Clinical Development Я 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

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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.

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Overview

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

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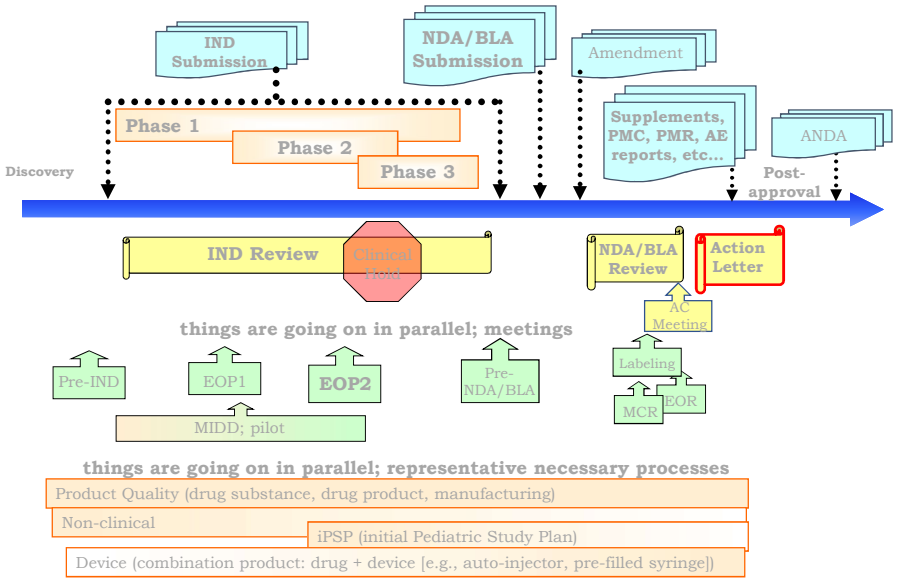
Regulatory Science

- 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
- 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/)

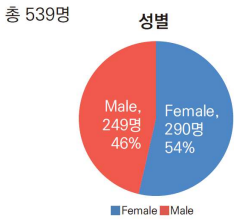
All things considered

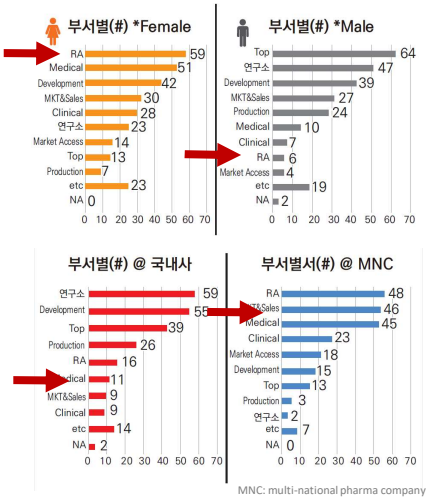


Modified from Beth Duvall-Miller, CDER Forum for International Regulatory Authorities, 2011

