Clinical Development 🆓 Us:
Regulatory Science and Strategic perspectives

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Cambridge, MA, USA

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Webinar
KAPAL

Heaviness of being success,
Lightness of being a beginner
DISCLAIMER

The opinions and information in this presentation are mine, and do not represent the views and/or policies of the LG Chem Life Sciences Innovation Center.

Overview

• Regulatory Science and Strategy
• Clinical Development
  • Case study
• Concluding thoughts
Regulatory Science

- **Regulatory Science** is the development and use of the scientific knowledge, tools, standards, and approaches necessary to assess the safety, efficacy, quality, potency, and performance of medical products and foods. - [www.fda.gov](http://www.fda.gov)

- 규제과학 (規制科學)?
  - Drug Evaluation and Research (심사, 평가, 연구)
  - Biologics Evaluation and Research (심사, 평가, 연구)
  - Reviews are considered as publication
    - [https://www.accessdata.fda.gov/scripts/cder/daf/](https://www.accessdata.fda.gov/scripts/cder/daf/)

Modified from Beth Duvall-Miller, CDER Forum for International Regulatory Authorities, 2011

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All things considered

- [Diagram showing the regulatory process](details of the diagram are not transcribed here, but it illustrates the multiple stages and interactions in the regulatory process]

- Product Quality (drug substance, drug product, manufacturing)
- Non-clinical
  - iPSP (initial Pediatric Study Plan)
- Device (combination product: drug + device [e.g., auto-injector, pre-filled syringes])

Modified from Beth Duvall-Miller, CDER Forum for International Regulatory Authorities, 2011
Regulatory scientists in industry

- Regulatory Affairs
- Regulatory Strategy
- Regulatory Intelligence

What we can learn from Review and Approval data
Review and Approval

https://www.fda.gov/media/105012/download

Review and Approval

https://www.phrma.org/Advocacy/Research-Development/Clinical-Trials
**Review and Approval**

**Annual approval of NME BLA or NDA**

<table>
<thead>
<tr>
<th>Year</th>
<th>NME BLA</th>
<th>NDA</th>
<th>Filing</th>
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<td>33</td>
<td>24</td>
<td>5</td>
</tr>
<tr>
<td>2006</td>
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<td>1</td>
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<td>2018</td>
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<td>2019</td>
<td>64</td>
<td>65</td>
<td>4</td>
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53: 2020
33: 11/1/2021

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**Review and Approval**

**Annual approval of Biosimilar**

<table>
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<th>Year</th>
<th>Approval</th>
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<tbody>
<tr>
<td>2015</td>
<td>1</td>
</tr>
<tr>
<td>2016</td>
<td>3</td>
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<tr>
<td>2017</td>
<td>5</td>
</tr>
<tr>
<td>2018</td>
<td>7</td>
</tr>
<tr>
<td>2019</td>
<td>10</td>
</tr>
<tr>
<td>2020</td>
<td>3</td>
</tr>
</tbody>
</table>
**Review and Approval**

**Expedited programs: 68% in 2020**

<table>
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<th></th>
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<tbody>
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<td>Exp</td>
<td>Orph</td>
<td>BT</td>
<td>1st</td>
<td>Exp</td>
<td>Orph</td>
</tr>
<tr>
<td>72%</td>
<td>64%</td>
<td>60%</td>
<td>31%</td>
<td>32%</td>
<td>37%</td>
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<tr>
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<td>47%</td>
<td>45%</td>
<td>30%</td>
<td>41%</td>
<td>40%</td>
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<tr>
<td>42%</td>
<td>52%</td>
<td>51%</td>
<td>38%</td>
<td>47%</td>
<td>45%</td>
</tr>
<tr>
<td>32%</td>
<td>48%</td>
<td>48%</td>
<td>27%</td>
<td>37%</td>
<td>39%</td>
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<tr>
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<td>62%</td>
<td>42%</td>
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<td>40%</td>
<td>39%</td>
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<tr>
<td>13%</td>
<td>25%</td>
<td>27%</td>
<td>13%</td>
<td>21%</td>
<td>22%</td>
</tr>
</tbody>
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**Expedited Regulatory Pathways**

