GOV01 FDA 在生物工程产品开发中的角色

Introduction

介绍：

大家常说的抗体、CAR-T、干细胞、溶瘤病毒等，均属于生物工程产品。在这类新药开发过程中，在进行临床试验前，以及后续的药物上市前，均需要 Food and Drug Administration (FDA)批准才能进行。随着生物工程产品的出现，FDA 的参与发挥着越来越重要的作用，从监管者变为了“参与者”。每一个生物技术公司都要学会并且学好与 FDA 的处世之道。本次主题着重介绍 FDA 与药物开发过程有关的知识，包括 FDA 组织的结构是什么样的？FDA 参考什么来做事情？FDA 如何处理药物申请事务？FDA 有哪些优惠及支助政策可以利用？作为审批过大量药物的 FDA，哪些信息资源是可以公开获取的？

声明：

作者 Johnson Han 从事生物制品开发工作，深深体会到国家监管在药物开发中的地位，然而 CFDA 可学习的信息太少，再者 CFDA 也是在学习美国 FDA，故而利用夜间及周末的时间，学习整理美国 FDA 相关资料，以便增加对国家监管的认知。由于学完后觉得受益匪浅，故将其系统性整理，分享给其他想对美国 FDA 有所了解的人。本人声明自己并未有在美国 FDA 工作经验，但主要参考资料均来源于 FDA 发布的资料。主要参考资料如下：

[1] M.C. Galli, M. Serabian, Regulatory Aspects of Gene Therapy and Cell Therapy Products,[Book] Springer International Publishing, 2015.
[2]FDA 官方网址. website：http://www.fda.gov/
[3] United States Code of Federal Regulations, Title 21.
[4] FDA Guidance for Industry.
[5] Wikipedia

备注：

FDA vs CFDA：本主题讲解的是*美国食品药品监督管理局*（*Food and Drug Administration, FDA*），当使用 FDA 这一缩略词时，专指*美国食品药品监督管理局*；中国对应的机构叫做*国家食品药品监督管理总局*（*China Food and Drug Administration，CFDA*）。当然，本主题讲解过程中未曾涉及 *CFDA*。只要翻译就有失真，文本的质量往往大打折扣，所以在不影响讲解的前提下，尽量使用英文资料，同时，建议各位加强对生物医学术语的学习，以便更好的学习理解一手材料（相关课程待公众号更新通知）。

表. 本次主题课程目录

lecture	lecture 名称	视频 ID	课时名称	课程发布时间
1	FDA 机构简介	FDA01L01	FDA 机构简介	2016/12/19
2	FDA 法律法规	FDA01L02		2016/12/20
3	FDA 在药物开发过程中的角色	FDA01L03		2016/12/21
4	FDA programs	FDA01L04		2016/12/22
5	从 FDA 可获得的信息	FDA01L05		2016/12/23

表注：本次主题为 Johnson Han 原创，发布于公众号，鼓励转载。本次主题共 4 章内容，总计？课时。每天发布一个课时视频，长度小于 15min，连续至本课程结束。

主题目录

1 FDA agency 简介

介绍：假设你去看病，起码你要知道去哪里挂号？去哪检查？去哪里拿药？当谈及 FDA，我们首先需要了解他的组织结构及相关人员，这将有助于我们之后对 FDA 行为事件的理解。