Regulatory scientists in industry

- **Regulatory Affairs**
- **Regulatory Strategy**
- **Regulatory Intelligence**

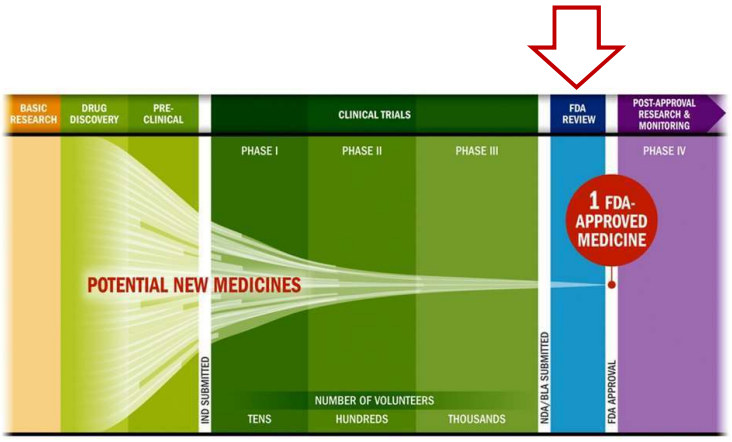




MNC: multi-national pharma company

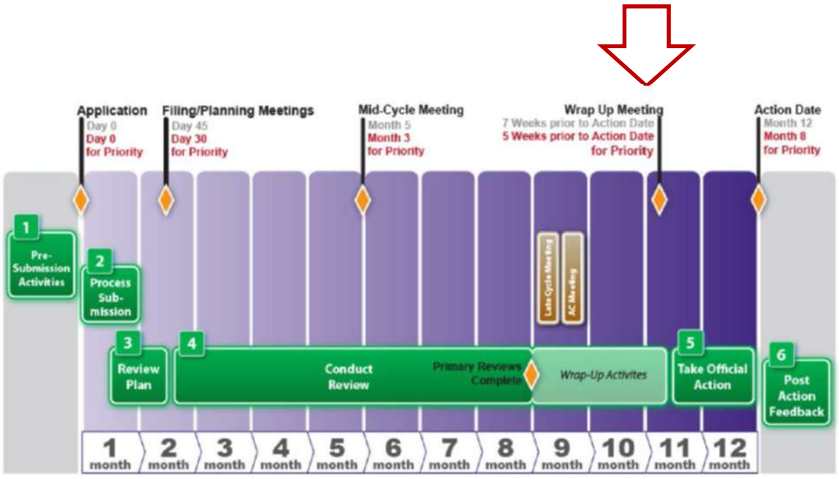
What we can learn from Review and Approval data

Review and Approval



https://www.phrma.org/Advocacy/Research-Development/Clinical-Trials

Review and Approval



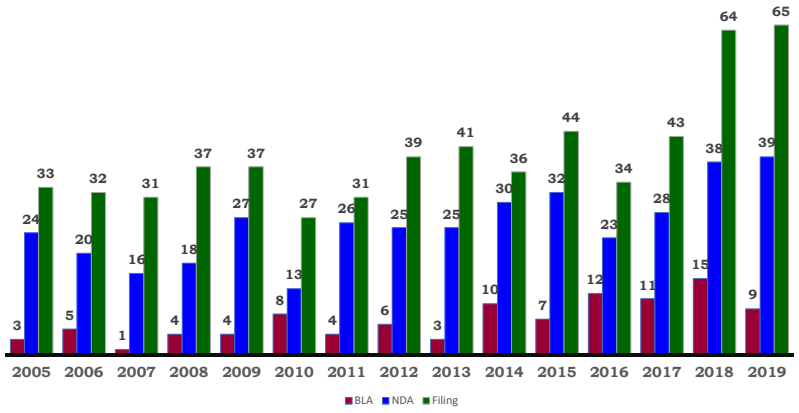
https://www.fda.gov/media/105012/download

