致力法規科學，守護生命健康
Regulatory Science,Service for Life

Real world Evidence in New Drug Review

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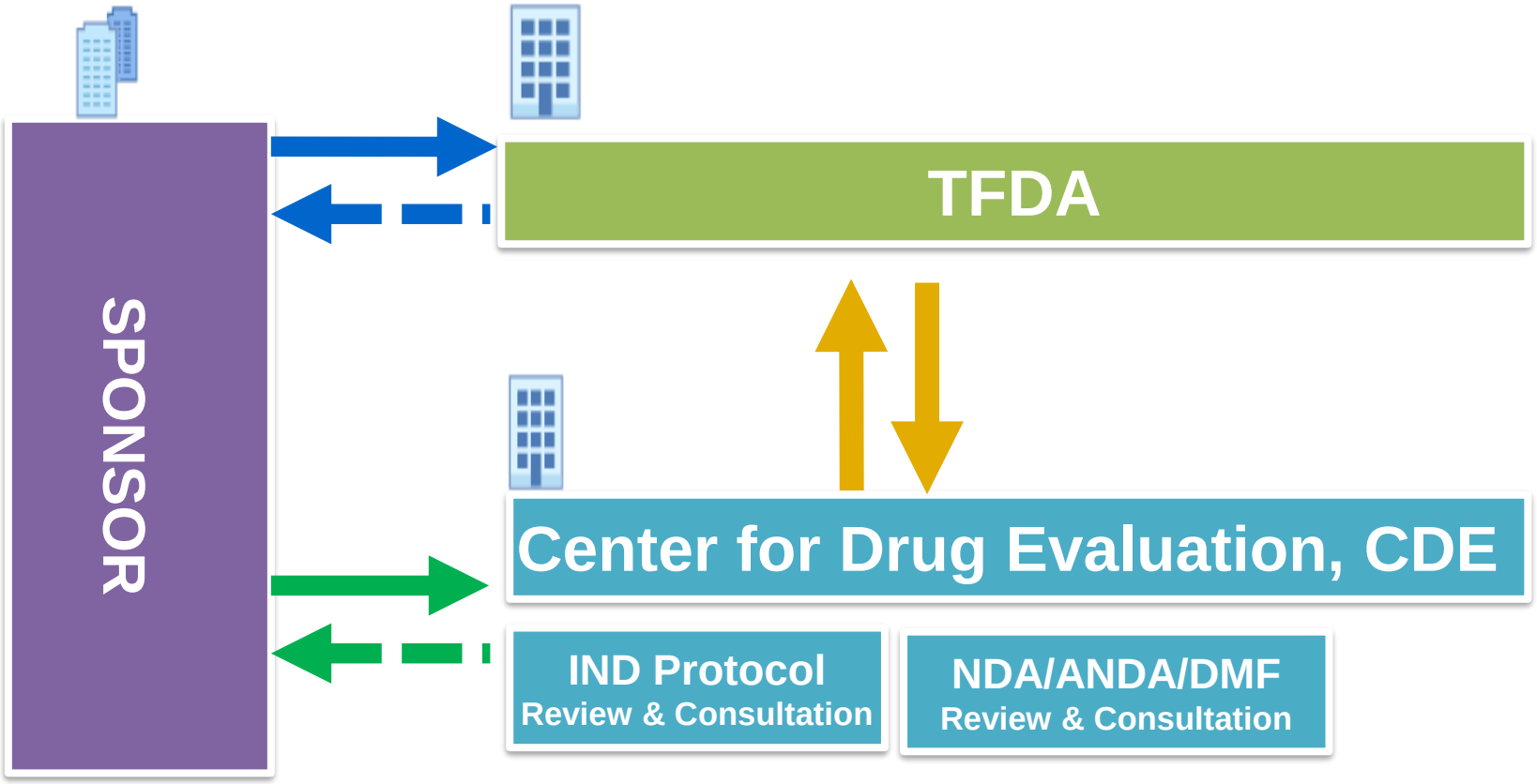
本次演講內容僅代表查驗中心之觀點，凡涉及政策方向及法規解釋與適用，應依衛生主管機關之指示為準。