FDA 的组织结构。哪种药归哪个部门审核监督。

1.1 组织结构

FDA 的上下级部门关系如图所示。其中与生物工程产品开发相关的部门共有三个，分别为生物制剂评估与研究中心、药物评估与研究中心、器械与放射中心。

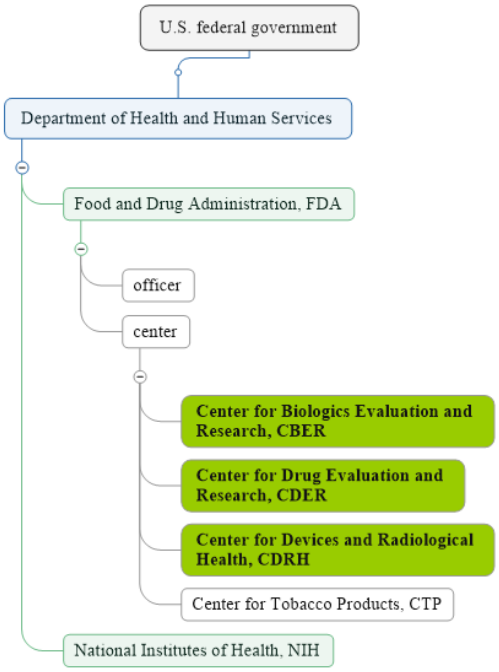


图. FDA 组织结构图

Program	Funding (in billions)
Management and Finance	
Departmental Management	$1.4
Public Health and Social Services Emergency Fund	$1.4
Operating Divisions	
Food and Drug Administration	$2.6
Health Resources and Services Administration	$10.4
Indian Health Service	$4.8
Centers for Disease Control and Prevention	$6.7
National Institutes of Health	$30.4
Substance Abuse and Mental Health Services Administration	$3.4
Agency for Healthcare Research and Quality	$0.4
Centers for Medicare and Medicaid Services	$906.8
Administration for Children and Families	$51.3
Administration for Community Living	$2.1
TOTAL	**1,020.3**

2015 Department of Health and Human Services Budget-in-Brief

1.2 部门职责

FDA 将产品归类为 drug（传统药物）、生物制品、人体细胞与组织相关产品、设备了三个核心部门负责不同类型的产品，

生物治疗相关核心部门及所管理药物

center name	管理药物
center for drug evaluation and research	drug，特殊：monoclonal antibodies
center for biologics evaluation and research	biologics；Human cell, tissue, and cellular and tissue-based product
center for devices and radiological health	Device
三个部门间合作	Combination Product (21 CFR3.2(e))

表注：从法律定义定义而言，单克隆抗体属于 biologics，但是归 CBER 管理。具体见 1.4

1.3 产品的定义

产品类别的定义

Biologic (42 USC262(i))	A virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except chemically synthesized polypeptide), or analogous product or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings
Drug (21 USC321(g)(1)	(A) Articles recognized in the offi cial US Pharmacopeia, offi cial Homeopathic Pharmacopeia of the United States, or offi cial National Formulary, or any supplement to any of them; (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any articles specifi ed in clause (A), (B), or **(C)**
Human cell, tissue, and cellular and tissue-based product (HCT/P)(21 CFR 1271.3(d)	Articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient. Examples of HCT/Ps include, but are not limited to, bone, ligament, skin, dura mater, heart valve, cornea, hematopoietic stem/progenitor cells derived from peripheral and cord blood, manipulated autologous chondrocytes, epithelial cells on a synthetic matrix, and semen or other reproductive tissue
Device (21 USC321(h))	An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is (1) recognized in the offi cial National Formulary, or the US Pharmacopeia, or any supplement to them; (2) intended for use in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of disease, in man or

	other animals; or (3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes
Combination Product (21 CFR3.2(e))	(1) A product composed of two or more regulated components, that is, drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity; (2) two or more separate products packaged together in a single package or as a unit and composed of drug and device products, device and biological products, or biological and drug products; (3) a drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specifi ed drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, for example, to refl ect a change in intended use, dosage form, strength, route of administration, or signifi cant change in dose; or (4) any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specifi ed investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect

