Establishment and Progress of the Standard System of Pharmaceutical Excipient in ChP

Chinese Pharmacopoeia Commission

Comprehansive Division
Xiaoxu Hong

ChP-EDQM Workshop on Pharmaceutical Excipients

18 September 2018 Strasbourg, France

Main Contents

- Overall Planning
- Work Progress
- Challenges
- Next Step……

国家药典委员会
CHINA PHARMACOPOEIA COMMISSION
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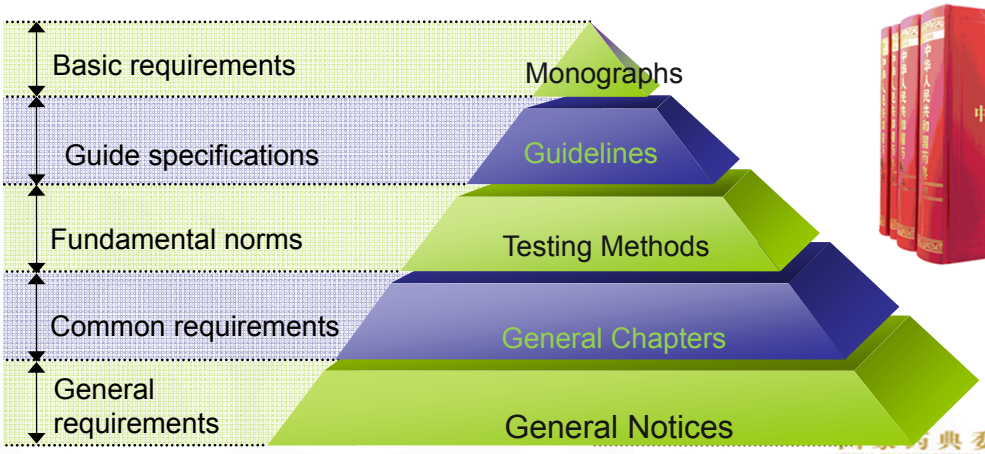
Standards System of Chinese Pharmacopoeia

General Notices and General Chapters of Chinese Pharmacopoeia (ChP) shall have the same effects on drug products specification unlisted in ChP but issued by other competent authority



Compilation Plan of ChP2020 Edition Vol. IV

To establish a scientific, comprehensive, verifiable and enforceable standard system

Planning of drug standard system improvement

Establish and improve standard system of ChP 2020 editon

Improve standard system of ChP
Improve overall quality control level
Strengthen drug standard system with ChP as the core

- Standard system of general requirements for preparation
- Standard System of pharmaceutical excipients
- Standard System of packaging material
- Molecular biological detection technology system
- Analysis and testing technology system

Systematic and normative, gaps filled in, international harmonized, features highlighted

Pharmacopoeia standards and technical information platform

Platform construction already completed

- Construction of standard nucleic acid sequence information service platform
- Construction of standard database of pharmaceutical excipients in various countries
- Pharmaceutical excipient standard information service material information platform
- Establishment of drug standard open database
- Design and planning of the new official website of the Pharmacopoeia
- Design of the World Pharmacopoeia English Website
- Construction of drug standard database

Planning。。。。

- Database of genotoxic impurities
- Safety evaluation database for inhaled pharmaceutical packaging mate
- Test results data analysis service platform
- Identification infrared map database of pharmaceutical excipients and pharmaceutical packaging materials

2018/9/19

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National Standards Excipients and Packaging Materials
- National Drug Safety 13th Five-Year Plan

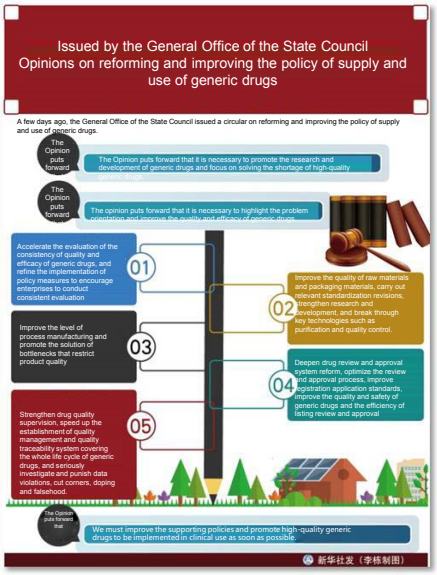
Strengthen supervision of pharmaceutical excipients and packaging materials

