Overview of the Pharmacopoeia of the People's Republic of China 2015, Volume III

Chinese Pharmacopoeia Commission

The Chinese and European Pharmacopoeias Workshop

October 17th, 2016, Strasbourg, France

国家药典委员会
CHINESE PHARMACOPOEIA COMMISSION
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Outline

- Background Information
- Main Contents
- Overview of Revisions
- Challenges Faced
- Development in Future

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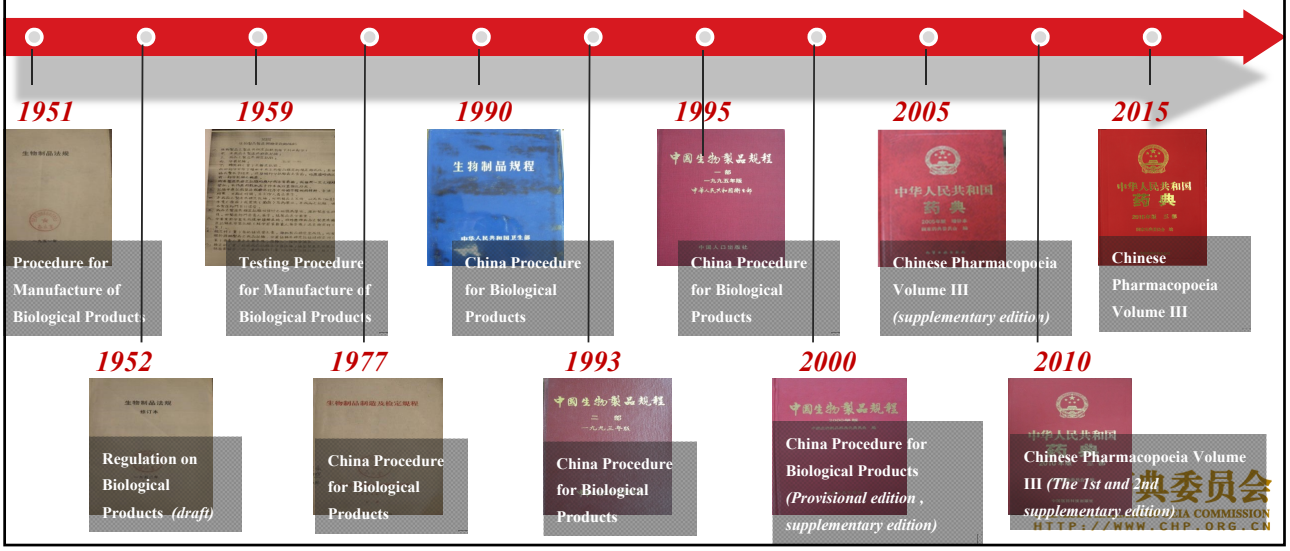
- Background Information



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– Basis for the development of standards

- Relevant domestic (or oversea) regulations and guidelines
- Enterprise registration standards (approved by CFDA)
- WHO guidelines on quality, safety and efficacy of vaccines
- Foreign pharmacopeias and standards
  - ✓European Pharmacopoeia
  - ✓ Foreign enterprise registration standards
- Batch-release test data from national control institutes

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4

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- Goals

- **To enhance the role of standards**
  - Production quality control
  - Government supervision
  - Product development advising
- **To raise the quality specifications**
  - Bring them gradually into line with international standards (WHO, FDA and European pharmacopoeias)
  - Maintain the safety and efficacy indicators consistent with international standards
- **To improve products included**
  - Cover all products included in the national list of essential medicines and the health insurance directory
  - Accelerate the admission of products newly approved for marketing
- **To enhance process control**
  - Quality control for critical raw materials and excipients
  - Application of advanced process technologies
  - Optimization of manufacture process
  - Elimination of backward and unreasonable technologies
  - Homogeneity control for intermediates and finished products
- **To make the document more scientific, more advanced and more practical**
  - Application of modern analytical technologies
  - Take into consideration the principle of "being cost-efficient and practical"
- **To improve the style of the pharmacopoeia**

Outline

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Slide 6

YM2 此处删去了修订概况了？
yann mao; 10/03/2016

Chinese Pharmacopoeia 2015, Vol III

ChP Since 1950

- Overview of Chinese Pharmacopoeia 2015, Volume III

Category			Edition 2010	Edition 2015	Addition	Revision	Not admitted in the edition 2010
General Notices			1	1		1	
General requirements for biological products			9	10	1	7	
General requirements			1	4	3	1	
General Chapters(testing methods)			149	170	22 (about 8%)	21	
Monographs	prophylaxis	Viral	27	25	1	21	3
		bacterial	21	23	3	9	1
	Therapeutic	Biotechnological products	34	38	5	33	1
		Blood products	17	20	3	17	
		Antibiotics	18	18		13	
		Others	1	2	1	1	
	Diagnostic reagents for in vivo tests		4	4		3	
	Diagnostic reagents for in vitro tests		8	7		3	1
Total number of products			130	137	13 (about 10%)	6	6

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The structure of Chinese Pharmacopoeia 2015, Volume III

ChP Since 1950

- General Notices
- General requirements for biological products
- Common testing methods and guidelines
- Monograhs
  - General requirements for vaccines → viral products, bacterial products
  - Recombinant DNA products, Recombinant monoclonal antibodies, General requirements for probiotics → Blood products, Recombinant products, Antitoxins, Antisera products, General requirements for probiotics
  - Diagnostic reagents for in vitro tests → Diagnostic reagents for in vivo tests & In vitro diagnostic products (managed as drugs)

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Chinese Pharmacopoeia 2015, Vol III

- General Notices

- General Provisions
- Monographs
- Appendices
- Title and Arrangements
- Basic requirements
- Precision and Accuracy
- Testing Methods and Limitation
- Standards, Reference and Reference Substances
- Units of Measurement
- Packaging, Labeling, Directions for use, Storage and Transportation
- Abbreviations
- Glossary of Terms for Biological Substances

General Notices - Basic requirements

- Requirements for production management
  - Shall comply with the requirements set forth in the Chinese GMP for Pharmaceutical Products
  - Special products
  - Strictly dedicated facilities (*Bacillus anthracis, Clostridium botulinum and Clostridium tetani* products)
  - Strictly dedicated equipment (human serum albumin)
  - Dedicated building and separated production facilities (BCG and tuberculin products)
- Requirement on manipulation
  - Manipulation with infective materials -- comply with the relevant requirements for biosafety set forth in officially issued regulations.