表注：来源于法律资料的定义，详见下文对 USC，CFR 的讲解。

1.3.1 产品的关系

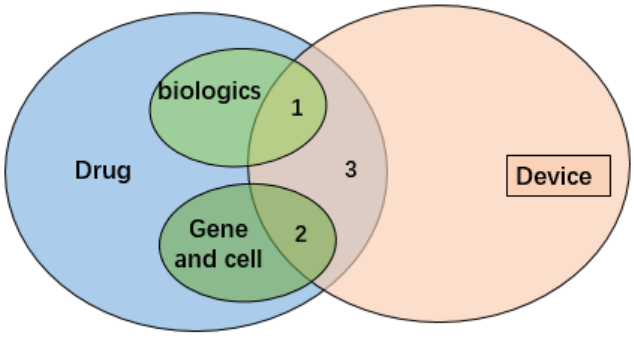
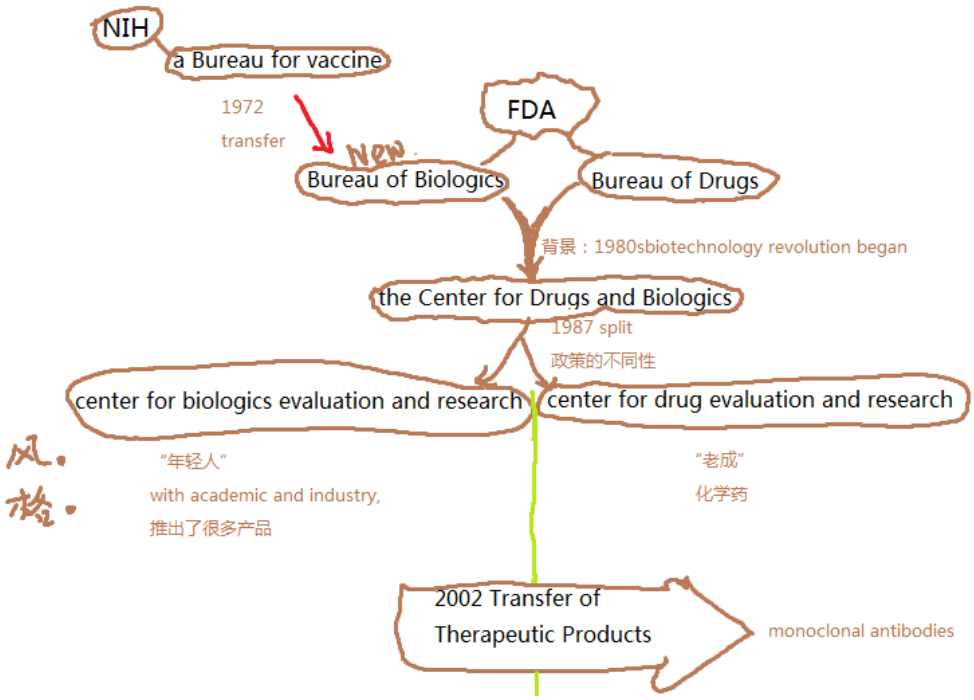


图.各种产品间的关系。

图注：1/2/3 是可能的 Combinaion Product 的情况

1.4 CBER 与 CDER 的前世今生

1.4.1 两部门的进化史。



注：参考 https://en.wikipedia.org/wiki/Center_for_Biologics_Evaluation_and_Research 绘制而成

1.4.2 关于部分生物制品归 CDER 管理说明

文件名称：《Transfer of Therapeutic Products to the Center for Drug Evaluation and Research (CDER)》

Website：

http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm133463.htm

2013 年 CBER 与 CDER 之间的产品调整

Categories of Therapeutic Biological Products Transferred to CDER

- Monoclonal antibodies for in vivo use.
- Proteins intended for therapeutic use, including cytokines (e.g. interferons), enzymes (e.g. thrombolytics), and other novel proteins, except for those that are specifically assigned to CBER (e.g., vaccines and blood products). This category includes therapeutic proteins derived from plants, animals, or microorganisms, and recombinant versions of these products.
- Immunomodulators (non-vaccine and non-allergenic products intended to treat disease by inhibiting or modifying a pre-existing immune response).
- Growth factors, cytokines, and monoclonal antibodies intended to mobilize, stimulate, decrease or otherwise alter the production of hematopoietic cells in vivo.[1]

2013 年 CBER 与 CDER 之间的人员部门调整

On October 1, 2003, the staff comprising CBER's Office of Therapeutics Research and Review also transferred to CDER. CDER created two new offices to accommodate the former CBER staff:

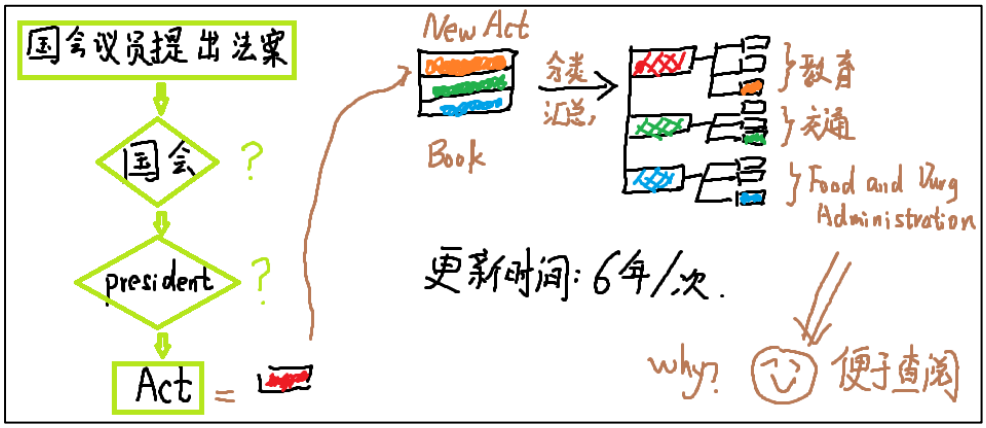
- The Office of Drug Evaluation VI, within CDER's Office of New Drugs, and
- The Office of Biotechnology Products, within CDER's Office of Pharmaceutical Science.

2 FDA 法律法规

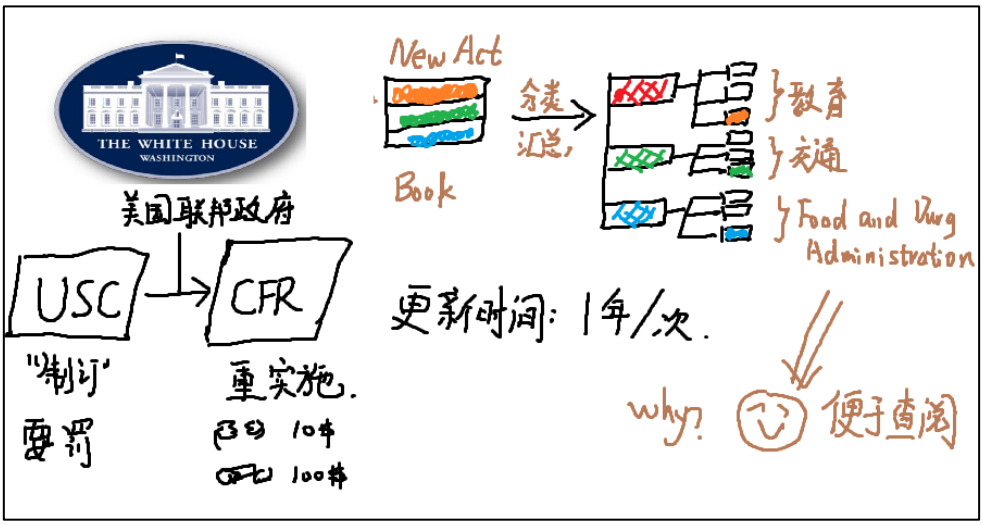
2.1 USC、CFR 的形成与关系

美国法典（United States Code, USC）

美国联邦法规（the Code of Federal Regulations, CFR）



美国法典的形成与整理更新

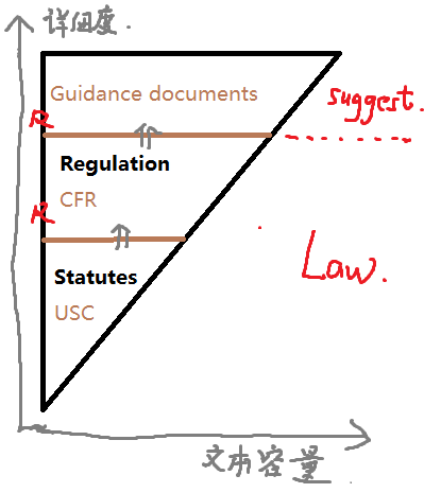


联邦政府的管理依据-美国联邦法规

2.2 FDA 相关的三类文件及相互关系

FDA 制定法规的参考是 21USC，制定的结果是 21CFR。然而法律毕竟是一种文字游戏，为了更加细致的、更加容易理解的表达 FDA 的政策，推出了一种，描述性、指导性的、容易理解的文本，称之 *Guidence for Industry*。因此，不用怕，FDA 的文件，归根结底就这三类。今后对于药品的指导性文件，也应该清晰的分类归类于这三类。对于 industry 者来说，我们只要关注 CFR 及相关其 Guidance