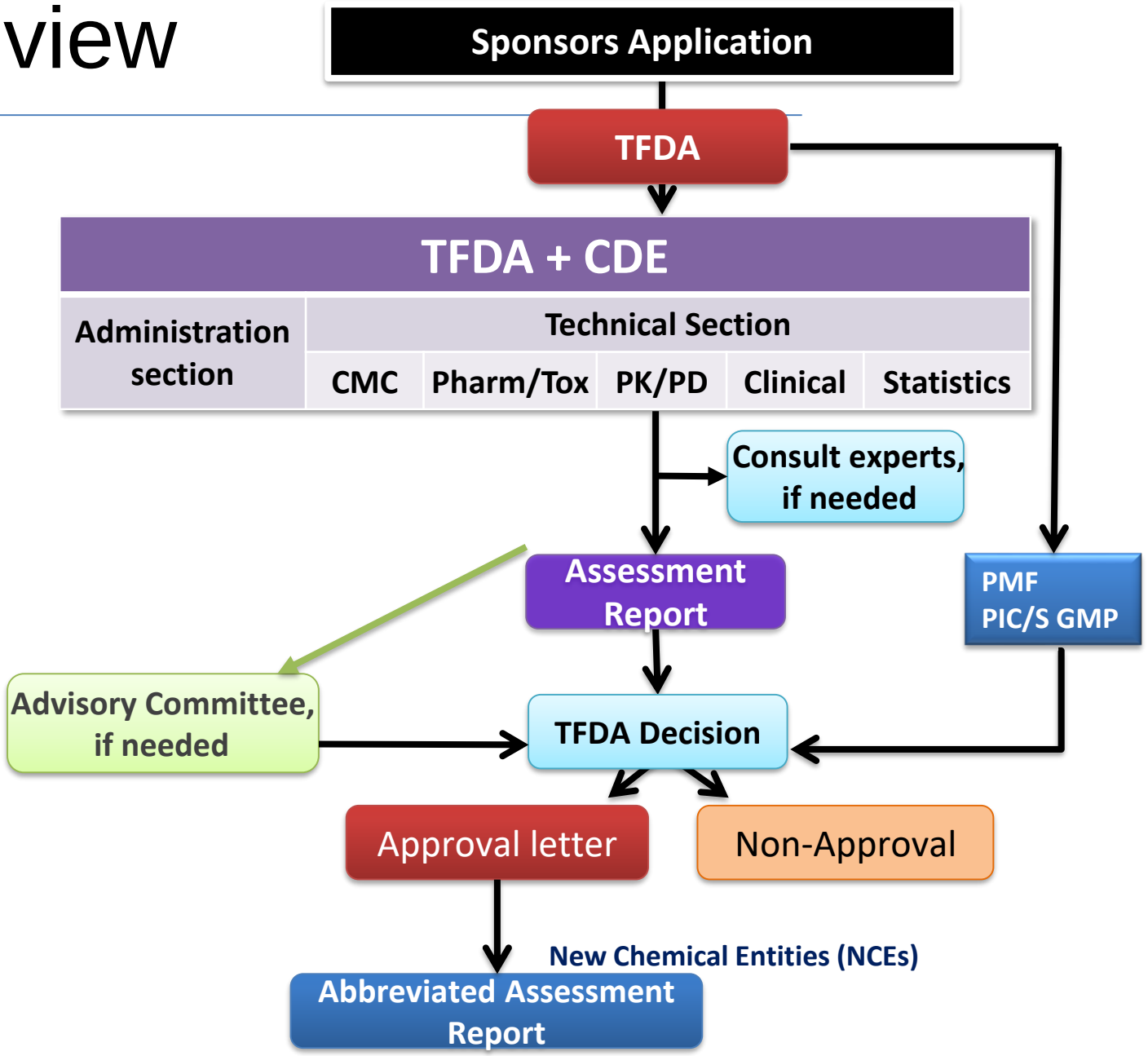
TFDA/CDE in Taiwan



Arrows in blue are for IND and NDA application. Arrows in green are consultation.

CDE was established at 1998 by DOH to assist TFDA to evaluate pharmaceuticals for marketing authorization.