https://www.phrma.org/Advocacy/Research-Development/Clinical-Trials

Review and Approval

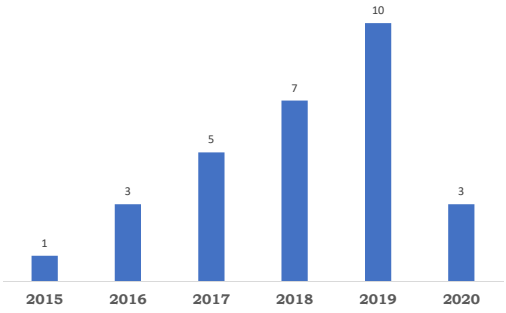
Annual approval of NME BLA or NDA

53: 2020
33: *11/1*/2021

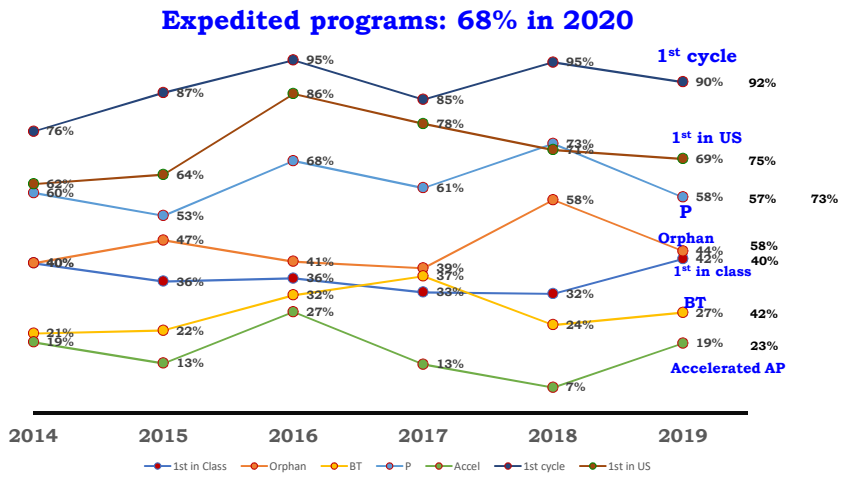


Review and Approval

Annual approval of Biosimilar



Review and Approval



https://www.fda.gov/drugs/development-approval-process-drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products

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Expedited Regulatory Pathways

	Fast Track	**Breakthrough Therapy**	**Accelerated Approval**	**Priority Review**
Qualifying criteria	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	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	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)	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

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Expedited Regulatory Pathways

	Fast Track	**Breakthrough Therapy**	**Accelerated Approval**	**Priority Review**
When to submit request	With IND or after Ideally, no later than the pre-BLA or pre- NDA meeting	With IND or after Ideally, no later than the end-of-phase 2 meeting	The sponsor should ordinarily 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	With original BLA, NDA, or efficacy supplement

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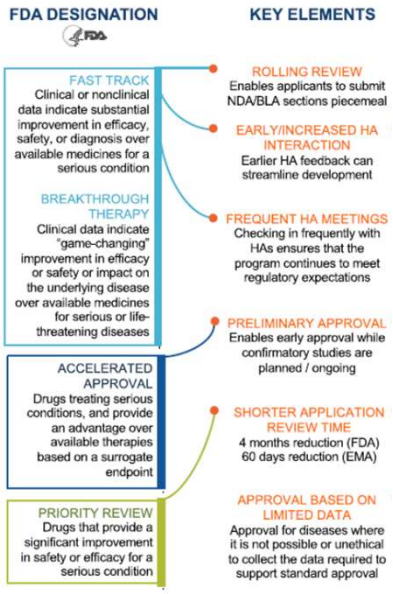
Expedited Regulatory Pathways



Clin Transl Sci (2020) 13, 451–461

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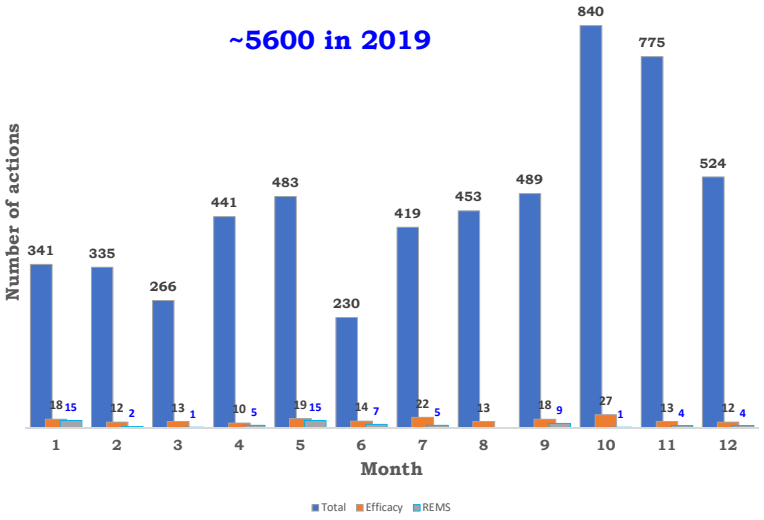
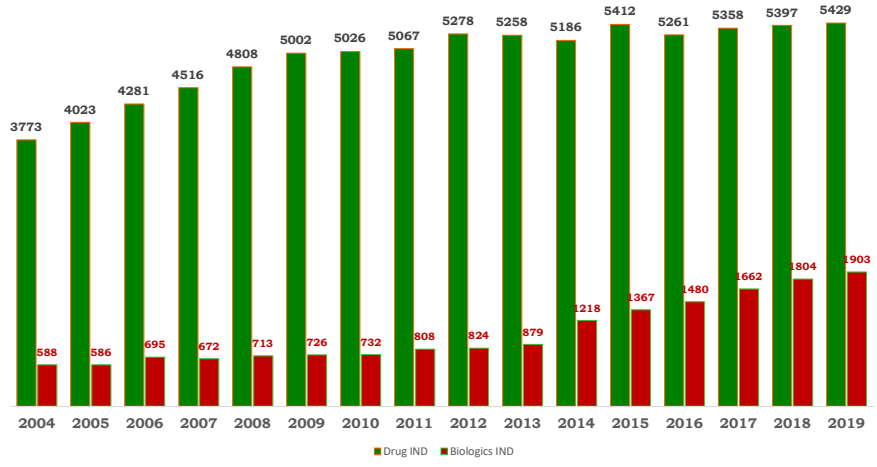
Review and Approval: after approval