就可以了。



三类文件

2.3 如何查阅 21 CFR

2.3.1 CFR 的结构

CFR 的结构：根据行业的不同，包括 51 卷，其中第 21 卷（21 CFR）是（food and drug administration），21 卷又分为 3 章（chapter），其中的第一章是食品与药物的管理法规，分 12 节（subchapter），每节所含不同数目的条款（parts）

United States Codes		*the Code of Federal Regulations*
Title 1	General Provisions	General Provisions
Title 2	The Congress	Grants and Agreements
Title 3	The President	The President
Title 4	Flag and Seal, Seat of Government, and the States	Accounts
Title 5	Government Organization and Employees	Administrative Personnel
Title 6	Domestic Security	Domestic Security
Title 7	Agriculture	Agriculture
Title 8	Aliens and Nationality	Aliens and Nationality
Title 9	Arbitration	Animals and Animal Products
Title 10	Armed Forces	Energy
Title 11	Bankruptcy	Federal Elections
Title 12	Banks and Banking	Banks and Banking
Title 13	Census	Business Credit and Assistance
Title 14	Coast Guard	Aeronautics and Space
Title 15	Commerce and Trade	Commerce and Foreign Trade
Title 16	Conservation	Commercial Practices
Title 17	Copyrights	Commodity and Securities Exchanges
Title 18	Crimes and Criminal Procedure*	Conservation of Power and Water Resources
Title 19	Customs Duties	Customs Duties
Title 20	Education	Employees' Benefits
Title 21	Food and Drugs	Food and Drugs
Title 22	Foreign Relations and Intercourse	Foreign Relations
Title 23	Highways	Highways
Title 24	Hospitals and Asylums	Housing and Urban Development
Title 25	Indians	Indians
Title 26	Internal Revenue Code	Internal Revenue (the Treasury Regulations)
Title 27	Intoxicating Liquors	Alcohol, Tobacco Products and Firearms
Title 28	Judiciary and Judicial Procedure	Judicial Administration
Title 29	Labor	Labor
Title 30	Mineral Lands and Mining	Mineral Resources
Title 31	Money and Finance	Money and Finance: Treasury
Title 32	National Guard	National Defense
Title 33	Navigation and Navigable Waters	Navigation and Navigable Waters
Title 35	Patents	Education
Title 36	Patriotic Societies and Observances	Reserved (formerly Panama Canal)
Title 37	Pay and Allowances of the Uniformed Services	Parks, Forests, and Public Property
Title 38	Veterans' Benefits	Patents, Trademarks, and Copyrights
Title 39	Postal Service	Pensions, Bonuses, and Veterans' Relief
Title 40	Public Buildings, Properties, and Works	Postal Service
Title 41	Public Contracts	Protection of Environment
Title 42	The Public Health and Welfare	Public Contracts and Property Management
Title 43	Public Lands	Public Health
Title 44	Public Printing and Documents	Public Lands: Interior
Title 45	Railroads	Emergency Management and Assistance
Title 46	Shipping	Public Welfare
Title 47	Telecommunications	Shipping
Title 48	Territories and Insular Possessions	Telecommunication
Title 49	Transportation	Federal Acquisition Regulations System
Title 50	War and National Defense	Transportation
Title 51	National and Commercial Space Programs	Wildlife and Fisheries
Title 52	Voting and Elections	
Title 54	National Park Service and Related Programs	

USC 与 CFR 卷对比

卷	章		节		条
title	chapter	chaptername	subchapter	subchapter name	including parts
21	I	food and drug administration	A	general	1-99
			B	food for human consumption	100-199
			C	drugs:general	200-299
			D	drugs for human use	300-369
			E	animal related products	500-599
			F	biologics	600-680
			G	cosmetics	700-799
			H	medical devices	800-898
			I	mammography	900-999
			J	radiological health	1000-1050
			K	tobacco products	1100-1150
			L（12）	unclassification	1210-1271
	II	DRUG ENFORCEMENT ADMINISTRATION			1300-1399
	III	OFFICE OF NATIONAL DRUG CONTROL POLICY			1400-1499