NDA Review


Sponsors Application
TFDA
TFDA + CDE
Administration section
Technical Section
CMC
Pharm/Tox
PK/PD
Clinical
Statistics
Consult experts, if needed
Assessment Report
PMF
PIC/S GMP
Advisory Committee, if needed
TFDA Decision
Approval letter
Non-Approval
New Chemical Entities (NCEs)
Abbreviated Assessment Report

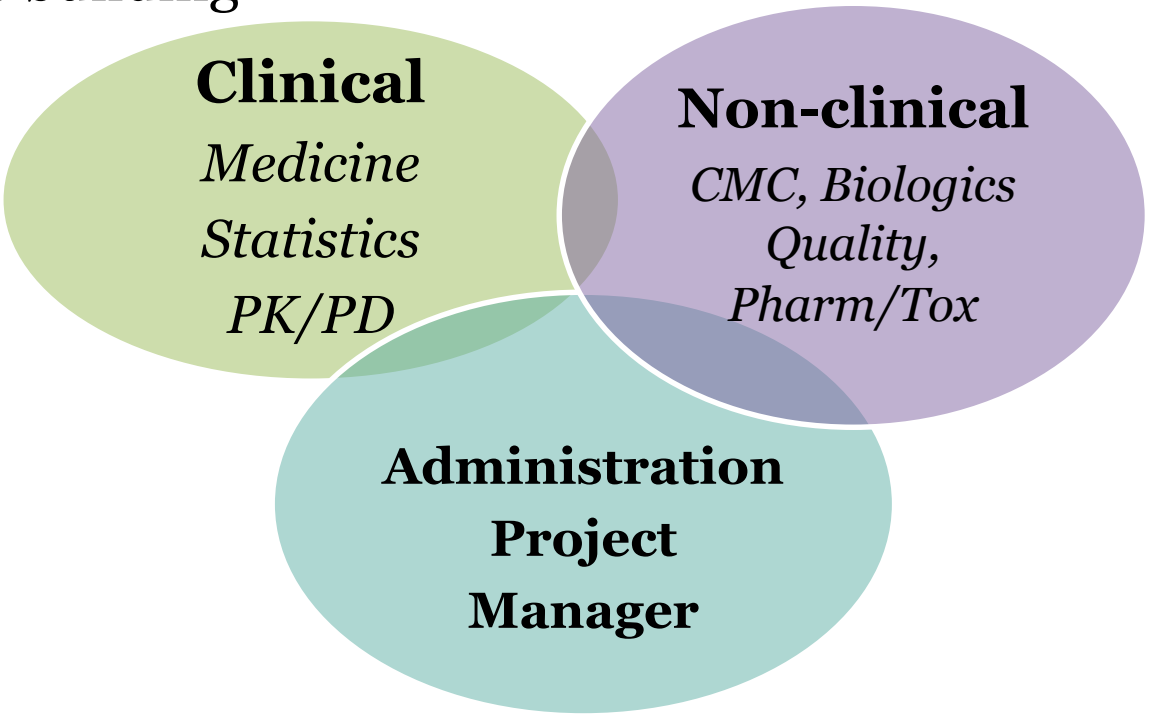
Comprehensive and Multidisciplinary – NDA Review