- Explore and establish a system for reviewing and approving the examination and approval of pharmaceutical excipients, pharmaceutical packaging materials and pharmaceuticals with key quality risk control as the core and filing management as the means.
- Further clarify the main responsibility of the pharmaceutical production enterprise, supervise and perform the auditing duties on the supplier.
- Carry out extended supervision on manufacturers of pharmaceutical excipients and pharmaceutical packaging materials.
- According to the degree of risk, the pharmaceutical products and pharmaceutical packaging materials are classified and managed to strengthen risk control.
- Improve the standard system of pharmaceutical excipients and pharmaceutical packaging materials.

Related regulations and technical documents on pharmaceutical excipients in China

- Article 4 of the Drug Administration Law: Raw materials, excipients, additives and agricultural inputs used by producers to produce products shall comply with the provisions of laws and administrative regulations and national compulsory standards.
- In June 2004, the "Decision of the State Council on Establishing Administrative Licensing for Administrative Approval Items Needed to Be Reserved" (Order No. 412 of the State Council) clearly reserved the "Registration of Pharmaceutical Excipients" and set it as an administrative licensing project.
- In 2004, SFDA issued a draft for the "Quality Management Regulations for the Production of Pharmaceutical Excipients"
- In 2006, the GMP of Pharmaceutical Excipients was officially promulgated and used as a guiding document, requiring the industry to refer to implement, which is not mandatory.
- On June 21st, 2005, SFDA issued the "Regulations on the Registration of Pharmaceutical Excipients" (provisional documents).
- In September 2005, SFDA issued the "Administrative Measures for Pharmaceutical Excipients" (discussion draft)
- In September 2010, SFDA issued the "Regulations on the Filing of Pharmaceutical Raw and Auxiliary Materials" (draft for comment). In November 2011, it was again publicly solicited for opinions, but it has not been officially released.
- On June 1st, 2012, SFDA issued the "Regulations on Strengthening the Supervision and Management of Pharmaceutical Excipients" (Draft for Comment), which was officially implemented on February 1st, 2013.
- On January 12th, 2016, requirements for the approval of the examination and approval of pharmaceutical packaging materials for medicinal materials (draft for comments)
- On May 12th, 2016, Announcement was issued on the examination and approval of the evaluation of pharmaceutical excipients, pharmaceutical packaging materials and pharmaceuticals (draft for comments)
- On May 12th, 2016, Announcement was issued on the examination and approval of the evaluation of pharmaceutical excipients, pharmaceutical packaging materials and pharmaceuticals (draft for comments)
- **On August 10th, 2016**, the announcement on the association evaluation of pharmaceutical excipients, pharmaceutical packaging materials and pharmaceuticals was officially released
- On May 11th, 2017, Notice of SFDA on Soliciting Opinions on the "Relevant Policies on Encouraging Drug and Medical Device Innovation to Accelerate the Examination and Approval of New Drugs for Medical Device Listing" (draft for comment) (No. 52, 2017)
- On May 22nd,2017, Interpretation of the related review policy for pharmaceutical packaging materials (1)
- On November 30th, 2017, Notice comments of SFDA on Adjusting the Reviewing and Approval of Raw Material Medicines, Pharmaceutical Excipients and Pharmaceutical Packaging Materials (No. 146 of 2017)
- On March 14th, 2018, Announcement on publicly soliciting on matters relating to the import and customs clearance of raw and auxiliary materials (draft for comments)
- On June 5th, 2018, Comments on the Public Solicitation of "Requirements for Registration of Pharmaceutical Excipients" (draft for comment) and Requirements for Registration of Pharmaceutical Packaging Materials (draft for comment)
- On July 19th, 2018, The API, excipients, packaging materials registration system is online (CDE)

Pharmaceutical excipients and pharmaceutical packaging materials play an increasingly prominent role in preparations



- ✓ Most of the pharmaceutical production of excipients, pharmaceutical packaging materials are of source confusion
- ✓ The registration of pharmaceutical excipients and medicines is subject to multiple management, and the use of pharmaceutical excipients and materials is highly dependent on the registration and approval results of the drug regulatory authorities.
- ✓ The responsibility subject is unclear
- ✓ A comprehensive and dynamic related association of pharmaceutical excipients and drug packaging materials has not been established.