CFR 第 21 章

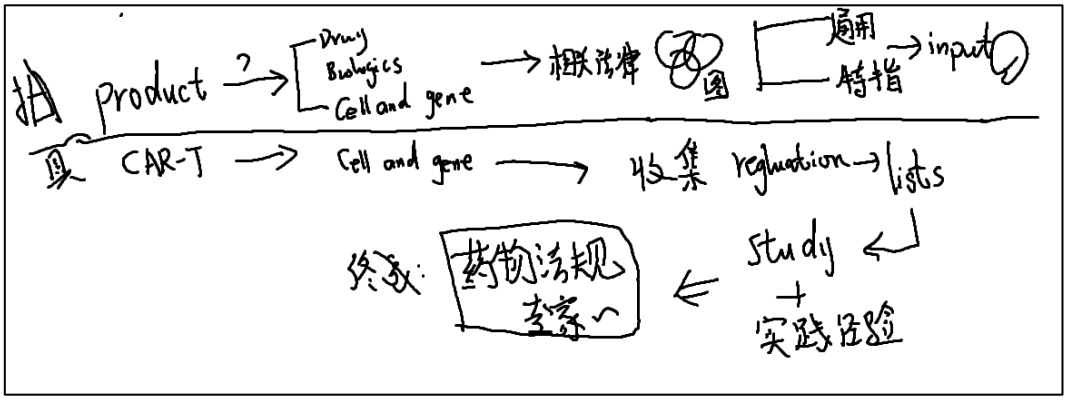
2.3.2 Review electronic code of federal regulation

Electronic Code of Federal Regulations
e-CFR™

http://www.ecfr.gov/

2.3.3 CAR-T 产品的法规整理

逻辑判断-收集-阅读、研究



自己产品法规的学习逻辑

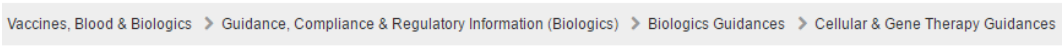
key regulatory provisions for Gene and cell therapy products
Regulation of Combination Products : 21 CFR 4
Protection of Human Subjects : 21 CFR 50
Institutional Review Boards (IRBs) : 21 CFR 56
Good Laboratory Practice (GLP) for Nonclinical Laboratory Studies : 21 CFR Part 58
Good Guidance Practices (GCP) : 21 CFR 10
Drugs : 21 CFR Parts 200–299, 300–369
• Labeling : 21 CFR 201
• Advertising : 21 CFR 202
• Current Good Manufacturing Practices :21 CFR 210–211
• IND Requirements : 21 CFR 312
• Clinical Trial Standards : 21 CFR 314
Biologics : 21 CFR Parts 600–680
• BLA Requirements : 21 CFR 600–690
Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) : 21 CFR 1271
Devices : 21 CFR Parts 800–898
• 21 CFR 807 Subpart E : Premarket Notification 510(k)
• 21 CFR 812 : IDE Requirements
• 21 CFR 814 : PMA Regulations
• 21 CFR 820 : Quality Systems Regulations/Good Manufacturing Practices (GMPs)

细胞与基因治疗相关的核心法规

2.4 如何查阅 Guidence for Industry

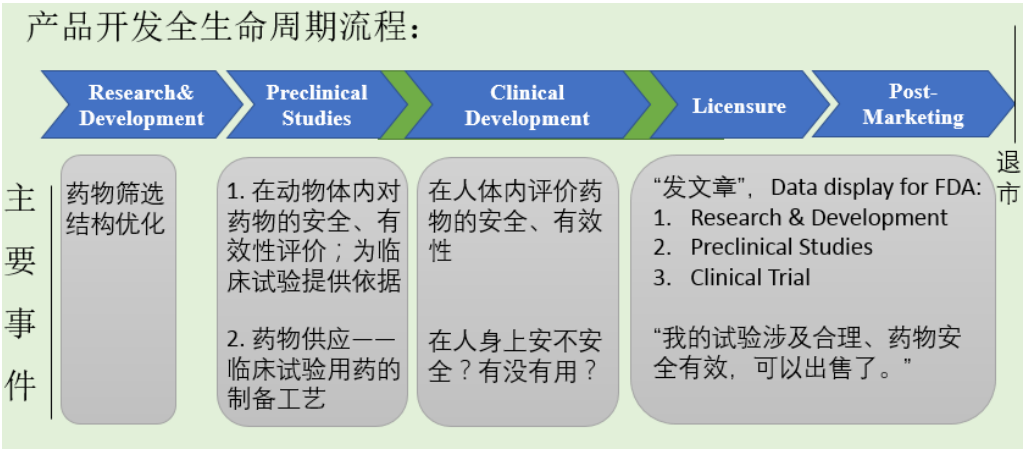
通过案例：Cellular & Gene Therapy Guidances，了解 FDA 网站及相应 Guidence 查找方法。