~5600 in 2019

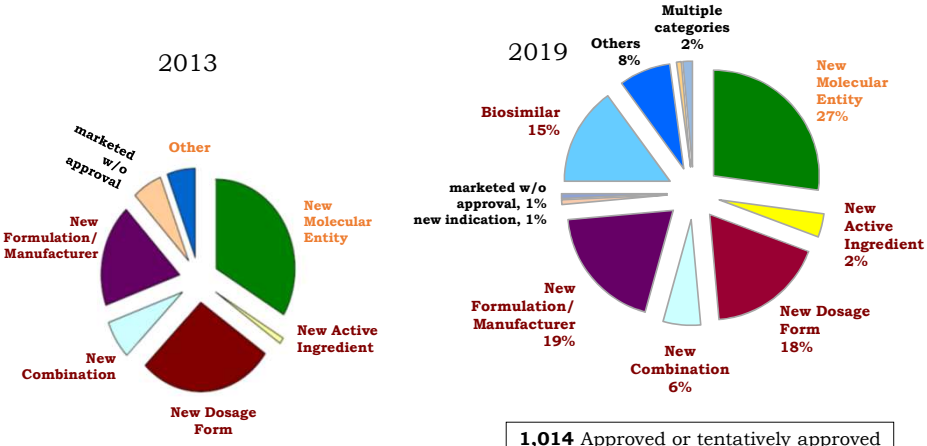


Review and Approval: IND

~7300 in 2019



Review and Approval: spectrum of BLA, NDA or ANDA



Drugs@FDA

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

https://www.fda.gov/drugs/generic-drugs/2019-office-generic-drugs-annual-report

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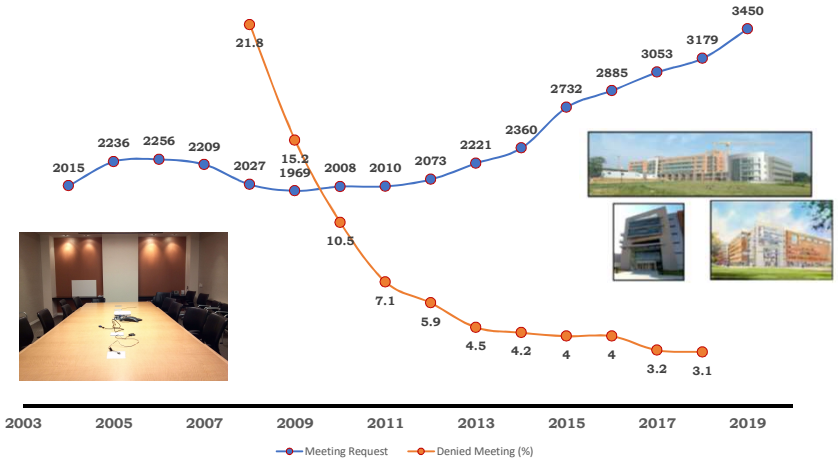
Review and Approval: Interaction with sponsors

