br&gt;Label Expansion&lt;br&gt;FDA approved blinatumomab for men with HR+, HER2-BC, based on RWD after drug was marketed.</td>
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<td><strong>China</strong>&lt;br&gt;Label Expansion&lt;br&gt;NMPA approved Prolia® (denosumab) for the treatment of postmenopausal women with osteoporosis.</td>
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<td><strong>2019</strong></td>
<td><strong>US</strong>&lt;br&gt;Label Expansion&lt;br&gt;FDA approved palbociclib for patients ≥12 years of age with metastatic MCC.</td>
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<td><strong>China</strong>&lt;br&gt;Label Expansion&lt;br&gt;NMPA approved tacrolimus to prevent organ rejection in adult and pediatric patients receiving lung transplantation.</td>
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<tr>
<td><strong>2020</strong></td>
<td><strong>US</strong>&lt;br&gt;First Drug Approval&lt;br&gt;NMPA granted approval for Fujihua® for adults with LA/m NSCLC previously received platinum-based chemotherapy.</td>
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<td></td>
<td><strong>China</strong>&lt;br&gt;Label Expansion&lt;br&gt;NMPA granted approval for YUTIQ® 0.18 mg for chronic non-infectious uveitis.</td>
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<tr>
<td><strong>2021</strong></td>
<td><strong>US</strong>&lt;br&gt;Label Expansion&lt;br&gt;FDA approved alpelisib for PIK3CA-related overgrowth spectrum.</td>
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<tr>
<td></td>
<td><strong>China</strong>&lt;br&gt;Label Expansion&lt;br&gt;NMPA granted approval for Allergan's glaucoma drainage tube.</td>
</tr>
<tr>
<td><strong>2022</strong></td>
<td><strong>US</strong>&lt;br&gt;Drug Approval&lt;br&gt;NMPA granted approval for YUTIQ® 0.18 mg for chronic non-infectious uveitis.</td>
</tr>
<tr>
<td></td>
<td><strong>China</strong>&lt;br&gt;Label Expansion&lt;br&gt;NMPA granted approval for Allergan's glaucoma drainage tube.</td>
</tr>
</tbody>
</table>

Abbreviations: BC = breast cancer; FDA = Food and Drug Administration; LA/m = locally advanced/metastatic; MCC = Merkel cell carcinoma; NMPA = National Medical Products Administration; NSCLC = non-small cell lung cancer; RWD = real-world data
RWE to Support Reimbursement through National Reimbursement Drug List (NRDL)

‘Golden ticket’ - Major public reimbursement mechanism and essential for market access in China

- Covers 98% of the China population
- Includes high-value, high price drugs
- Listing essential to get into public hospitals

NRDL gets updated annually and there is an opportunity for RWE input

Preparation and Application
(formulate eligibility criteria and initial assessment)

Review
(expert review and recommendations)

Negotiation
(formulate suitable price and include in the NRDL)

Manufacturers can submit applications
Clinical assessment will be based on efficacy, safety, economic impact, innovation, and equity

Manufacturers submit dossier, including health economics evaluations
Local RWD can be used for cost-effectiveness analysis and budget impact analysis
- For budget impact analysis, local RWD is a preferable data source
- For estimation of clinical effectiveness, RWE can be standalone or supplementary evidence

China Pharmacoeconomic Evaluation Guidelines 2020
Question. What types of data did you use/are thinking of using in China?
Different Types of RWD and Real-world Studies in China

Primary Data Collection
- Chart Review
- Pragmatic Trials
- Patient-reported Data

Secondary Use of Data
- Electronic Medical Records
- Claims/Insurance Data
- Disease/Product Registry
- Social Media Platforms
- Mobile Devices

Organized data collection system not primarily used for research purposes/secondary re-usable data platform
# Emerging Data Sources in China

<table>
<thead>
<tr>
<th>Administrative Claims</th>
<th>EMRs</th>
<th>Disease Registry</th>
</tr>
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</table>
| ▪ National Claims Database (from urban employee/resident medical insurance, e.g., Urban Employee Basic Medical Insurance [UEBMI])  
  ● Inpatient and outpatient claims  
  ● Resampled annually  
  ● Regional, e.g., Beijing, Tianjin, Guangzhou | ▪ Individual hospitals with various EMR systems  
 ▪ Regional EMR data of multiple hospitals in a specific region  
  ● e.g., Yinzhou District in Ningbo, Xiamen, Fuzhou, Shandong  
 ▪ EMR data platforms covering multiple hospitals of different regions  
  ● HLT, LinkDoc, Digital Health China  
  ● Convenient samples  
  ● EMR database  
  ● National Anti-tumor Surveillance System (NATDSS), linked to death registry  
  ● Linkage between different levels of hospitals is lacking  
  ● Regional EMRs potentially can be linked to regional claims data, e.g., Yinzhou District in Ningbo and Xiamen EMRs. | ▪ Oncology  
 ▪ Cardiovascular disease  
 ▪ China National Rare Diseases Registry System |


Abbreviations: EMR = electronic medical record; HLT = Happy Life Technology
Study Design and Analysis Considerations with Use of Secondary Data in China