General Notices - Basic requirements

- Source Material
  - Shall comply with the specifications set forth in Volume III of Chinese Pharmacopoeia
  - For materials not compiled in Chinese Pharmacopoeia, the standards shall be established which should meet the requirements for production and quality control
- Excipients
  - Shall be subject to the approval by the NRA.
- Culture medium used in production
  - shall be free from any substances that may cause adverse reactions in humans
- Source water
  - Shall meet the national standards of potable water
- Purified water and water for injection
  - Shall meet the compendia standards laid down in Volume II

General Notices - Basic requirements

- Antibiotics
  - Penicillin or β-lactam antibiotics must not be used at any stage in the production process
  - No antibiotics shall be used as a preservative for final product
  - The use of antibiotics during the production shall be avoided as much as possible. If it has to be added, the antibiotics with relatively low safety risk should be selected. In addition, the antibiotics added in the product shall be removed effectively by consequent process which shall be validated. For viral vaccines, antibiotics may only be used during the stage of cell preparation.
  - When any antibiotics is added during production, its residual content of final product shall be tested and the limit shall be defined.

General Notices - Basic requirements

Preservatives

- The addition of preservatives (especially those containing mercury) to the intermediates and final product of an injection shall be avoided as much as possible.
- Preservatives shall not be included in single-dose injections in the freeze-dried form.
- For single-dose injections in liquid form, the addition of preservatives shall be avoided as far as possible.
- Any preservatives must not be added in the injections for intravenous use.
- Determination of the dose of preservatives to be used:
  - A minimum addition of preservative shall be adopted by which an effectiveness of antimicrobial preservation can be obtained
  - Multidose preparations： taking into account likely contamination during use and the maximum recommended period of use after opening of a container

General Notices - Preservatives

Common preservatives

- Thimerosal

  0.001% - 0.01%, equal to 10μg-100μg/ml

- 2-phenoxyethanol

  0.06%-1.00%, 0.6mg-10mg/ml, general dosage 2.0-6.0mg/ml

- Phenol

  < 3.0g/L

Basic requirements- Animals used in production and control tests

- Live vaccines for injection - specific pathogen-free (SPF) animals
- Oral and inactivated vaccines - clean, SPF or germ free animals
- Viral or bacterial seed for production need to be passaged via animals -SPF animals
- Animals used for quality control
  - unless otherwise specified, shall satisfy the standards for clean or SPF animals, and mice to be used shall come from the closed colony animals
- Flocks from which chick embryos or embryo cells are provided for production -SPF animals
- Animal-derived raw materials
  - Serum of bovine origin： come from herds certified to be free of bovine spongiform encephalopathy
  - Trypsin： free from contamination of adventitious or endogenous agents

Animals used for production of viral vaccines

Preparations	Category	Cell sources	Animal grade
Japanese encephalitis vaccines, attenuated live	Live	Hamster kidney cells	SPF
Tick-borne encephalitis vaccines, inactivated	Inactivated	Hamster kidney cells	Clean grade
Inactivated HFRS bivalent vaccines	Inactivated	Hamster / gerbil kidney cells	Clean grade
Rabies vaccines for human use	Inactivated	Hamster kidney cells	Clean grade
Live attenuated measles vaccines	Live	Chicken embryo fibroblast	SPF
Live attenuated mumps vaccines	Live	Chicken embryo fibroblast	SPF
Live attenuated measles-mumps vaccines	Live	Chicken embryo fibroblast	SPF
Live attenuated measles-rubella vaccines	Live	Chicken embryo fibroblast (measles)	SPF
Live attenuated measles, mumps and rubella (MMR) vaccines	Live	Chicken embryo fibroblast (measles-mumps)	SPF
oral live attenuated poliovirus vaccines	Live	Monkey kidney cells	Healthy
Live attenuated poliomyelitis vaccines in dragee candy	Live	Monkey kidney cells	Healthy
Live attenuated yellow fever vaccines	Live	Allantoic fluid of the chick embryo	SPF
Live attenuated rubella vaccines	Live	Rabbit kidney cells	SPF

Basic requirements-Production process

- Validated and approved by CFDA
- Define the number of passages of a virus or the number of subcultures of a bacterium and the cell substrates
- process with defined parameters， effectiveness of process
- Control of contamination to virus harvest for viral vaccines

Basic requirements－Quality Control

- Quality Control
  - safety, efficacy and controllability
- Reagents used in the production process
  - Removal process
  - Process validation
  - Determination of residual reagents
  - A range of limit shall be set in the quality specification which is metrizable.
- Diluent used for vaccines
  - Admitted in the Chinese Pharmacopoeia： meet the requirements laid down in the Chinese Pharmacopoeia
  - Not admitted in the Chinese Pharmacopoeia： the related production process and the quality standards shall be approved by CFDA
  - Control items
    - pH, sterility, pyrogen / bacterial endotoxin, abnormal toxicity....

General Notices - Terms

- ✓ Understanding of relevant terms
- ✓ Standardization
  - What
  - How

For example:

Working Seed Lot:

The homogeneous suspension of live virus / live bacteria obtained through passage from the master seed lot according to the methods approved by the drug administration under the State Council, which is used for production of vaccines after being sub-packaged equally and stored; the virus seeds removed from the working seed lot should not be returned for storage again, whether the bottle is opened or not.

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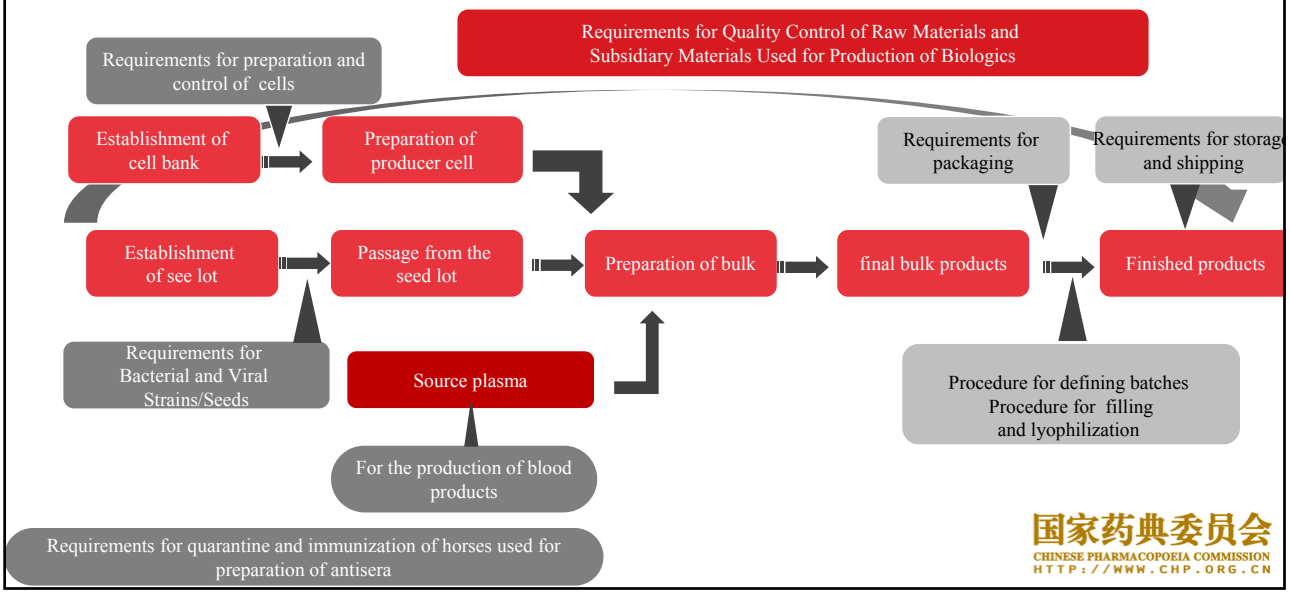
19

