China NMPA Drug Regulatory Framework Reform

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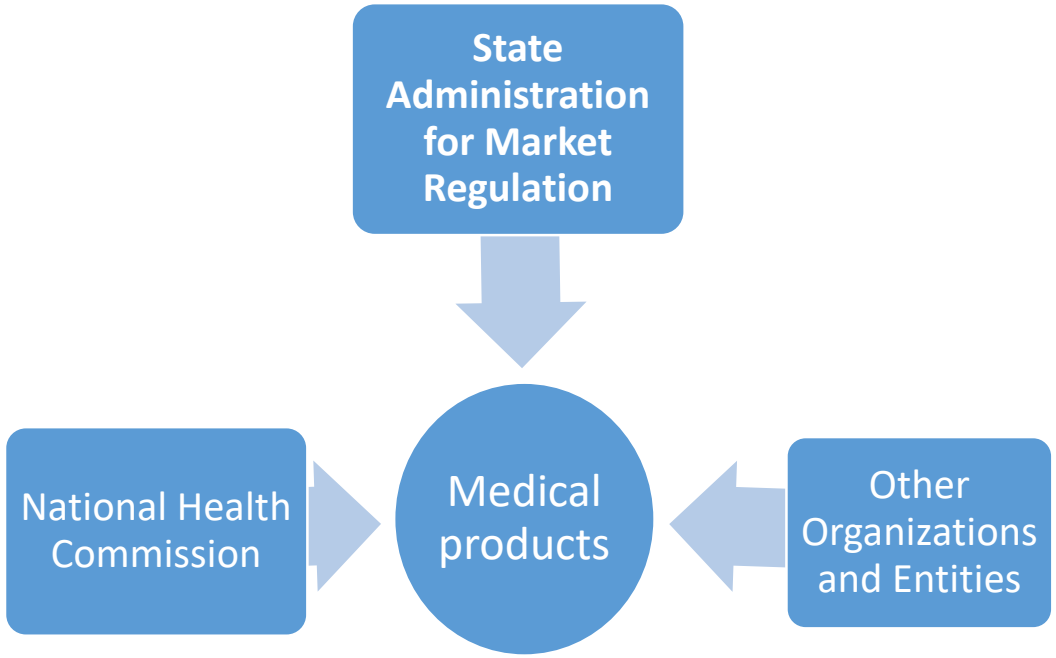
Agenda

- I. Organization
- II. Main Drug Regulations in China
- III. Drug Regulatory framework Reform
- IV. Challenges and Future Perspectives

I. Organization



03/21/2018: SAMR Established

Merger of
-state administration for industry & commerce of the PRC
-General Administration of Quality Supervision of the PRC
-China Food and Drug Administration

I. Organization: SAMR

I. Organization: NMPA's Affiliated Institutions

National Medical Products Administration

National Institutes for Drug Control	National statutory Institutions and the highest technical arbitration body for drugs and biological products
Chinese Pharmacopoeia Commission	Organize Chinese Pharmacopoei compilation, formulate and revise national Pharmaceutical standards as statutory national drug standard management agency
Center for Drug Evaluation	Responsible for technical review of drug registration application as NMPA Drug Registration technical review Agency
National Committee on the Assessment of the Protected Traditional Chinese Medicinal Products	Undertake national TCM protection and technical review of health food, cosmetics approval
Center for Medical Device Evaluation	Responsible for technical review of import medical devices and domestic Class Ⅲ medical Devices
Center for Complaints and Report	Accept complaints for illegal activities in medicines, medical devices, health food and cosmetics in development,production, distribution, use and catering food service
Center for Drug Reevaluation (National Center for ADR Monitoring)	Responsible for conducting druc adverse reactions and medical device adverse events monitoring at home and abroad
China Center for Food and Drug International Exchange	Responsible for conducting international cooperation and exchange activities to serve administration of food, drugs, medical devices and cosmetics
Center for Food and Drug Inspection	Responsible for conducting quality system audit and unannounced inspection for drugs and medical devices