Concepts change of standard proposed by general notices in ChP

Verification of analytical methods

- The suitability of the method shall be verified when the method is prescribed by pharmacopoeia

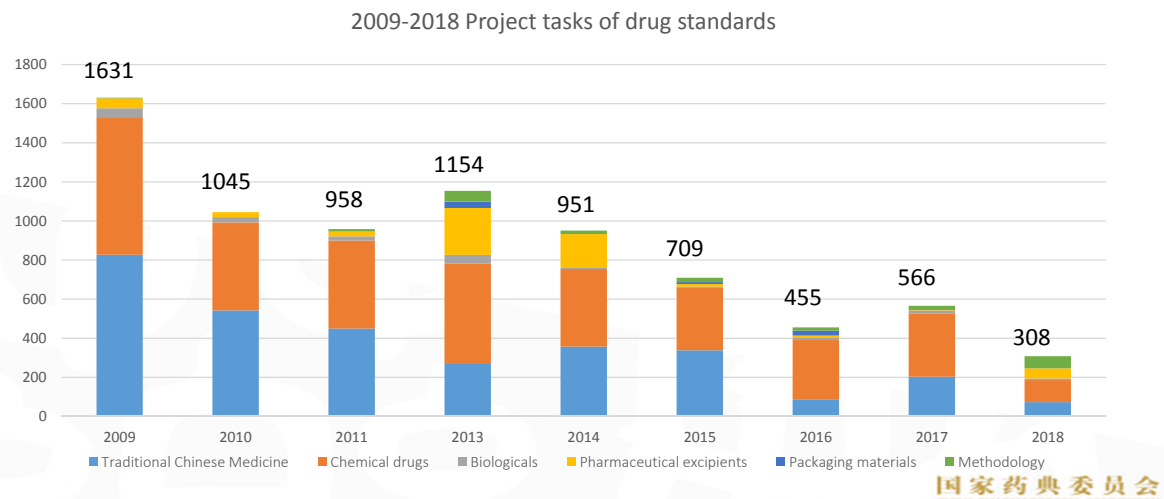
Suitability of excipients

- Administration route
- use of the drug preparation, composition,
- dosage,
- applicable population
- Safety, stability, risk level