Unstructured data and NLP
- Lack of specific coding of diagnoses/treatments
- Outcomes recorded in free texts, e.g.,
  - Response to treatment
  - Reason for treatment discontinuation
  - Line of therapy
- Application of NLP with manual review
- Assessment of validity of NLP algorithm

Longitudinality
- Non integration of different healthcare services
- Availability of baseline and follow-up period

Population Representativeness
- Convenient samples of hospitals from certain regions
- Tertiary/specialist care hospitals over-represented in the EMR databases

Availability/definition of endpoints of interests
- Inpatient data are generally more complete compared to outpatient data
- For endpoints not available
  - Creation of proxies
  - Missing data
  - Imputation
  - Sensitivity analysis

Abbreviations: EMR = electronic medical record; NLP = natural language processing
Summary

- Indicators that China will be leading the way
  - Active promotion of use of RWE in regulatory and reimbursement decisions
  - Fast emerging data landscape with advancement of new technology
  - Great potential in oncology and rare disease research
  - Increased attention to patient privacy protection

- Potential considerations
  - Data quality and data accessibility
  - Proper study design and execution
Real-World Evidence Generation Ecosystem in China

An Innovator’s perspective

Sunil Garg
Senior Director, Lead of Evidence Generation Operations
Astellas Pharma, Singapore

September 21, 2022
The speaker is a paid employee of Astellas. This presentation is intended for information purpose only and does not replace independent professional judgement. This presentation is not intended to be legal or medical advice. Statements of acts, position taken, and opinions expressed are those of the speaker individually and, unless expressly stated to contrary, do not necessarily reflect the opinion or position of the speaker’s employer, Astellas, or any of its subsidiaries and/or related entities.
CHINA: CHANGING LANDSCAPE

1. National Reimbursement Drug List (NRDL)
   - Volume-based centralized drug procurement policy; updated annually
   - Pressure on drug prices cut will remain; local RWE to support cost effectiveness and budget impact will be key to NRDL negotiations
   - Generic Quality Consistency Evaluation (GQCE) has put pressure on innovator’s matured products

2. Shorter launch time for innovative and rare disease products/stronger patent laws
   - Accelerated approval pathways and breakthrough therapy designations
   - New amendment (4th) to patent laws brings provision for patent term extension and patent linkages
   - Legal provision to challenge patent violations

3. Increasing regulatory focus on RWE
   - Release of relevant guidelines, i.e., Guiding principles of real-world evidence supporting drug development and review (trial)
   - Development of networks, platforms and database, i.e., Establishment of Hainan Real World Data Research Institute.
   - RWD for Clinical Evaluation of Medical Devices is one of the key projects in the Drug Regulatory Science Action Plan, i.e., market authorization of medical device for surgical management of refractory glaucoma with the submission of clinical RWE of racial differences
EXPERIENCES

• Different practice and understanding on patient privacy and informed consent requirements, i.e., informed consent requirements for chart review

• Data completeness: separate accessibility to different HIS/EMR modules, i.e., use of technology vendors to work with hospital IT for data access across HIS modules

• High legal and compliance risks: data ownership and commercial rights concerns multi-center EMR data

• Data technology vendors working practices and legality

• Inconsistent data variables with inconsistent vocabulary in different hospitals EMR – difficult data curation and analysis.
LESSONS LEARNED

• Feasibility assessment and review of data variable early on before conducting an RWE study; data source may include, e.g.,
  • Digital Health China & Linkdoc (National Oncology EMR)
  • National Cancer Center/1 Yong Cloud (National Anti-Tumor Drug Surveillance System)
  • Yidu Cloud (National Multi-disease EMR)
  • Ningbo, Gennlife (Multi EMR & Disease Claims)
  • Tianjin EHR (Regional Database)

• Use of data vendor/development of technology for a single window access to patient data spread across the HIS/EMR modules

• Work with site GCP/R&D in drafting a consistent and defined procedures to RWE data access to third parties
FUTURE DIRECTION

- Stakeholder collaborations and consortium to build RWE infrastructure by shaping RWE standards and sharing best practices
- Capacity building by investing in RWE education & infrastructure across stakeholders
- Provision of central Ethics committee to provide a single window clearance to RWE studies
- Simplify HGRAC regulations and requirements: a clear risk-based approach would be helpful
- Regulator to optimize the policy for RWD access, use and patient privacy protections, interoperability with overseas data, guidance on the use of new types of data (health mobile data, electronic wearable device data)
- Uncertainty in government polices: a value-based approach recommend in reimbursement assessments.
- Improvement in methodology and analytical technology by the CROs/data IT vendors
- Patient centric approach for a robust and meaningful RWD
Digitally and analytical enable environment with healthcare as a strategic priority

Rising China contribution to global pharma revenue

Multinationals are at a crossroads – not just for the sales numbers but strategically it’s too hard to miss the opportunity to ride the dragon. With broadening access to newer therapies and increasing evidence, China could lead the wave of an innovation-driven ecosystem.