II. Regulations

Laws:

-Drug Administration Law of the PRC(2015 amendment)

-Implementation Rules of the Drug Administration Law of the PRC

Many regulations including:

-Drug Registration Regulation

Two main types of guidance:

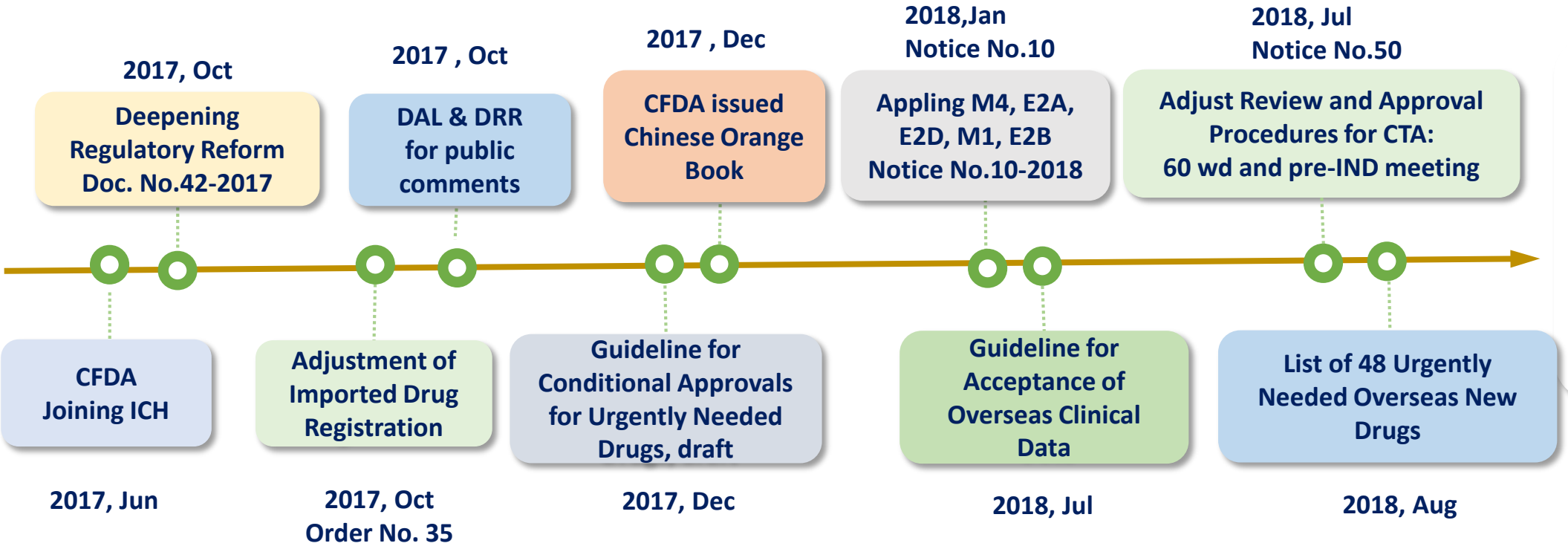
-Generally clarifications of policy- e.g.

-technical standards.

All posted on NMPA’s website

Be noted that product quality needs to meet with those standards in Chinese Pharmacopeia

III. Drug Regulatory Reform



Objectives

-Eliminate registrasion backlog
-Encourage R&D
-Follow international standards

DAL: Drug Administration Law

DRR: Amendment to Drug Registration Regulation

III. Drug Regulatory Reform: Clearing Backlog

Creating an efficient process to clear the severe registration backlog of drug applications

- roughly form 2015 to the end of 2017

-increased the drug registration fee

-mandated self-examination and inspection of clinical data

-identification of redundant generic applications

-rejection of deficient applications

III. Drug Regulatory Reform: Encouraging Innovation

Encouraging innovation

-MAH (Doc. 44 & 42)

-Approval process acceleration

-Clinical trial management

-Lifecycle management

-Intellectual property protection: exploring a drug patent linkage system, initiating a patent term restoration pilot programme, implementing a clinical trial data protection system