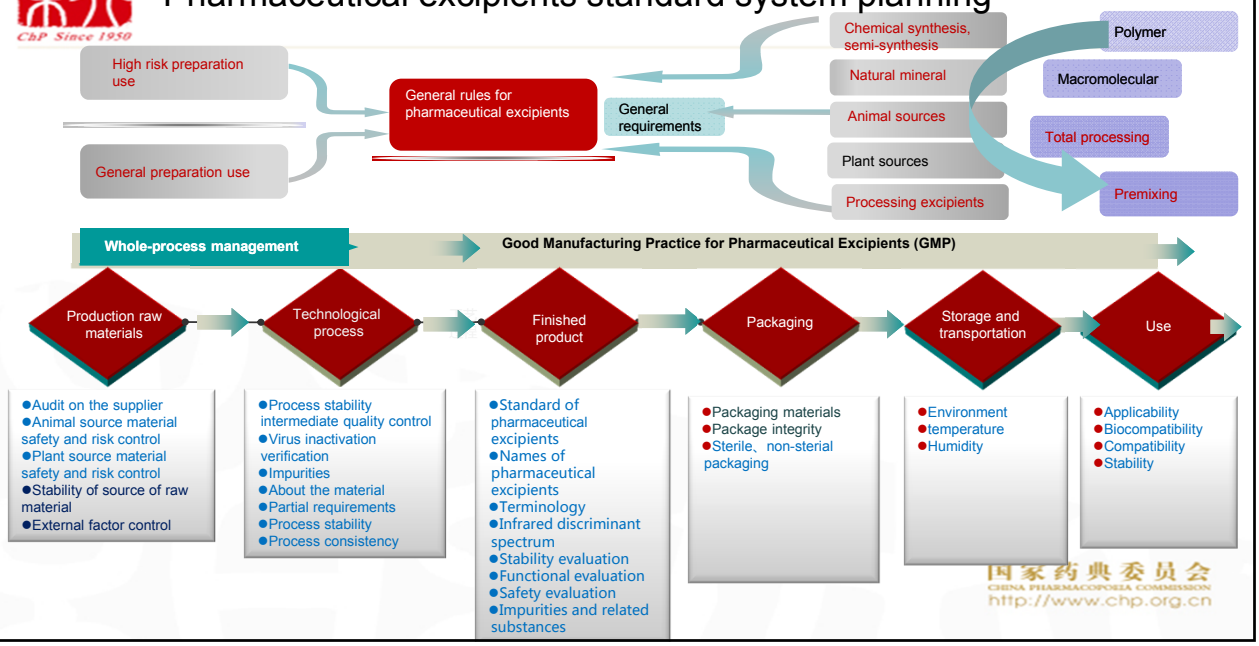
Suitability of packaging material

- Nature of the packaging material, composition, use of drug preparation, features of drug preparation
- Safety, stability, risk level

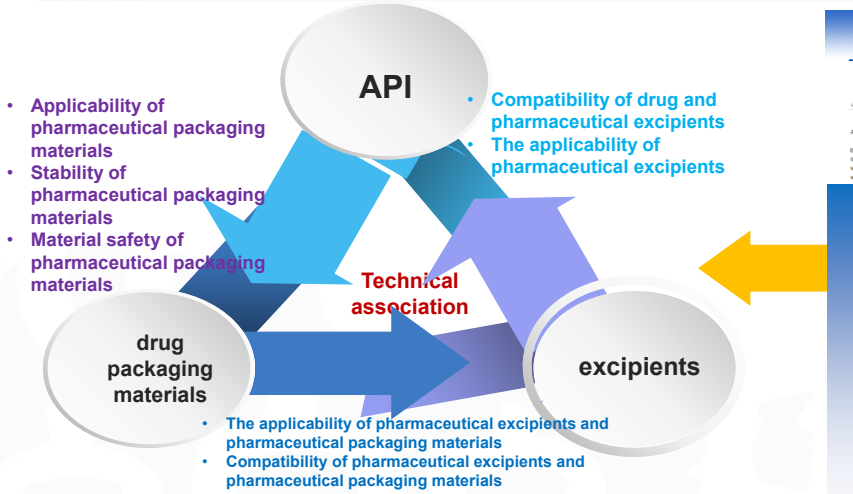
Project establishment of pharmaceutical excipients standards



Pharmaceutical excipients standard system planning



Technical system for joint quality evaluation of pharmaceutical excipients and packaging materials and preparations