Frequency of regulatory meetings is increasing



Modified from CDER New Drugs Program: 2019 Update

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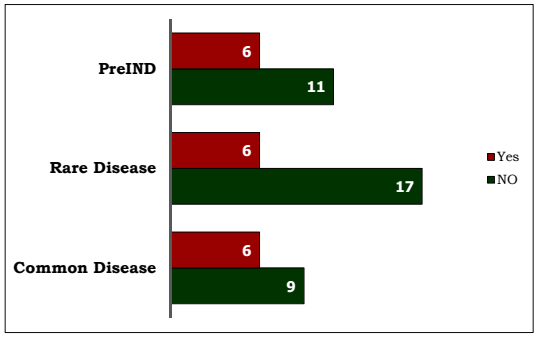
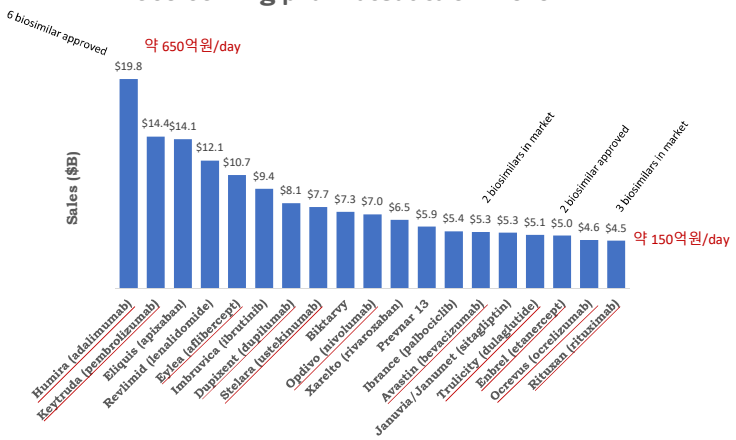
Potential impact of interaction with the Agency on clinical development duration



Clinical Development (years)

Best-selling pharmaceuticals in 2020



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

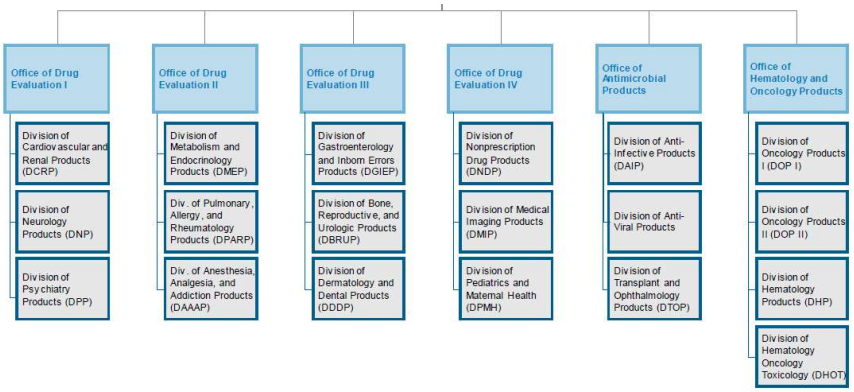
Happening in CDER/FDA and its potential impact in new drug development