Participation of Chinese patients in global studies for simultaneous development

Rise of domestic biotech R&D: leading chimeric antigen receptor T-cell (CAR-T) therapies

Changing regulatory landscape

Data quality

Patent protection mechanism

High attrition rates/talent crunch

Market access constrains and cost driven reimbursement negotiations
The Challenges and Opportunities in Conducting Real World Study in China

Prepared by:
Haijun Cao, M.D, PhD

Prepared for:
ISPOR Asia Pacific Summit

21 Sept 11:30-12:30pm (Korean time) 2022
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Question. What is your level of experience with conducting RWE studies in China?
Growing investment in healthcare data-related companies boost RWS development in China

Distribution of RWD companies in the world

Total Investment of RWE in China (Billion Yuan)

Reference: CB Insights China. 生物医药领域的真实世界数据行业报告2021
Cornerstone of RWS start-up: EC and HGRAC

EC and HGRAC Regulatory development in China

_Tentative Measure on the Management of Human Genetic Resource_ was issued, as the fundamental document on the use and protection of HGR in China.


_Renewed the guideline on the application procedure of HGR use in international cooperative scientific researches._

_Regulations of the People’s Republic of China on the Management of Human Genetic Resources_ issued, aimed protecting and using HGR effectively.

_HGRAC office further optimized the approval procedure and timeframe for HGR related international cooperative scientific researches._

_HGR related regulations incorporated into Biosecurity Law, elevating the protection of HGR to the level of national law._

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**Ethnical committee (EC)**

- Any institution conducting HGR related scientific studies is required to set ethnical committee, to guarantee the ethnic issues in studies.
- Any studies involving HGR, including non-interventional retrospective studies, is required to pass the ethnical examination prior to the kickoff of the study.
- Ethnical examination criteria includes the ethnic and scientific standard of the study design, the design of the consent form, fairness for the study subjects, etc.

**Human Genetic Resource Administration of China (HGRAC)**

- HGRAC operates under the Ministry of Science and Technology of PRC to regulate the use and protection of HGR in China.

*All policy are available at [中国政府网 中央人民政府门户网站](www.gov.cn)*  
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HGRAC process for RWS projects in China

Starting

For research projects with international sponsorship

If meet any of the following:
1. Sample size is greater than 500
2. Rare diseases
3. Special locations, family, or ethnicity

<table>
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<th>International collaboration review</th>
<th>Collection</th>
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Publish on international journals or make results public to international use
Site start-up and management to promote RWS execution in China

Phase 1: Feasibility assessment and Study design
- Study feasibility assessment
- Site feasibility assessment
- DMP development
- Research protocol

Phase 2: Site start-up and management
- Site/PI interest research/communication
- Project start-up and training
- Leading site EC review
- EC* approval
- HGRAC*
- Contract
- Sub sites EC review

Phase 3: Data management and statistical analysis
- Data extraction
- Data curation and management
- Statistical analysis

Phase 4: Study report and publication
- Study summary and report

EC: Ethics Committee; HGRAC: Human Genetic Resources Administration of China
PI mapping and site selection

50% Research project related
- Sample size
- Operation risk

35% Principal Investigator
- Members of academic associations
- Authors of guidelines and consensus
- Publications
- Hospital titles

15% Hospital and Department
- Overall rank of hospital
- Rank of oncology department
- Research capacity
- Oncology department capacity

Source

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<th>Research</th>
<th>Authors of guidelines and consensus</th>
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<tr>
<td></td>
<td>Members of academic associations</td>
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<tr>
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<td>Conference speakers</td>
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<td>PIs of key competitors</td>
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</table>
Rigorous SSU pre-planning to manage RWS operation

- PI visit and site survey
- Start-up
- EC approval
- HGRAC notice
- Contract
- Data extraction
- Close-out

Illustrative only

- Hospital checklist of documents for submission
- Sufficient time for hospitals to review site start-up materials.

- The SSU process could be complex and need to get prepared well
- Several weeks or several months for EC approval could be possible

- Upon contract finalization, the signing procedure can be completed within 1 month
- 2-4 months for HGRAC approval.
Solid and efficient technology provides opportunities for conducting RWS from different hospitals

Data Processing & Modelling
- Medical Research
- Clinical Diagnosis & Treatment
- Epidemic Response
- Public Health Supervision Monitoring
- Population Health Management

Data Processing
- Knowledge-based Data Processing
- Data Standardization

Data Mining & Modelling
- Structured Search
- Knowledge Graph / Knowledge Base
- NLP

Data Standards and Schema Matching
- Hospital Information System (HIS, PACS, LIS, EMR, NIS...)
- Out-of-Hospital Data (Follow-up Visits, Wearables, Environment...)

Applications & Solutions

Data Integration

Big Data Architecture Standard System
- Big Data Security System
- Big Data Compliance System
- Big Data Authentication System
Future considerations and actions to advance RWE in China

- Data authorization and compliance to obtain real world data is a huge challenge.
- Site start-up and management should follow the regulations of EC, HGRAC, and hospitals requirement, a big challenge for management of project timeline.
- Professionally qualified personnel and multi-background teams are required to manage hospital-based data and multi-source data collection and analysis.
Q&A