<table>
<thead>
<tr>
<th>Qualifying criteria</th>
<th>Fast Track</th>
<th>Breakthrough Therapy</th>
<th>Accelerated Approval</th>
<th>Priority Review</th>
</tr>
</thead>
<tbody>
<tr>
<td>A drug that is intended to treat a serious condition AND nonclinical or clinical data demonstrate the potential to address unmet medical need OR A drug that has been designated as a qualified infectious disease product.</td>
<td>A drug that is intended to treat a serious condition AND preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies.</td>
<td>A drug that treats a serious condition AND generally provides a meaningful advantage over available therapies AND demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality (IMM) that is reasonably likely to predict an effect on IMM or other clinical benefit (i.e., an intermediate clinical endpoint).</td>
<td>An application (original or efficacy supplement) for a drug that treats a serious condition AND, if approved, would provide a significant improvement in safety or effectiveness OR Any supplement that proposes a labeling change pursuant to a report on a pediatric study under 505A OR An application for a drug that has been designated as a qualified infectious disease product OR Any application or supplement for a drug submitted with a priority review voucher.</td>
<td></td>
</tr>
</tbody>
</table>
Expedited Regulatory Pathways

<table>
<thead>
<tr>
<th>Fast Track</th>
<th>Breakthrough Therapy</th>
<th>Accelerated Approval</th>
<th>Priority Review</th>
</tr>
</thead>
<tbody>
<tr>
<td>When to submit request</td>
<td>With IND or after ideally, no later than the pre-BLA or pre-NDA meeting</td>
<td>With IND or after ideally, no later than the end of phase 2 meeting</td>
<td>The sponsor should continually discuss the possibility of accelerated approval with the review division during development, supporting, for example, the use of the planned endpoint as a basis for approval and discussing the confirmatory trials, which should usually be already.</td>
</tr>
</tbody>
</table>

Expedited Regulatory Pathways

<table>
<thead>
<tr>
<th>FDA DESIGNATION</th>
<th>KEY ELEMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fast Track</td>
<td>ROLLING REVIEW Enables applicants to submit NDA/BLA sections piecemeal</td>
</tr>
<tr>
<td>Breakthrough Therapy</td>
<td>EARLY/INCREASED HA INTERACTION Earlier HA feedback can streamline development</td>
</tr>
<tr>
<td>Accelerated Approval</td>
<td>FREQUENT HA MEETINGS Checking in frequently with HA ensures that the program continues to meet regulatory expectations</td>
</tr>
<tr>
<td>Priority Review</td>
<td>PRELIMINARY APPROVAL Enables early approval while confirmatory studies are planned/ongoing</td>
</tr>
<tr>
<td>Drugs treating serious conditions, and provide an advantage over available therapies based on a surrogate endpoint</td>
<td>SHORTER APPLICATION REVIEW TIME 4 months reduction (FDA) 60 days reduction (EMEA)</td>
</tr>
<tr>
<td>Drugs that provide a significant improvement in safety or efficacy for a serious condition</td>
<td>APPROVAL BASED ON LIMITED DATA Approval for diseases where it is not possible or unethical to collect the data required to support standard approval</td>
</tr>
</tbody>
</table>
Review and Approval: after approval

~5600 in 2019

Number of actions vs Month

Total Efficacy REMS

Review and Approval: IND

~7300 in 2019

Drug IND Biologics IND

Modified from CDER New Drugs Program: 2019 Update
**Review and Approval: spectrum of BLA, NDA or ANDA**

2013

- New Molecular Entity: 45%
- New Active Ingredient: 7%
- New Formulation/Manufacturer: 19%
- New Combination: 8%
- New Dosage Form: 5%
- Other: 4%

2019

- New Molecular Entity: 27%
- New Active Ingredient: 2%
- New Formulation/Manufacturer: 18%
- New Combination: 6%
- New Dosage Form: 6%
- Multiple categories: 2%
- Others: 8%
- Biosimilar: 15%
- marketed w/o approval: 5%
- new indication: 1%