Contents – General requirements for biological products



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General requirements for biologics

– Requirements for cells

- Overall requirements
  - Cell lines / strains
    - ✓ Source data
    - ✓ Culture history
  - Establishment of cell banks

    Cell banks
    - Primary Cell Bank (PCB)
    - Master Cell Bank (MCB)
    - Working Cell Bank (WCB)
  - Cell culture media
  - Cell bank management

Requirements for cells – Cells for Production

Cell Line	Definition	Advantages	Disadvantages
Primary cell lines (PCLs)	• Originating from healthy animal organs, tissues or embryos, including kidneys of monkeys, susliks, gerbils, rabbits and dogs, or animal fetuses and other tissues, and normal tissues such as chick embryos and quail embryos; Digested by proper digestive juices, and cultured by dispersed tissue cells	• Easy to prepare; • Low requirement on culture media; • Generally susceptible to various kinds of viruses	• Easy to contaminate endogenous or exogenous infective factors during preparation; • Cells with different animal sources have varying susceptibilities to virus; • Low yield, high cost, large disparity between different cell batches; • Unable to build cell banks for comprehensive verification
Diploid cell lines (DCL)	• Originating from normal fetal tissues and including two genomes	• Suitable for comprehensive verification; • Production based on cell bank system can ensure the consistency and stability of cell preparation; • Safe and non-tumorigenic	• Limited passage, and unsuitable for mass production; • High requirement on culture medium, and difficult to adopt serum-free culture; • Difficult for transfection and genetic engineering construction
Continuous cell lines (CCLs)	• Originating from the passage or transformation of human or animal tumor tissues or normal tissues, and applicable to suspension culture or carrier culture and mass production	• Unlimited life; • Fast-growing, easy-to-culture; • Applicable to modern culture modes (e.g., bioreactor culture), and large-scale virus culture	• There is the risk of potential infective factors which may not be detected by current detection methods; • Residual host protein and host DNA may lead to tumorigenic and carcinogenic risks

Requirements for cells – Cells for Production

Cell Type	Cell Strain	Variety
Human diploid cells (HEL)	2BS	Live attenuated rubella vaccine
		Live attenuated hepatitis A vaccine
		Inactivated hepatitis A vaccine
		Live attenuated varicella vaccine
		Oral polio vaccine
		Rabies vaccine for human use
	KMB17	Live attenuated hepatitis A vaccine
		Inactivated hepatitis A vaccine
	MRC5	Live attenuated rubella vaccine
		Live attenuated varicella vaccine
		Inactivated hepatitis A vaccine
CCLs	Vero	Rabies vaccine for human use (freeze-dried, liquid)
		Freeze-dried inactivated Japanese encephalitis vaccine
		Hemorrhagic fever with renal syndrome (HFRS) bivalent vaccine
		Inactivated hepatitis A vaccine
		Inactivated enterovirus 71 vaccine
		Inactivated polio vaccine*

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Requirements for cells – Cells control

Test Item		MCB	WCB	Terminal Cell Production
Cell identification		+	+	+
Sterility test		+	+	+
Mycoplasma test		+	+	+
Endogenous and exogenous virus contamination test	**In vitro culture**	+	+	+
	In vivo inoculation	+	-	+
	Species specificity virus	+	-	-
	Retrovirus	+	-	+
Cell tumorigenicity		+	-	+

Terminal cell production: Terminal generation cells prepared by the scale or production
"+" Required; "—" Non-mandatory

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General requirements for biologics

– Requirements for Bacterial and Viral Strains/Seeds Used for Production and Quality Control of Biologics

- General Consideration
- Classification (*Catalogue of Infective Pathogenic Microorganism in Humans*)
- Approval, distribution, verification and storage of bacterial and viral strains
- Seed lot system
- Passage and production operation
- Management of users
- Registration
- Classification of bacterial strains/seeds
- Control tests
- Storage
- Destruction
- Demand, distribution and transportation

General requirements for biologics

- Requirements for Defining Batches of Biologics

- The coding principle for batch number
  - XXXX (YY) XX (MM) XX (DD) Serial number – XX (Sub-lot) E.g., 201309001-1
- The principle for defining batch, sub-lot and batch number
  - ❖ Batch number

    Define the batch number of the product when the bulk is mixed, prepared, diluted or filtered as a final bulk product after dilution
  - ❖ Sub-lot
    - ✓ Subpackaged into several bottles
    - ✓ Mixed or diluted product (if more than two filters are used for filtration)
    - ✓ By packaging machine
    - ✓ When different freeze dryers are used or it is freeze-dried in several times
    - ✓ Subpackaged syringe is replaced during the subpackaging process

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- Monographs

- Variety admission principle
  - Reasonable technology, controllable quality, safety and reliable efficacy
  - Meet the needs for prevention and control of infectious diseases and treatment of clinical diseases in China
  - Satisfy the requirement of national strategic reserves

- Variety selection scope
  - Varieties admitted in Volume III of *Chinese Pharmacopoeia* 2010
  - Non admitted in Volume III of *Chinese Pharmacopoeia* 2010

  Varieties in the various versions of *Chinese Requirements for Biological Products*;

  Varieties newly approved and listed (domestic production)

27

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Variety	*ChP*	*WHO*	*EP*	*USP*
Anthrax vaccine	●	○	●	○
BCG (treatment)	○	●	●	●
BCG (prevention)	●	●	●	●
Cholera (liquid/freeze-dried)	○	○	●	○
Cholera (oral/inactivated)	○	●	●	○
Diphtheria, tetanus	●		●	○
Diphtheria, tetanus (non-antigenic)	●		●	○
APDT	●	●	●	○
WPDT	●	●	●	○
DPT-HIb	○		●	○
Diphtheria vaccine	●		●	○
Diphtheria vaccine (non-antigenic)	●		●	○
Hib conjugate vaccine	●	●	●	○
Epidemic cerebrospinal meningitis polysaccharide vaccine	●	●	●	○
Group A meningococcus polysaccharide conjugate		●		○
Group C meningococcus polysaccharide conjugate	○	●	●	○
Acellular pertussis	●	●	●	○
Whole-cell pertussis	●		●	○
Pneumococcal polysaccharide vaccine	○	●	●	○
Typhoid vaccine	●	●	●	○
Typhoid Vi polysaccharide vaccine	●	●	●	○
Typhoid (oral, live)	○	○	●	○
Oral bivalent vaccine of S. Flexneriza-S. Sonnei	●	○	○	○
Leptospira	●	○	○	○
Brucella	●	○	○	○
Plague	●	○	○	○
Recombinant tetravalent dengue fever	○	●	○	○