Team Approach

- Multidisciplinary
- Communication
- Consensus building

Decision Making

- Multidisciplinary
- Communication
- Consensus building

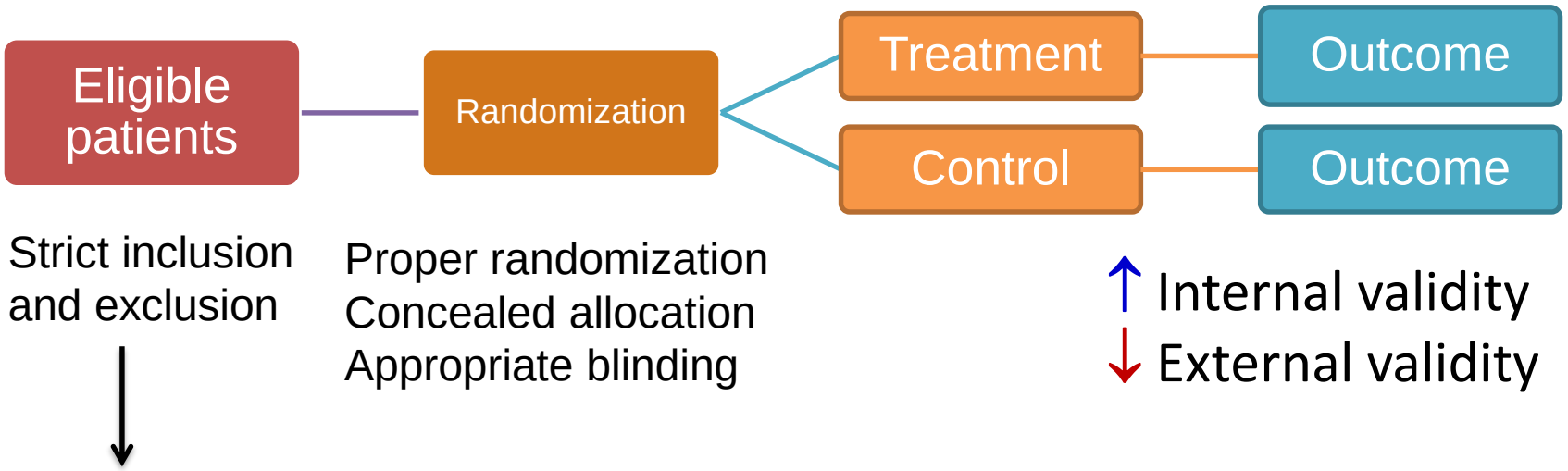


NDA Review Team in CDE

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**



Minimize the chance of bias from
patient selection, treatment assignment, patient evaluation and data analysis

The Drawbacks of RCT

- Time consuming, burdensome, expensive
- Questionable generalization

Increasing use of real-world evidence to support decision making

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

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

US FDA guidance, 2017

What is or is not real world data

- Real world evidence can be generated from any study design as long as the data source is from routine care and the design is highly pragmatic.
- RCT is not RWD ?
- Observational study such as The Framingham Heart Study is RWD?
- Blood pressure level can be considered RWD or not RWD

Salford Lung Study
- Pragmatic trial

NEJM 2016 Vol. 375 No. 13

A pragmatic trial in ordinary patients in everyday care
– Effectiveness of Fluticasone Furoate-Vilanterol for COPD in Clinical Practice

- To evaluate the effectiveness and safety of the once daily inhaled combination of fluticasone furoate (100 µg) and vilanterol (25µg) (fluticasone furoate–vilanterol) as compared with existing maintenance therapy (usual care)

Prospective, multicenter, randomized (1:1), controlled, open-label

- Randomization performed by means of a centralized randomization service, with stratification according to baseline maintenance therapy and presence or absence of a COPD exacerbation in the previous 12 months
- The study enrolled patients in primary care, aged 40+ years, had received a documented diagnosis of COPD from a general practitioner, taking inhaled ICS and/or LABA and/or LAMA, exacerbations in the last 3 years, consented

Primary endpoint: the mean annual rate of moderate or severe exacerbations

- Established electronic health record
- Most patients had contact with trial staff at recruitment, at the baseline visit, and at 12 months

TASTE trial
- Pragmatic trial

NEJM 2013 Vol. 369 No. 17

A pragmatic trial nested in an existing registry

- To evaluate the effects of thrombus aspiration in patients with STEMI undergoing a primary PCI

Prospective, multicenter, randomized (1:1), controlled, open-label

- Enrolled trial participants (N=7244) from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR)
- To thrombus aspiration followed by PCI or to PCI only

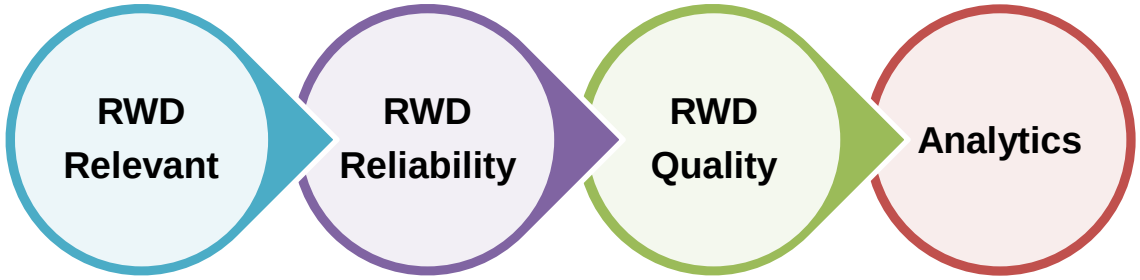
Primary endpoint: All-cause mortality at 30 days

- Data on mortality obtained from the national population registry
- Secondary endpoints obtained from the SWEDEHEART registry and the national discharge registry

Drug development uses of RWD/RWE

- Natural history information
- Trial and endpoint planning
  - Site selection, endpoint ascertainment
- Use of external control- historical or concurrent

Ability of RWD to generate RWE depends on



Sufficient? Sufficient? Assured? Adequate?