-China’s joining the International Conference on Harmonization

III. Drug Regulatory Reform: Hotspots of 2018

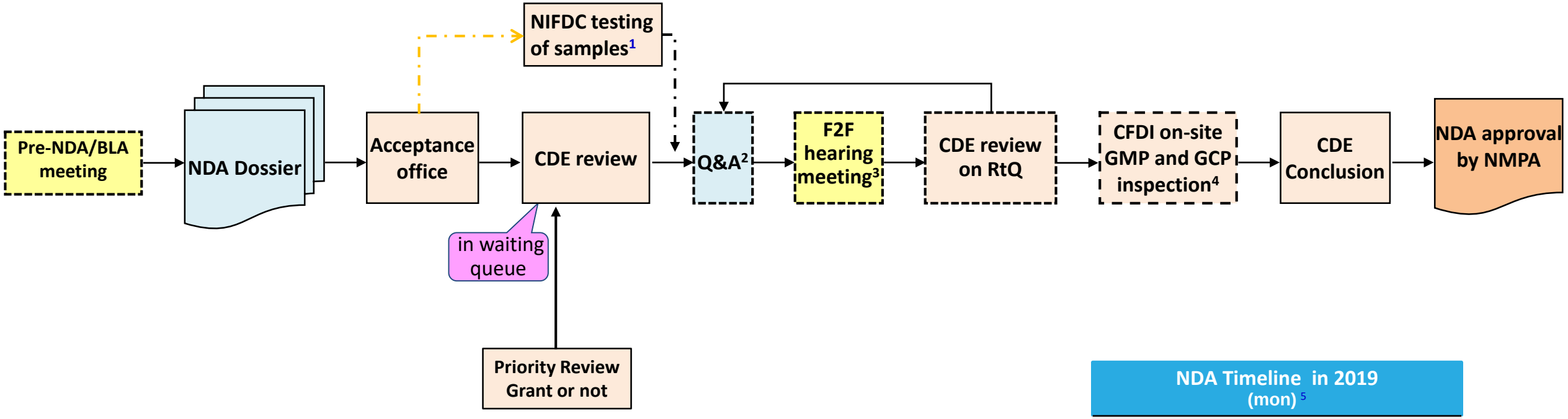
- Optimize procedures for IND/NDA approval
- Acceptance of overseas clinical trial data
- Conditional approval
- Change management based on risk assessment
- Breakthrough therapy and advanced therapy in China
- ICH guidance alignment/Integration : CFDA decided to apply five ICH Secondary Guidelines: M4, E2A, E2D, M1, E2B(R3)

III. Drug Regulatory Reform: Hotspots of 2018

Optimize the Procedures for IND/NDA Approval

- 60 working days for the approval timelines of IND, 150wds for NDA
- Ph 1 trial is allowed in China to enable China joining global simultaneous development
- Review based registration test and inspection
- One CTA approval is valid for Phase I, II and III trials
- CHANGE MANAGEMENT based on risk assessment
- A linked review and approval regime (similar to US DMF) for API, excipients and packaging materials with DP application together

NDA/BLA Process for Import Products



NDA Timeline in 2019 (mon)[5]	
Priority review	120 working days
Standard review	150 working days

Notes:

The steps outlined by dotted line maybe skipped

[1] Testing: in parallel to CDE review, 3 batches of DS & DP samples for biologics

[2] CDE question release after review finished and QC testing report transferred to CDE