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Variety	*ChP*	*WHO*	*EP*	*USP*
Inactivated hepatitis A vaccine	●	●	●	○
Inactivated hepatitis A vaccine (virion)	○	●	●	○
Freeze-dried live attenuated hepatitis A vaccine	●	●	○	○
Recombinant hepatitis B vaccine	●	●	●	○
Combined hepatitis A and hepatitis B vaccine	●	○	●	○
Recombinant human papilloma virus vaccine	○	●	●	○
Split influenza virus vaccine	●	●	●	●
Influenza virus subunit vaccine	○	●	●	●
Influenza virus subunit vaccine (virion)	○	●	●	○
Whole influenza virus vaccine	●	●	●	●
Whole influenza virus vaccine (cell culture)	○	●	●	○
Influenza vaccine subunit vaccine (cell culture)	○	●	●	○
Live attenuated influenza vaccine		●		○
MMR combined vaccine	●	●	●	●
MMR-varicella combined vaccine	○	●	●	○
Live attenuated measles vaccine	●	●	●	●
Live attenuated rubella vaccine	●	●	●	●
Live attenuated mumps vaccine	●	●	●	●
Inactivated polio vaccine	○	●	●	●
Oral polio vaccine	●	●	●	○
Rabies vaccine for human use	●	●	●	○
Rotavirus vaccine	○	●	●	○
Herpes zoster virus vaccine	○	○	●	○
Live attenuated varicella vaccine	○	●	●	○
Inactivate tick-borne encephalitis vaccine	●	●	●	○
Live smallpox vaccine	○	●	●	○
Live attenuated yellow fever vaccine	●	●	○	○
Live attenuated Japanese encephalitis vaccine	●	●	○	○
Freeze-dried inactivated Japanese encephalitis vaccine (VERO)	●	●	○	○
Hemorrhagic fever with renal syndrome bivalent vaccine (VERO/susliks, gerbils)	●	●	○	○

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Vaccines admitted by relevant Domestic or Foreign Pharmacopoeias or WHO

ChP Since 1950

Variety	ChP	WHO	EP	USP
APDT - Hepatitis B vaccine	○	○	●	○
APDT - Inactivated polio vaccine	○	○	●	○
APDT - APDT - Inactivated polio-Hib	○	○	●	○
APDT - APDT - Inactivated polio-Hib (combined)	○	○	●	○
APDT - APDT - Inactivated polio (non-antigenic)	○	○	●	○
APDT - hepatitis B - Inactivated polio-Hib	○	○	●	○

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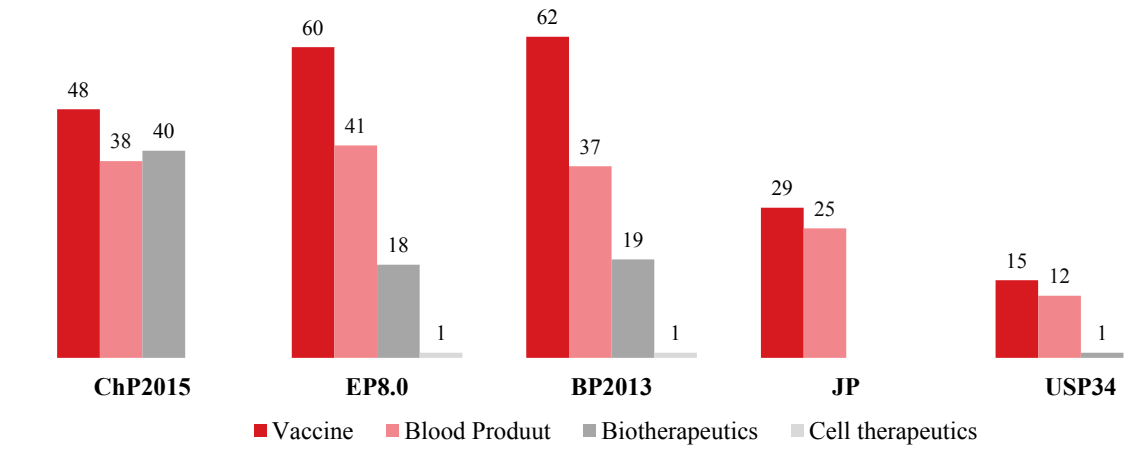
Biological products admitted by different Pharmacopoeias



The development of vaccines in China

- vaccine preparation
  - live vaccine → inactivated vaccine
  - inactivated vaccine → refining → purification
  - Purification of whole virus (bacteria) → components
  - univalent vaccine → combined vaccine
  - liquid → lyophilization
- production process

tissue culture → cell culture → recombinant antigen produced by genetic engineering

Kolle flask → spinner bottle → cell factory（bioreactor）

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- framework of monographs

- Drug name
  - **Should follow the applicable nomenclature rules for biological products in Work Manual of National Drug Standards**
  - **Should include Chinese generic name, Chinese Pinyin name, and English name**
- Definition, components, and indications

  Briefly describe the starting raw materials, production process, components, and indications
- Basic requirements

  Overall Requirements for the production and control of products should be laid down, including: equipment, raw materials and excipients, water, instruments, animals for production and control should meet the relevant requirements in *General Notices*.
- Production

  Mainly includes the preparation of single virus harvest liquid, bulk, final bulk, and final products.
- Control

  Includes the test of single-use virus harvest liquid, bulk, final bulk, and final products.
- Storage, transport and expiry
- Instructions for use