'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



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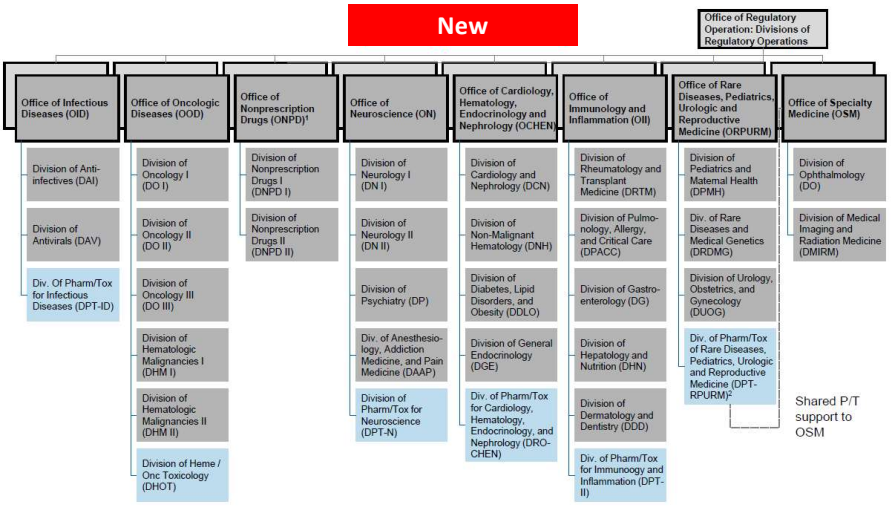
after **under new drugs regulatory program modernization**



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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**.'

https://www.fda.gov/about-fda/economic-impact-analyses-fda-regulations/definition-term-biological-product-proposed-rule-preliminary-regulatory-impact-analysis

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Review and Approval: How to do

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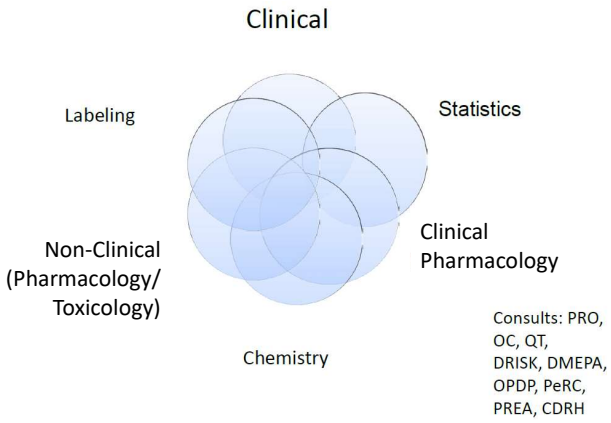
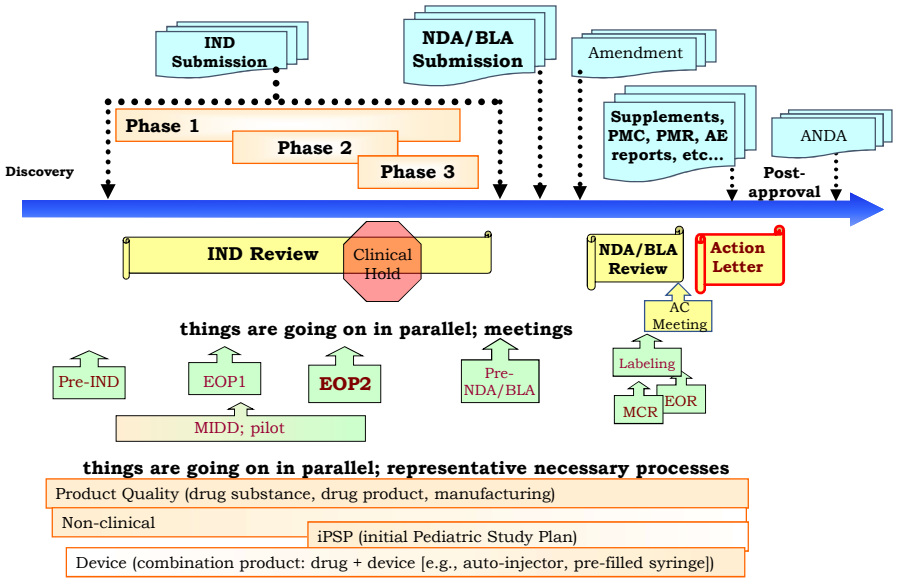
Review: takes a village of disciplines