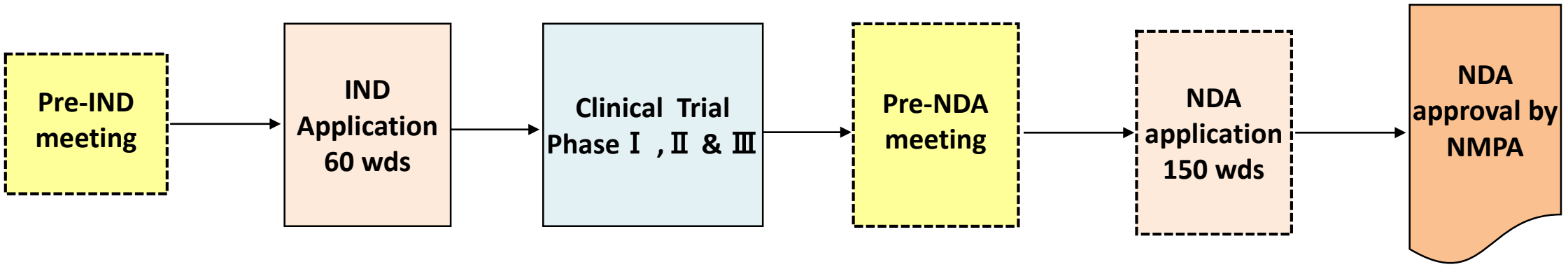
[3] F2F hearing meeting: arranged by CDE if CDE has inquires and need F2F tripartite communication with applicant and CDE external experts

[4] Pre-approval GCP inspection required since Jul 2015, focus on authenticity of data

[5] Assuming QC testing and GCP inspection are not critical path

III. Drug Regulatory Reform: Hotspots

pre-IND/NDA consultation meeting



III. Drug Regulatory Reform: Hotspots

Accelerate Review and Approval of Drugs In Urgent Medical Needs

- Implement the priority review and approval: AIDS, Tuberculosis, Viral hepatitis, Rare disease, Malignant tumor, Pediatric, Diseases with high incidence or unique in elderly people
- Conditional Approval to Meet the Medical Need, e.g., orphan drugs, innovative drugs targeting life threatening diseases without effective therapies
- CPP is no longer required for NDA submission: would shorten China approval gap with US/EU.

III. Drug Regulatory Reform: Hotspots

Guidelines for Acceptance of Overseas Clinical Trial Data

Foreign data can be accepted if the data package meets China's regulatory requirements:

For Approved overseas orphan drugs and those drugs which are effective in treating life threatening diseases without any current available treatment in China , sponsors could submit NDA applications directly (they needn't first submit an IND application) , if it has been proven to be effective among all races and ethnic groups. This process is Not suitable for vaccines.

For an NDA registration of drugs being developed Globally Simultaneously, sponsors should submit an unabridged clinical trial data package that contains all of the clinical trial data obtained from all regions, both in china and overseas.

Changes management based on risk assessment

- CFDA published Guideline for Site Changes to An Approved NDA/ANDA (draft for comments)

III. Drug Regulatory Reform: Hotspots

ICH guidance alignment/Integration

- CFDA held several meetings and seminars to discuss the applicability of ICH guidelines, find controversial articles, by comparing CHINA's current drug regulations, Chinese pharmacopeia and guidelines.
- CFDA decided to apply five ICH secondary guidelines, namely M4, E2A, E2D, M1, E2B(R3)
- We Encourage applicants to submit their application dossier in CTD form, in addition we held many lectures about M4
- We Invited foreign pharmaceutical companies, to introduce Q12, as it is related to QbD , and continuous manufacture