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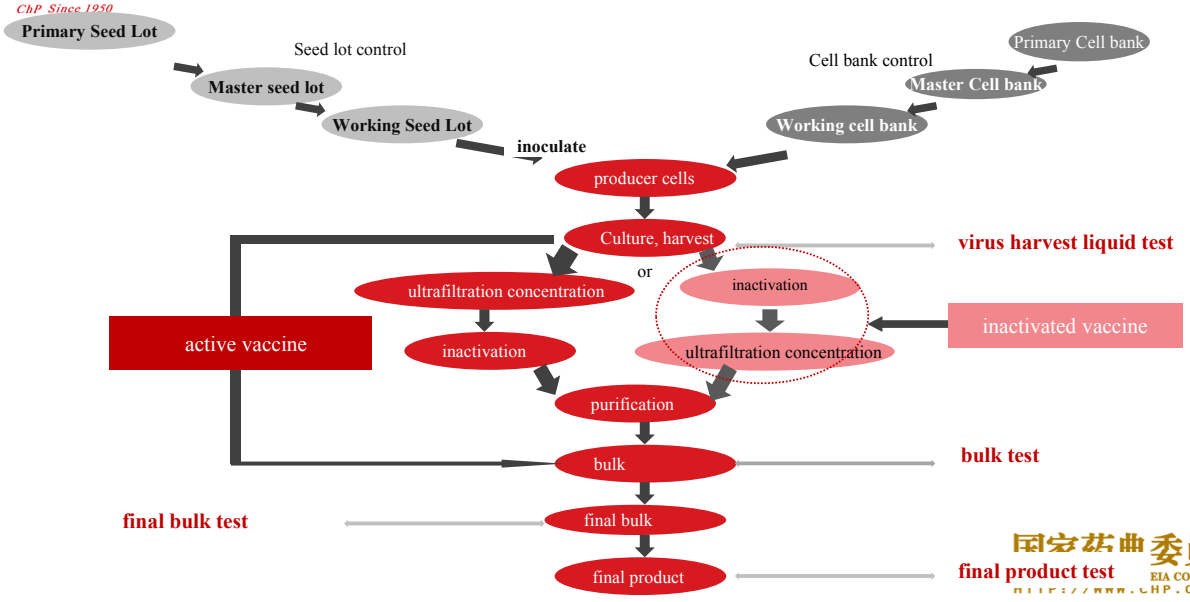
33

Manufacturing process for viral vaccines



Requirements for virus seeds for production -1

- Establishment of seed lot

  Should follow "Requirements for Bacterial and Viral Strains/Seeds Used for Production and Quality Control of Biologics".

  - name and origin of virus seed
  - passage limit for seed lot at each level
  - virus seed background
    - ✓ passage background
    - ✓ the types of culture cells (isolated from virus seed)
    - ✓ the names of seed lots should be standardized
  - Passage of virus seed
    - ✓ should carry out serial passage, mix well, and ensure homogeneity and stability
    - ✓ No penicillin or β-lactam antibiotics or antibiotics that are different from those used in the production process should be used in the virus seed preparation process
    - ✓ the working seed lot is for vaccine production.
- Seed lot control:
  - Identification (serology, gene sequencing)
  - presence of bacteria, mycoplasma
  - virus titer (sensitivity of animal tests and cell culture)
  - adventitious virus agent (a test of high sensitivity for corresponding specific adventitious virus)

Requirements for virus seeds for production - 2

- immunogenicity test (establishment of animal models/serological methods/methods for protection of animal immunity, operability, strain of the animals for experiments, and standard strain of challenge virus)
- gene sequencing of virus seeds (the gene sequence of the master seed lot and working seed lot should be the same with that of the primary seed lot)

- storage of seed lots
  - state of seed lot (freeze-dried /liquid)(the storage status of seed lots should be the same wherever possible)
  - the storage time of working seed lots should, as a rule, be specified.
  - the expiry of working seed lots should be determined based on validation.

Requirements for cells for production

- Establishment of cell banks

  Should follow "Requirements for Preparation and Control of Animal Cell Substrates Used for Production of Biologics".

  - name and origin of cell line
  - passage limit for the primary, master, and working cell banks
  - the passage of the cell for vaccine production
  - passage should be standardized.

    DCLs: (2BS, MRC-5)

    - ✓ one passage is completed when the population is doubled.
    - ✓ the age limit for the cells for production is to be within the first 2/3 of the life span

    CCLs: Vero

    - ✓ expanse with appropriate proportion
    - ✓ For WHO MCB-p134, vaccine production≤p150
    - ✓ For p126-127 cells provided by NIFDC, vaccine production ≤p148
    - ✓ For P127 cells provided by ATCC, vaccine production ≤p150

- Specification on cell lots
  - Cells produced by cell resuscitation, expansion till virus inoculation from one or multiple lines of cells from the working cell bank are one lot.
  - Cells produced by cell resuscitation, expansion till virus inoculation from one or multiple lines of cells from the same working cell bank are to be used for production of one lot of vaccine.
- Cell test

  adventitious virus agent test: sensitive tests, transmission electron microscope, PERT, gene sequencing, etc.

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Requirements for production process control - 1

- Components of culture solution and maintenance solution
- No antibiotic materials should be used in the maintenance solution
- The final concentration of the antibiotic to be added to the maintenance solution should be based on its antibacterial effect.
- Use of antibiotics

  Should follow the requirements on use of antibiotics in "General Notices" of Chinese Pharmacopoeia Volume III
  - Use of penicillin or β-lactam antibiotics should be avoided wherever possible or prohibited.
  - should select antibiotics of low risks, and no more than one antibiotic should be selected.
  - antibiotics of suitable concentrations should only be used in the process of production and cell culture and should not be used as preservatives.
  - validation and restriction of the effect of removal by process should comply with the requirements of Chinese Pharmacopoeia (≤50ng/ml)
- Chemical reagents used in the production process

  Should follow the requirements in Chinese Pharmacopoeia Volume III
  - quality control standards should be established based on the stage of the process used for varieties not listed in Chinese Pharmacopoeia
  - restricted organic solvents should be avoided; if used, it should be removable by the subsequent process stages and the residual amount should be within the specified limit.
  - the effect of removal by process should be validated and restrictive standards should be established for inactivators, antibiotics, chemical reagents for purification process, DNA enzymes, etc.
  - establishment and standardization of test methods

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Requirements for production process control - 2