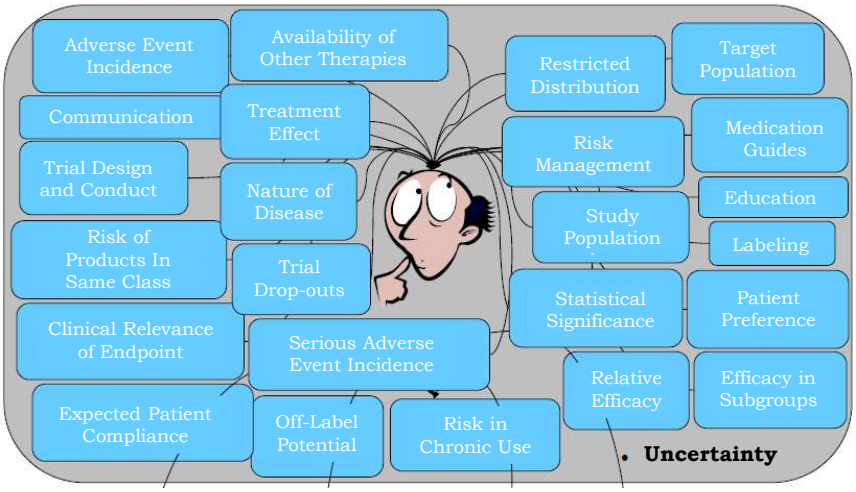
Modification from https://www.fda.gov/media/105012/download 29

All things considered



Modified from Beth Duvall-Miller, CDER Forum for International Regulatory Authorities, 2011 30

Things on the regulator's mind



John Jenkins, 2012 An FDA/Investor Meeting 31

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

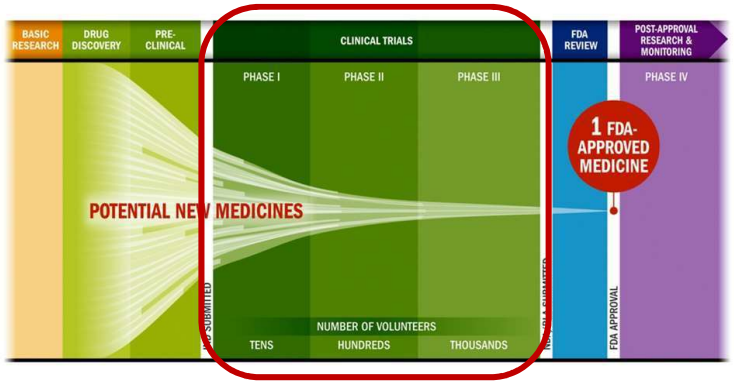
- Takes less time
- Often includes numerous assumptions
- False assumptions will lead to incorrect conclusions
- *More difficult to obtain regulatory acceptance*