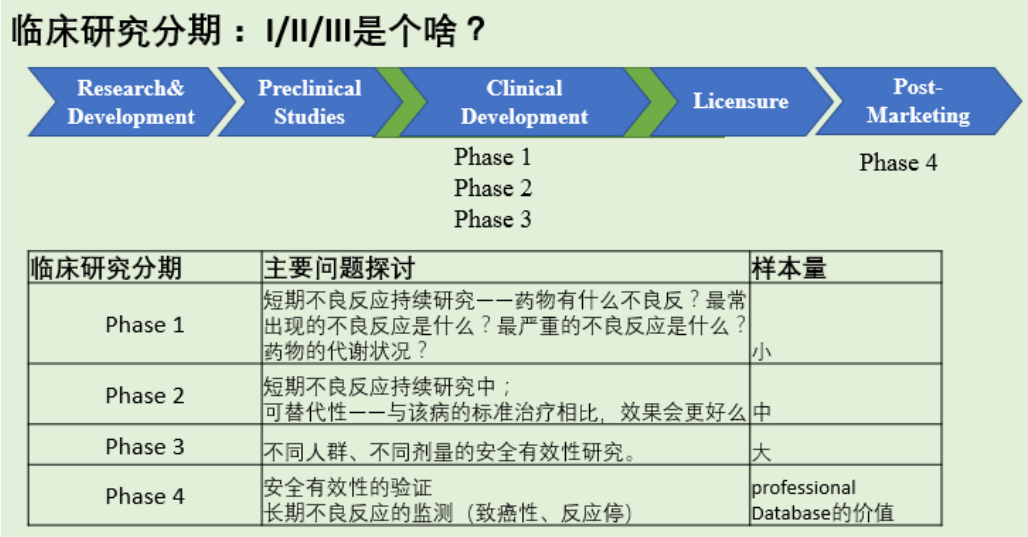
登陆 FDA 官方网址，http://www.fda.gov/ > Site Map>



3 FDA 在药物开发过程中的角色

3.1 药物开发全生命周期



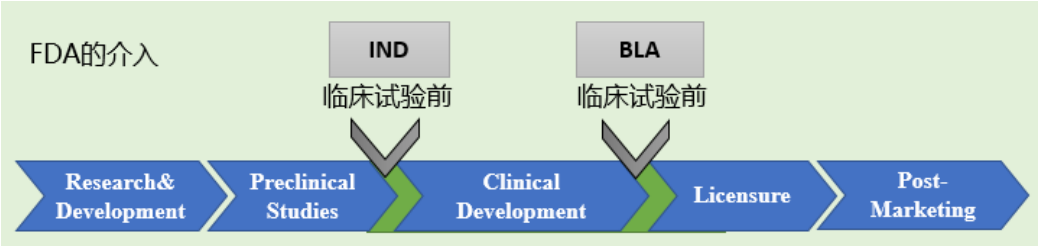


临床研究分期	主要问题探讨	样本量
Phase 1	短期不良反应持续研究——药物有什么不良反？最常出现的不良反应是什么？最严重的不良反应是什么？药物的代谢状况？	小
Phase 2	短期不良反应持续研究中； 可替代性——与该病的标准治疗相比，效果会更好么	中
Phase 3	不同人群、不同剂量的安全有效性研究。	大
Phase 4	安全有效性的验证 长期不良反应的监测（致癌性、反应停）	professional Database的价值