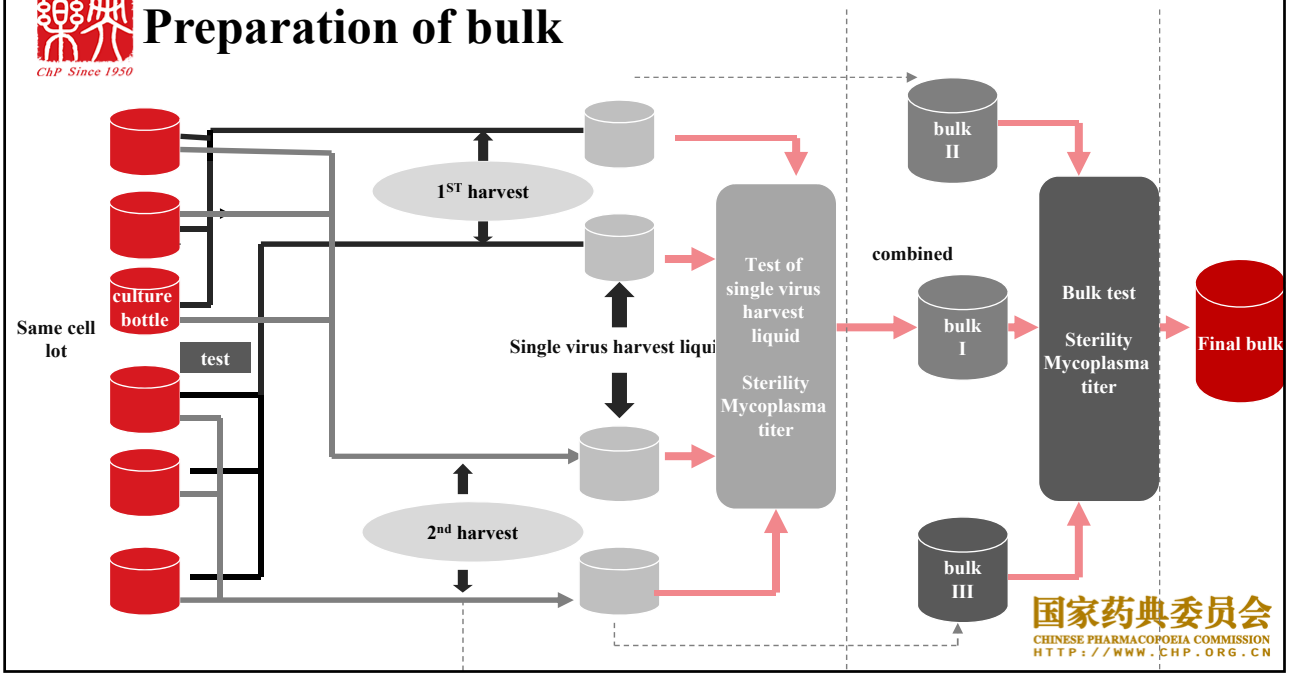
- Virus inoculation and harvest
  - the amount of virus inoculated is expressed as MOI (multiplicity of infection，MOI，the ratio of virus quantity to cell quantity when infected)
  - Virus of the same working seed lot is to be inoculated at the same MOI.
  - Limit on harvest times (allowed deviation is no more than 1 time) should be set in cases where virus is harvested for multiple times,
  - control of contamination in cases of multiple harvests

  If one bottle of cells are contaminated, any single harvest liquid related with this bottle of cells should not be used for production.
- Single virus harvest substances

  Substances obtained from the same harvest of the same cell lot can be combined into a single harvest liquid if qualified on tests.
- Tests of single virus harvest substances
- Storage of single virus harvest substances

  The temperature and duration of storage of single virus harvest substances should be based on the evaluation of product stability.

Preparation of bulk



Requirements for production process control -2

- Viral inactivation
  - the stage of process for viral inactivation should be based on the rationality of the production process.
  - Through process validation
    - ✓ to determine the type and concentration of the inactivator, and the temperature and duration of inactivation*
    - ✓ to determine the range of content of proteins in the virus liquid before virus inactivation to ensure a good effect of virus inactivation
  - if virus inactivation is performed after ultrafiltration concentration, the folds by which ultrafiltration concentration is performed should be within the limit of protein content determined by the virus inactivation stage.
  - when the duration of viral inactivation has expired, sampling should be performed for each of the inactivation container immediately and the samples should be tested individually to validate the effect of inactivation. ;
    - ✓ Amount to be sampled? Representativeness?
    - ✓ can the virus liquid used in viral inactivation test be used in the subsequent process stages?
- purification
  - method: Column chromatography / gradient zone centrifugation
  - purification parameters should be determined based on the process validation
  - the range of content of proteins in the virus liquid should be determined before purification to ensure a good effect of purification

Requirements for production process control -3

- Preparation of final bulk products
  - Prepare a final bulk product based on the defined content of antigen or protein
  - Live vaccine: based on virus titer
  - Inactivated vaccine: prepare according to the defined protein content. Also, the limit for antigen content should be specified. If it is to prepare according to the defined antigen content, the limit for protein content should be specified.
  - All the excipients and their content should be specified.
  - The use of excipients should be approved by China Food and Drug Administration.
  - The specification of excipients shall comply with state pharmaceutical standard (pharmacopoeial standard/standards with state approval)
  - The use of preservatives shall comply with related provisions in the General Notices of Volume III of current edition of pharmacopoeia.
    - Avoid using mercury-based preservatives in the manufacturing process as possible
    - Avoid adding preservatives in single-dose injections as possible.
    - If any preservative is added, the concentration of the preservative should be determined according to the effective antibacterial effect.
  - Products containing adjuvants:
    - type of the added adjuvant
    - content of the adjuvant (the proportion to antigen)
    - test for absorption effect, and the establishment of indicators (as the performance indicators for product stability)

Control test on viral vaccines

- Control of single virus harvest
  - sterility, mycoplasma
  - virus titer
  - protein content
  - antigen content?

  (It is require to standardize the test for antigen content and unify the units to ensure the inter-batch consistency within inter- and intra- manufacturing enterprises)

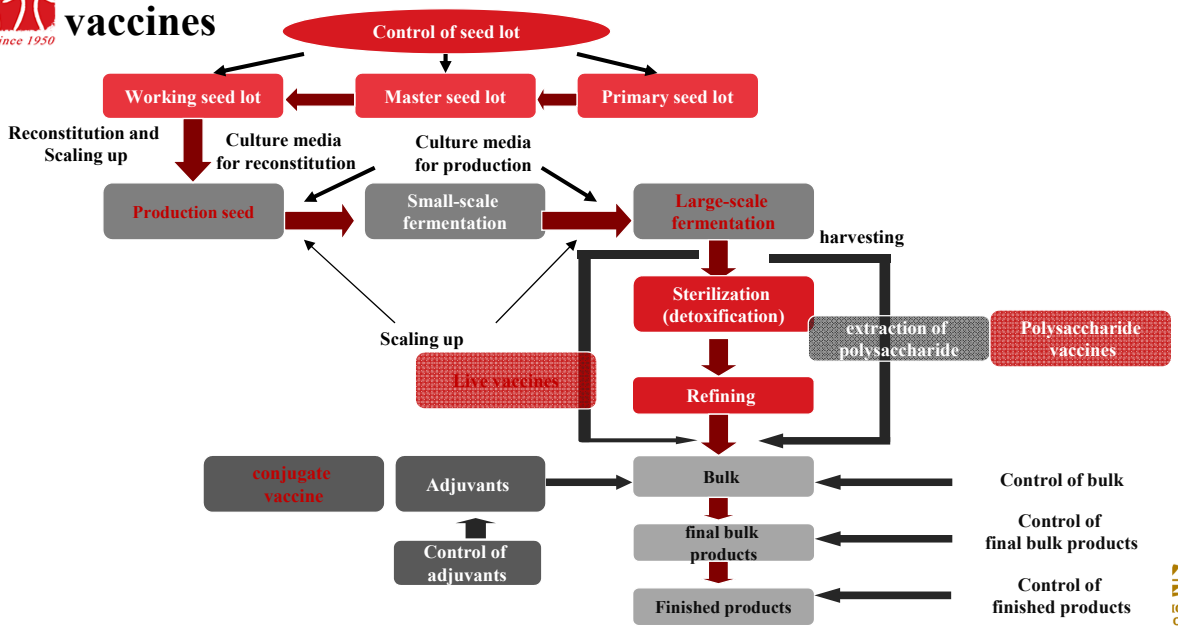
Control of viral vaccines

- Control of bulk
  - sterility, mycoplasma
  - validation of viral inactivation (conducted after viral inactivation; validate the sensitivity of test method)
  - test of antigen content
  - test of protein content
  - viral content (live vaccines)
  - test of other residual chemical reagents
- products containing adjuvants:
  - Test of bovine serum albumin residue
  - Test of DNA residue of Vero cells (Vero cellular matrix)
  - Test of protein residue of Vero cells (Vero cellular matrix)
  - Test of DNAzyme residue (Vero cells)