Lynne Yao, Pediatric Dose Selection, OCP/MCERSI Workshop, 2020 32

Clinical Development; Case study

Clinical development

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

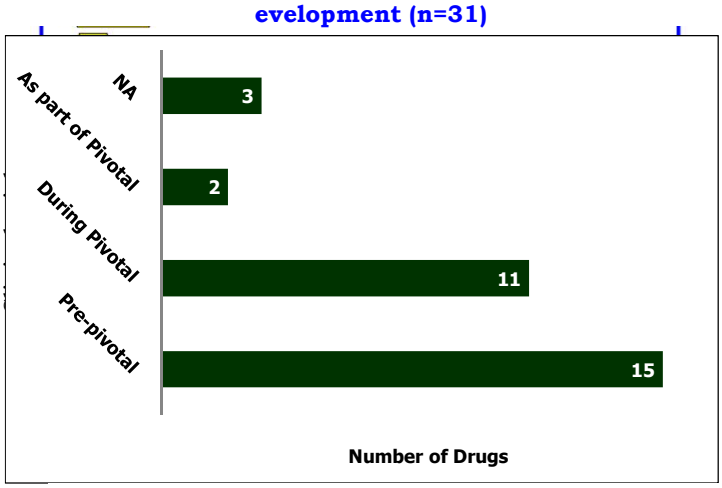


Balance between serial and parallel paradigm

https://www.phrma.org/Advocacy/Research-Development/Clinical-Trials 34

Case Study 1: Drug X

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



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

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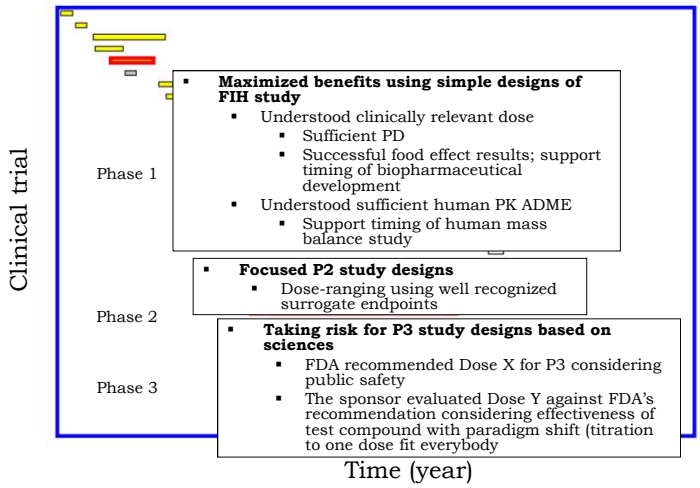
Case Study 1: Drug X

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

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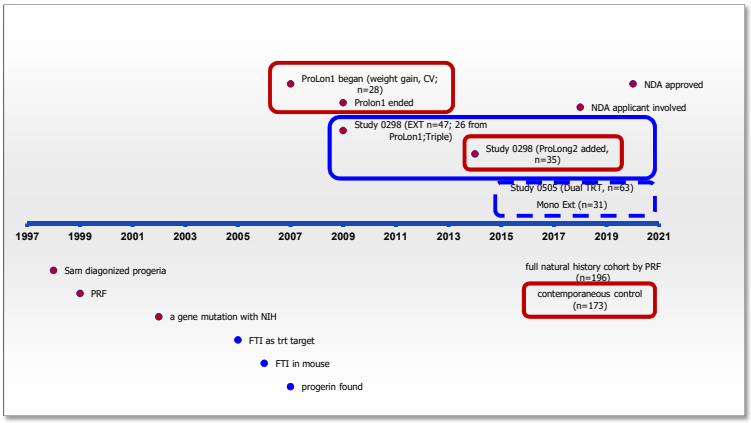
Case Study 2: lonafarnib for progeria [Hutchinson-Gilford syndrome (disorder)]

- **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

Reference; Integrated Review (244 pages), Summary of Regulatory Action; Drugs@FDA 39

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**

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Concluding Remarks

4/4/2003

2007

2013

2015

Linezolid 2019

2016 2018

2017

Eticovo
Hadlima 2019
Ontruzant

2019

Name	First-in-Class	Orphan	Fast Track	Breakthrough	Priority	Accelerated Approval	Met PDUFA Goal	First Cycle Approval	First in the United States
Accrufer									
Adakveo									
Aklief									
Balversa									
Beovu									
Brukinsa									
Cablivi									
Caplyta									
Dayvigo									
Egaten									
Enhertu									
Evenity									
ExEm Foam									
Fetroja									
fluorodopa F 18									
Ga 68 DOTATOC									
Givlaari									
Ibsrela									
Inrebic									
Jeuveau									
Mayzent									
Nourianz									
Nubeqa									
Oxbryta									
Padcev									
Pigray									
Polivy									
pretomanid									
Reblozyl									
Recarbrio									
Reyvow									
Rinvoq									
Rozlytrek									
Scenesse									
Skyrizi									
Sunosi									
TissueBlue									
Trikafta									
Turalio									
Ubrelvy									
Vyleesi									
Vyndaqel									
Vyondys 53									
Wakix									
Xcopri									
Xenleta									
Xpovio									
Zulresso									

Comp'd by SK Biopharm

SK Life

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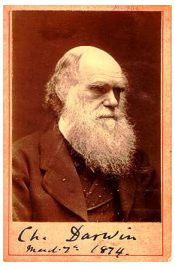
https://www.fda.gov/media/134493/download

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)

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Question?

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Back up