Minimize source of bias?

Translate RWD into RWE

Define a meaningful question

Choose an appropriate design and/or RWD source

Protocol and analysis plan

Conduct study
Analyze RWD

Complete study report
RWE

Taiwan experience with RWD/RWE

- Pre-Market efficacy assessment
  - Provide critical efficacy evidence (e.g. rare disease)
  - As a historical control for single arm study
- Pre-Market safety assessment
  - PSURs/PBRERs from other countries could be one of the sources of pre-marketing safety evaluation in Taiwan
- Post-market safety surveillance
- Change of approved product label
  - Update label information of drug-drug interaction and safety

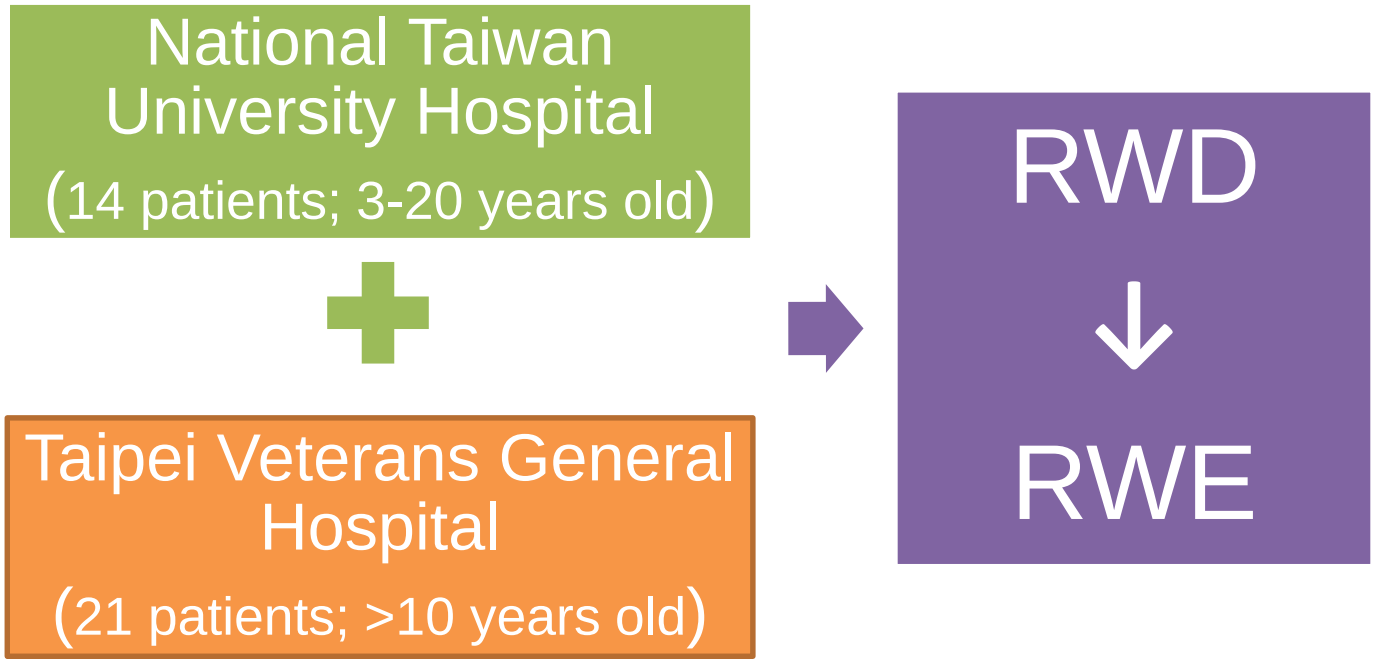
Case study 1 – Rare disease

- In Taiwan, the approval of tetrahydrobiopterin for 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 Phe level)
  - Well-collected patient clinical data (real world data)

Case study 1 – Rare disease

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



Case study 2 –Historical Control

- Indication of Folotyn: relapsed or refractory peripheral T-cell lymphoma(PTCL). Clinical benefit such as PFS or OS has not been demonstrated
- Pivotal study: single arm study, historical comparison with RWD from 4 hospitals

Prospect of use of RWD/RWE

- New indication
- Rare disease
- Confirmatory trial for regular approval after accelerated approval

敬請指教

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