Control of viral vaccines

- Control of final bulk products
  - sterile
  - test for residual chemical reagents
- Control of finished products
  - Identification: rapid specific test should be established as possible.
  - Appearance
  - Filling volume
  - Osmolality (to ensure the consistency of the products)
  - content and residue of chemical reagents
  - Activity:
  - Objectively evaluate the effectiveness of the products
  - Method standardization, including the unification of animal species, dosage, observation time and unit of potency.
  - thermal stability test:
  - The determination of the test method is based on the relevance with the stability of the products under the storage temperature.
  - Other safety tests:
  - Sterility, bacterial endotoxin, abnormal toxicity, residue of antibiotics

Flow chart of the manufacturing process for bacterial vaccines



Requirements for bacteria for production

- Establishment of seed lot

Shall comply with "Requirements for Bacterial and Viral Strains/Seeds Used for Production and Quality Control of Biologics"

- name and source of bacteria
- establishment of seed lot:
- background of bacterial passaging
  - ✓ It should be not more than 5 generations from the master seed lot to working seed lot.
  - ✓ Culture media for passaging
  - ✓ Standardize the name of bacteria (e.g.: CMCC, China Medical Culture Collection Center)
- Bacterial passaging
  - ✓ consecutive passaging and mixing to guarantee uniformity and stability
  - ✓ working seed lot is used for the production of vaccines.

Requirements for bacteria for production

- Control of seed lot:
  - Identification

  morphology: microscopy and cultivation characteristics.

  biochemical reaction

  serology
- Gene sequencing for the antigen
  - virulence test (establishment of animal model)
  - Immunity test (animal test)
  - Immunogenicity test (serological method and establishment of animal model)
  - safety test (reversion to virulence)

Culture media for production

- Shall comply with the requirements under General Notices
  - No substance that might arise adverse reactions in human should be used.
- Specify the composition of the formulation
  - culture media for reconstitution and culture media for production
- The culture medium that containing goat blood or mammalian elements is limited to the use in reconstitution.
- It is not allow to contain animal serum elements.
- Stability of culture medium

Requirements for the manufacturing process of bacterial vaccines-inoculation and cultivation

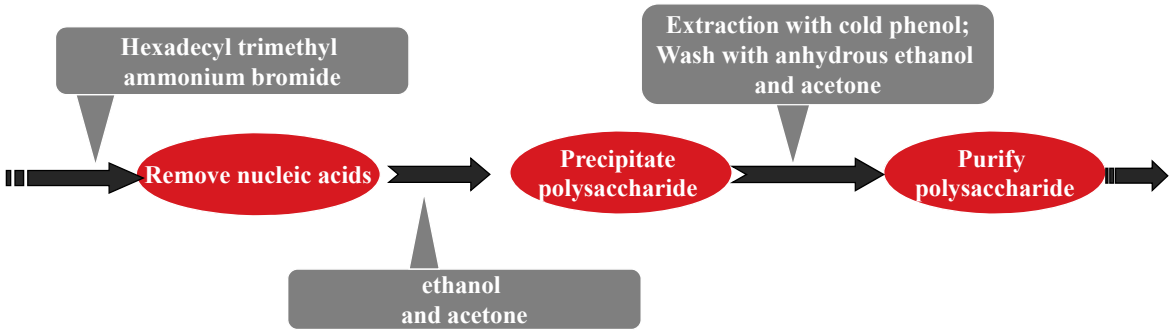
- Determine the generations from working seed lot to vaccines.
- Inoculation proportion

  Proportion of number of bacteria produced after inoculating the production seed lot to the production culture medium to the volume of culture medium
- Cultivation conditions
  - Time
  - Temperature
  - CO_2 level
  - pH
  - Number of live bacteria
- Control of culture
  - Bacterial count
  - Pure strain

Requirements for the manufacturing process of bacterial vaccines-inoculation and cultivation

- Sterilization(detoxification) and effectiveness validation
- Sterilizing agent (detoxifying agent): formaldehyde
- Tests after sterilization (detoxification):
  - Method of cultivation: (selection of culture media)
  - Animal test: establishment of animal model

Requirements for the manufacturing process of bacterial vaccines-extraction of polysaccharide



Control of bacterial vaccines

- Potency test
  - Live vaccines: viable count
  - Inactivated vaccines: potency test in animals
  - Assay: content of active ingredients (such as: polysaccharide)
- Safety test: virulence
- Adjuvant absorbing effect:
  - Effectiveness
  - Stability

Vaccine stability

- In-process intermediates and finished products
- The stability of identical product produced by different manufacturers are different.

(Formulation composition, content, proportion, process difference, appearance, etc.)

- The methods used to evaluate the stability should be different(the manufacturers might determine the evaluation methods for stability according to the characteristics of their products on the basis of the methods provided in the guideline of WHO).
- Thermal stability test
  - Considering that most vaccines are sensitive to temperature, the purpose of thermostability test is to set requirements for vaccine storage and cold chain system through potency test to add thermostability tests.
  - As the indicator of the production consistency of vaccines.
  - Thermal stability test should not be used to provide predicted value for real-time stability.
- real-time stability test, including the appropriate physical, chemical and biological tests suitable to the vaccines.
- During the R&D stage, stability control parameters should be determined according to the characteristics of the products. The parameters should be able to reflect the biological activities of products or intermediates and the stability of products is assessed through evaluating the stability of consecutive batches.
- These stability parameters will provide the basis for the evaluation of product stability when the process or used materials change.