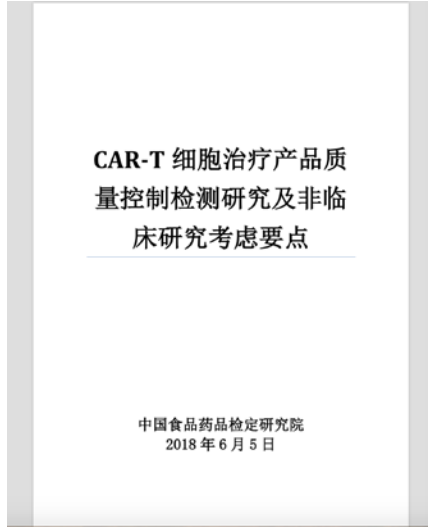
III. Drug Regulatory Reform: Hotspots

PD-1/PD-L1 NDA Application in China

Enterprise	Drug	Date of NDA filing	Indication
BMS	Nivolumab Injection	2017/11/1	second-line NSCLC(Approved)
Merck & Co., Inc	Pembrolizumab Injection	2018/2/11	Melanoma(Approved)
TopAlliance Biosciences Inc.	Teruipuli monoclonal antibody injection	2018/3/20	Melanoma
Innovent Biologics, Inc.	Sintilimab injection	2018/4/19	Classical Hodgkin lymphoma
Heng Rui Pharmaceutical	Camrelizumab for Injection	2018/4/23	Classical Hodgkin lymphoma
Beigene Ltd.	Tislelizumab injection	2018/9/4	Classical Hodgkin lymphoma

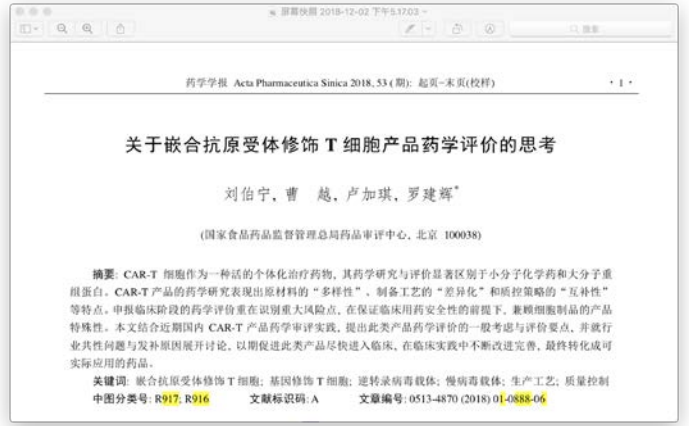
III. Drug Regulatory Reform: Hotspots

CAR-T CMC Requirements


CAR-T 细胞治疗产品质量控制检测研究及非临床研究考虑要点

中国食品药品检定研究院
2018 年 6 月 5 日

-CAR design : costimulatory domains, scFv affinity
-Quality of T cells: T cell subsets, vectors, culture condItions
-Host Specific Factors : TME, ICMs, Tumor heterogeneity
-Quality Control:
  -plasmid: DNA sequencing, concentration , DNA homogeneity,
    HOST CHROMOSOMAL DNA, host RNA, host protein, residual antibiotics
  -virus vector: CAR gene identify, host DNA, host protein,
    BSA, size distribution of residual DNA, viral titer
  -CAR-T: CAR expression, cell viability, CAR+T cells, CD3+ T cells,
     residual beads, in vitro IFN-gamma secretion, sterility,
    replication competent lentivirus


药学学报 Acta Pharmaceutica Sinica 2018, 53 (期): 起页-末页(校样)

关于嵌合抗原受体修饰 T 细胞产品药学评价的思考

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摘要: CAR-T 细胞作为一种活的个体化治疗药物, 其药学研究与评价显著区别于小分子化学药和大分子重组蛋白。CAR-T 产品的药学研究表现出原材料的“多样性”、制备工艺的“差异化”和质控策略的“互补性”等特点。申报临床阶段的药学评价重在识别重大风险点, 在保证临床用药安全性的前提下, 兼顾细胞制品的产品特殊性。本文结合近期国内 CAR-T 产品药学审评实践, 提出此类产品药学评价的一般考虑与评价要点, 并就行业共性问题与发补原因展开讨论, 以期促进此类产品尽快进入临床, 在临床实践中不断改进完善, 最终转化成可实际应用的药品。

关键词: 嵌合抗原受体修饰 T 细胞; 基因修饰 T 细胞; 逆转录病毒载体; 慢病毒载体; 生产工艺; 质量控制

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IV. Challenges

- Globalization: Global simultaneous development
- New technologies & new methods
- ICH guidance alignment/Integration
- Drug life cycle management, e.g., drug withdrawal system building
- Drug Accessibility, encouraging development of biosimilars

IV. Future Perspectives

- Reviewer pertaining and continuous training
- Information system building
- Regulatory science

Thanks!