**1,014** Approved or tentatively approved Abbreviated New Drug Applications (ANDAs)


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**Review and Approval: Interaction with sponsors**

Frequency of regulatory meetings is increasing

[Graph showing trend with data points]
Potential impact of interaction with the Agency on clinical development duration

<table>
<thead>
<tr>
<th>Clinical Development (years)</th>
<th>Interaction with the Agency?</th>
</tr>
</thead>
<tbody>
<tr>
<td>PreIND</td>
<td>Yes</td>
</tr>
<tr>
<td>Rare Disease</td>
<td>Yes</td>
</tr>
<tr>
<td>Common Disease</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Best-selling pharmaceuticals in 2020

Herceptin (trastuzumab): 26th in 2020, 5 biosimilars in markets

Modified from Drug Discovery & Development, 5/14/2021
Happening in CDER/FDA and its potential impact in new drug development

‘new drugs regulatory program modernization’

- Integrated Review for Marketing Applications
  - Developing a streamlined interdisciplinary review process and template to support the new integrated review for assessing NDA/BLAs

- IND Review Management
  - Streamlining the IND scientific review processes for managing IND applications, beginning with 30-Day Safety Reviews and Protocols

- Post-Market Safety Management
  - Creating a standardized, consistent, and effective approach to post-market drug safety

- Assessing Talent
  - Developing an effective and consistent process for hiring, onboarding, developing and evaluating new Clinical and Pharm/Tox reviewers

- Reorganization and Transition Management
  - Planning, coordinating, and implementing modernization and organization changes at the future Office and Division levels across the New Drugs Program

- Administrative Operations
  - Optimize administrative and clerical staff roles, structure, and functions to enhance customer focus and employee engagement

Modified from CDER New Drugs Program: 2019 Update
before

after under new drugs regulatory program modernization
latest definition of biological product

‘On March 23, 2020, the BPCI Act requires that an approved marketing application for a “biological product” under section 505 of the FD&C Act shall be deemed to be a license for the biological product (i.e., an approved BLA) under section 351 of the PHS Act.’

The Food and Drug Administration (FDA or the Agency) is proposing to amend its regulation that defines “biological product” to incorporate changes made by the Biologics Price Competition and Innovation Act of 2009 (BPCI Act), and to provide its interpretation of the statutory terms “protein” and “chemically synthesized polypeptide.” Under that interpretation, the term protein would mean any alpha amino acid polymer with a specific, defined sequence that is greater than 40 amino acids in size.


Review and Approval: How to do
**Review: takes a village of disciplines**

Clinical

Labeling

Statistics

Non-Clinical (Pharmacology/Toxicology)

Chemistry

Consults: PRO, OC, QT, DRISK, DMEPA, OPDP, PnRC, PREA, CDRH

**All things considered**

IND Submission

NDA/BLA Submission

Amendment

Post approval

Supplements, Pmc, PMR, AE reports, etc...

ANDA

Phase 1

Phase 2

Phase 3

IND Review

Clinical Hold

NDA/BLA Review

Action Letter

AE Meeting

Labeling

MCR

things are going on in parallel; meetings

Pre-IND

EOP1

EOP2

Pre NDA/BLA

things are going on in parallel; representative necessary processes

Product Quality (drug substance, drug product, manufacturing)

Non-clinical

iPSP (initial Pediatric Study Plan)

Device (combination product: drug + device e.g., auto-injector, pre-filled syringe)

Modified from Beth Duvall-Miller, CDER Forum for International Regulatory Authorities, 2011
**Things on the regulator’s mind**

- Adverse Event Incidence
- Availability of Other Therapies
- Communication
- Trial Design and Conduct
- Risk of Products In Same Class
- Clinical Relevance of Endpoint
- Expected Patient Compliance
- Treatment Effect
- Nature of Disease
- Trial Drop-outs
- Serious Adverse Event Incidence
- Off-Label Potential
- Risk in Chronic Use
- Restricted Distribution
- Target Population
- Risk Management
- Study Population
- Statistical Significance
- Relative Efficacy
- Efficacy in Subgroups
- Medication Guides
- Education
- Labeling
- Patient Preference