Biotechnology products

- General requirements for recombinant DNA products for human use

- ✓ Introduction
- ✓ Production
- ✓ Quality control
- ✓ Storage
- ✓ Shelf life
- ✓ Labeling

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Biotechnology products

- General requirements for recombinant DNA products for human use

- Production
  - Basic requirements
- Control of engineering cell
  - expression vectors and host cells
  - cell bank system
  - quality control of cell bank
  - genetic stability of cell matrix
- In process control
  - cell cultivation
  - production with limited passages
  - continuous cultivation and production
  - extraction and purification
  - bulk
  - final bulk product
  - finished product
- Manufacturing process change

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Biotechnology products

- General requirements for recombinant DNA products for human use

- Quality control
  - Property analysis
    - Physicochemical properties
      - Primary structure
      - Galactosylated modification
      - Higher structure
    - Biological properties
      - Chemoimmunological properties
      - purity
      - impurities
- product related substances/impurities
  Process related impuritiee
  contaminant
  - Product test
  - Packaging and container closure systems

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- Admitted therapeutic biotechnology drugs

Code	Agent	Code	Agent
1	Recombinant Human Erythropoietin for Injection (CH0 cells)	21	Recombinant Human Interferon γ for Injection
2	Recombinant Human Erythropoietin Injection (CHO cells)	22	Recombinant Human Interleukin-2 for Injection
3	Recombinant Human Interferon for Injection α1b	23	Recombinant Human Interleukin-2 Injection
4	Recombinant Human Interferon α1b Injection	24	Recombinant Human Interleukin-2(I) for Injection
5	Recombinant Human Interferon αlb Eye Drops	25	Recombinant Human Granulocyte Colony-stimulating Factor Injection
6	Recombinant Human Interferon α2a for Injection α2a	26	Recombinant Human Granulocyte/Macrophage Colony-stimulating Factor for Injection
7	Recombinant Human Interferon α2a Injection	27	Recombinant Bovine Basic Fibroblast Growth Factor Liniment Solution
8	Recombinant Human Interferon α2a Vaginal Suppository	28	Recombinant Bovine Basic Fibroblast Growth Factor Liniment
9	Recombinant Human Interferon α2a for Injection (Yeast)	29	Recombinant Bovine Basic Fibroblast Growth Factor Gel
10	Recombinant Human Interferon for Injection α2b	30	Recombinant Human Epidermal Growth Factor Liniment
11	Recombinant Human Interferon α2b Injection	31	Recombinant Human Epidermal Growth Factor Liniment Solution (I)
12	Recombinant Human Interferon α2b Eye Drops	32	Recombinant Human Epidermal Growth Factor Gel (Yeast)
13	Recombinant Human Interferon α2b Vaginal Suppository	33	Recombinant Streptokinase for Injection
14	Recombinant Human Interferon α2b Cream	34	Murine Anti-human CD3 Monoclonal Antibody for injection (abolished, not admitted)
15	Recombinant Human Interferon α2b Gel	35	Recombinant Human Interleukin-11 for Injection (Yeast) (Newly Added)
16	Recombinant Human Interferon α2b for Injection (Yeast)	36	Recombinant Human Interleukin-11 for Injection (Newly Added)
17	Recombinant Human Interferon α2b for Injection (P.putida)	37	Nimotuzumab Injection (Newly Added)
18	Recombinant Human Interferon α2b Injection (P.putida)	38	Recombinant Bovine Basic Fibroblast Growth Factor Eye Drops (Newly Added, supplement II of Version 2010)
19	Recombinant Human Interferon α2b Spray (P.putida)	39	Recombinant Human Epidermal Growth Factor Eye Drops (Yeast) (Newly Added, supplement II of Version 2010)
20	Recombinant Human Interferon α2b Ointment (P.putida)		

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The Specification of therapeutic biotechnology products

- Test Procedure for the Bulk of Recombinant Human Interferon α2a for Injection

Test	Method	Specification
Biological acitivity	bacteria inhibition assay (General Principle 3532)	
Protein content	Lowry method (Method 2 of General Principle 0731)	
Specific activity	Biological activity/protein content	≥1.0×10^8IU/mg
Purity (SDS-PAGE)	Non-reducing SDS-PAGE (Method 5 of General Principle 0541)	≥95.0%
Purity (HPLC)	HPLC (General Principle 0512)	≥95.0%
Molecular weight	Reducing SDS-PAGE (Method 5 of General Principle 0541)	$19.4\times10^3\pm10\%$
Residue of exogenous DNA	Test for Residue of exogenous DNA (General Principle 3407)	≤10ng/dose
IgG residue	enzyme-linked immunosorbent assay (General Principle 3416)	≤100ng/dose
Residue of host proteins	enzyme-linked immunosorbent assay (General Principle 3412)	≤0.1% of total proteins
Activity of residual antibiotics	Inhibition zone test (General Principle 3408)	Negative
Bacterial endotoxin	Limulus amebocyte lysate (LAL) test (General Principle 1143)	＜$10EU/3\times10^6$IU
Isoelectric point	isoelectric focusing (Method 6 of General Principle 0541)	4.0-6.5, should be consistent with the reference standard
Wavelength of maximum absorbance	Ultraviolet spectroscopy (General Principle 0401)	Should be 278±3 nm
Peptide mapping	Trypsin/RP-HPLC (General Principle 3405)	Should be consistent with reference chromatogram.
N-terminal sequence	Edman degradation (with amino acid sequencer)	Should be (M)CDLPETH-SLGSRRTL

Test methods

- Unless otherwise specified, it should be tested according to the methods included in pharmacopoeia. If the manufacturer use any method that is not included in the pharmacopoeia, a comparative test between the applied method and the statutory method to confirm that there is no significant difference in test result between the two methods. Retest of NCL should be performed according to the pharmacopoeial method.

- If the manufacturer use any method that is not included in the pharmacopoeia, it should be validated with relevant methods and is allowed to be used only after approved by CFDA.

- Notes: Though related general test methods are stipulated in the pharmacopoeia, it is required to conduct method suitability studies before applying the method, especially for the tests of impurities and residual chemical reagents, to confirm that the product will not interfere with the test method so as to guarantee the accuracy of the test results.

Challenges

- Manufacturing process
  - ✓ Rational process
  - ✓ Process validation
- In-process control
- Control of raw materials and excipients
  - ✓ Quality control
  - ✓ Content control
- Test method
  - ✓ Establishment of test method
  - ✓ Validation of test method
  - ✓ Suitability of test method

Challenges faced

- quality consistency
- product stability
- control of impurities
- safety risk evaluation

Outline

- Background Information
- Main Contents
- Overview of Revisions
- Challenges Faced
- Development in Future

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– Development in future

- Admission of Chinese Pharmacopoeia standards for new products
  - IPV、 EV71、 biotechnology products
- Further improve the common technical requirements for whole-process control
- Strengthen technical requirements related to virus contamination and safety
- Technical requirements related to therapeutic biological products of new classes
- Nomenclature standards for biological products（INN）
- Quality control of raw materials and excipients for production of biological products
- Future alignment with the international advanced levels in terms of overall quality control.

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Thank you!

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