3.2 FDA 的介入

IND, investigational new drug application

BLA, Biologics license application



3.3 药物开发全生命周期项目管理

3.3.1 Industry 方面

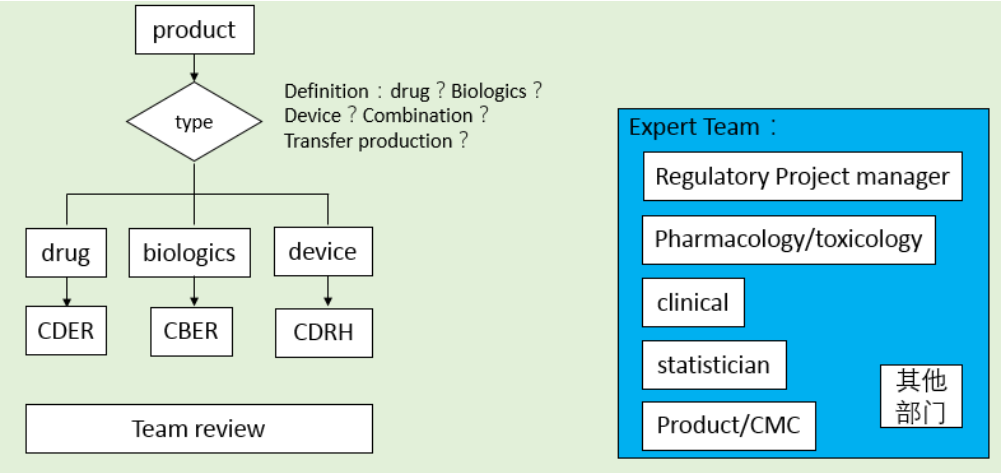
逆推思维，需求思维

3.3.2 FDA 方面

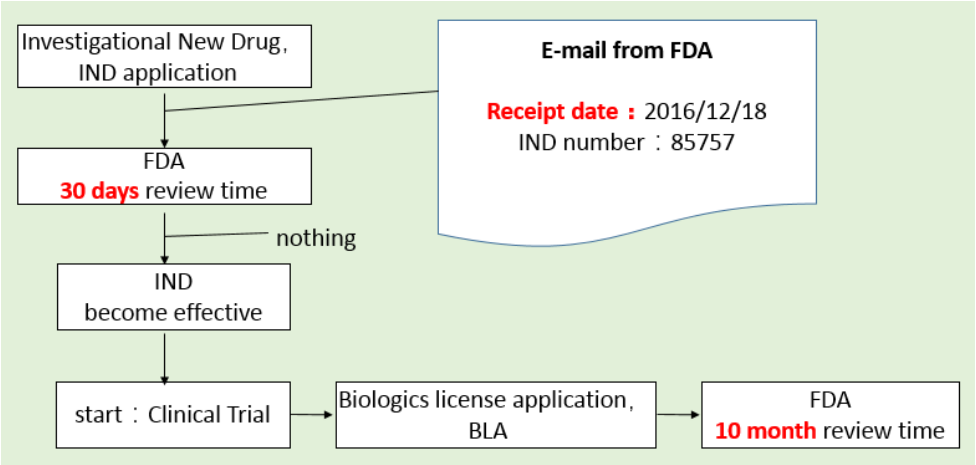
指导性，增加交流机制（meeting）

客观需求：New > flexibility > 基础：FDA 评审的科学专业素质的要求

3.4 FDA 新药审批流程讲解



FDA 对 IND 审批的分工



新药审批的时间问题

4 FDA program

4.1 重大疾病相关项目

4.1.1 Fast Track Designation

4.1.2 Breakthrough Therapy Designation

4.1.3 Accelerated Approval

4.1.4 Priority Review

4.2 罕见病项目

4.2.1 Orphan Drug Designation

4.2.2 Rare Pediatric Disease Priority Review Vouchers

5 FDA accessible database

5.1 Regulations：21 CFR

已讲过的

5.2 Guidence for Industry

已讲过的

5.3 官方网址：

案例：FDA 组织结构图下载。

5.4 FDA 批准的药物查询

Drugs@FDA

About？

包含哪些信息？

Information about FDA-approved brand name and generic prescription and over-the-counter human drugs and biological therapeutic products.

案例：

drug name	active ingredient	corporation
Opdivo	Nivolumab	Bristol-Myers Squibb

6 最后的话

6.1 视频下载方式

6.2 资料购买方式

Word 课件（pdf 课件）、Excel 数据