*Uncertainty*

**Things on the Regulator’s mind: case-by-case**

**Things to consider depending on situations: example for a pediatric dose selection**

A scenario with more Data/Knowledge:
- Takes more time
- Requires early planning
- Difficult to obtain in certain age groups
- Ultimately could support more streamlined approaches

A scenario with less Data/Knowledge:
- Takes less time
- Often includes numerous assumptions
- False assumptions will lead to incorrect conclusions
- *More difficult to obtain regulatory acceptance*

Lynne Yao, Pediatric Dose Selection, OCP/MCERSI Workshop, 2020
Clinical Development; Case study

Clinical development

- Costs an average of $2.6 billion
- <12% will be approved
- At least 10 years on average

Balance between serial and parallel paradigm

https://www.phrma.org/Advocacy/Research-Development/Clinical-Trials
Case Study 1: Drug X

Alignment of the Food-Effect Study with clinical development (n=31)

<table>
<thead>
<tr>
<th>As part of Pivotal</th>
<th>During Pivotal</th>
<th>Pre-pivotal</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>2</td>
<td>15</td>
</tr>
</tbody>
</table>

Number of Drugs

Modified from Safaa Burns through Elimika Pfuma, AAPS Workshop, Baltimore, 2015

Gantt Chart for clinical trials conducted for Drug X

- **Maximized benefits using simple designs of FIH study**
  - Understood clinically relevant dose
  - Sufficient PD
  - Successful food effect results; support timing of biopharmaceutical development
  - Understood sufficient human PK ADME
  - Support timing of human mass balance study

- **Focused P2 study designs**
  - Dose-ranging using well recognized surrogate endpoints

- **Taking risk for P3 study designs based on sciences**
  - FDA recommended Dose X for P3 considering public safety
  - The sponsor evaluated Dose Y against FDA’s recommendation considering effectiveness of test compound with paradigm shift (titration to one dose fit everybody)
Case Study 2: lonafarnib for progeria [Hutchinson-Gilford syndrome (disorder)]

- Progeria
  - premature aging disease
  - accumulation of defective progerin (farnesylated prelamin A) or progerin-like proteins
  - die before the age of 15 years due to accelerated cardiovascular disease (e.g., heart failure, myocardial infarction, or stroke)
  - ultra rare: < 1 in 25 million
- Highly motivated family/subject matter experts lead new drug approval
- Summary of regulatory actions

Case Study 2: lonafarnib for progeria [Hutchinson-Gilford syndrome (disorder)]

- Highly motivated family/subject matter experts lead new drug approval
  - Over 20 years family journey with science; Sam Berns, Dr. Leslie Gordon (mom), Dr. Scott Berns (dad) and Audrey Gordon (aunt)
  - vs. a story of John Crowley with business success; MYOZYME for Pompe’s disease (movie ‘Extraordinary Measures’)

Reference; Integrated Review (244 pages), Summary of Regulatory Action; Drugs@FDA
Case Study 2: lonafarnib for progeria [Hutchinson-Gilford syndrome (disorder)]

- **Winning regulatory strategies**
  - Effectiveness
    - using pooled data from two adequate and well-controlled trials
    - showed a survival advantage compared to matched untreated controls
    - together with confirmatory evidence from mechanistic studies
  - Safe
    - lack of a control arm limits
    - drug interaction (DDI)
    - risk can be adequately mitigated through labeling and further evaluated during routine pharmacovigilance
      - Post-marketing requirement
        - carcinogenicity
        - thorough QT study
        - DDI
    - Benefit/Risk Framework, mortality (hard endpoint) benefit outweighs the risks

Concluding Remarks

- **Regulatory science is one of crucial disciplines in drug development, in my opinion**
- **Drugs@FDA is one of the best information source for the regulatory strategies**
Concluding Remarks

“It is not the strongest species that survive, nor the most intelligent, but the ones most responsive to change”

Origin of Species
Charles Darwin
(1809-1882)
Question?

- smchung@lgchem.com
- Text to +1-857-600-9899

Back up