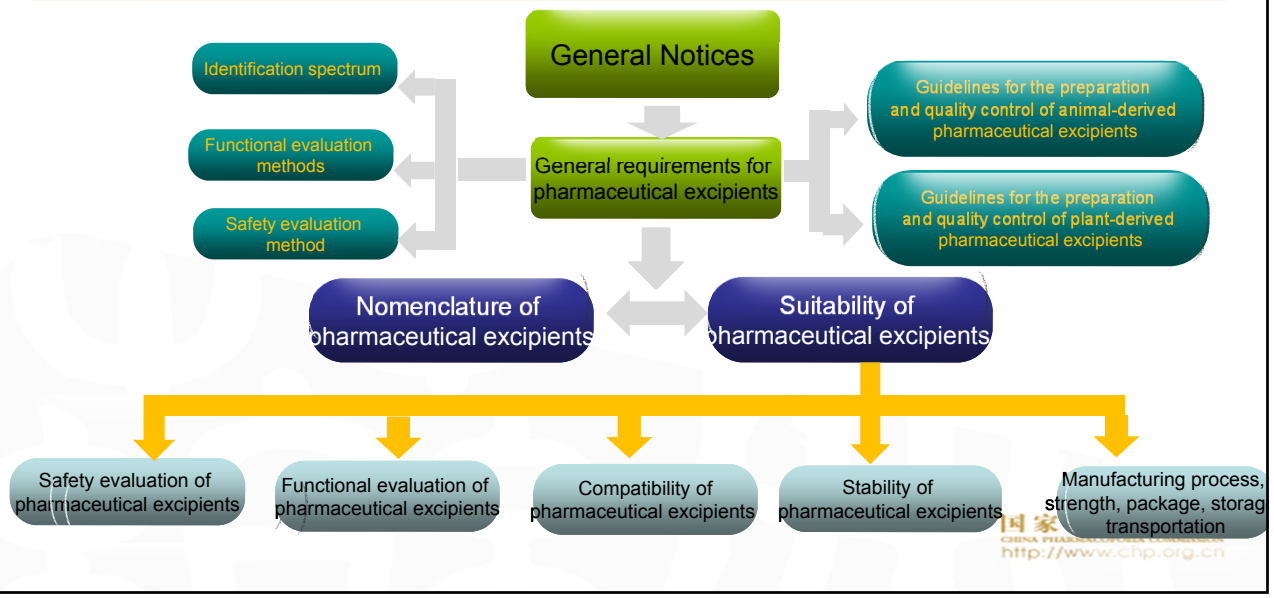
Key Work of National Pharmacopoeia Commission

- Establish and improve the standard system for pharmaceutical excipients
- Comprehensively regulate the source and process control requirements of pharmaceutical excipients
- Strengthen the safety control requirements of excipients
- Production, packaging, storage, transportation management specifications

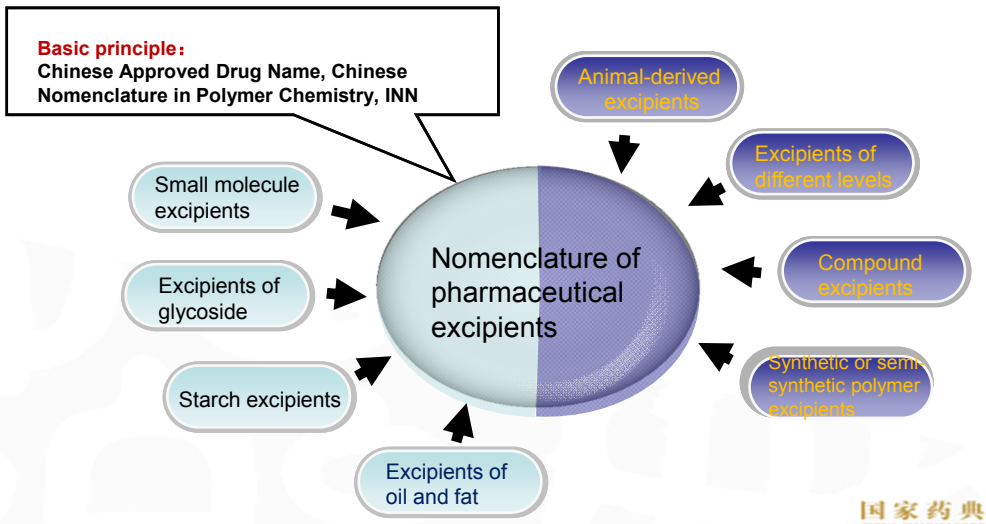
2018

- ✓ The quality control system of pharmaceutical excipients and pharmaceutical packaging materials was established to ensure the quality of final products
- ✓ Provide standard technical support to the implementation of the related review and approval system

Framework of standard system of pharmaceutical excipients in ChP



Nomenclature of pharmaceutical excipients (public)



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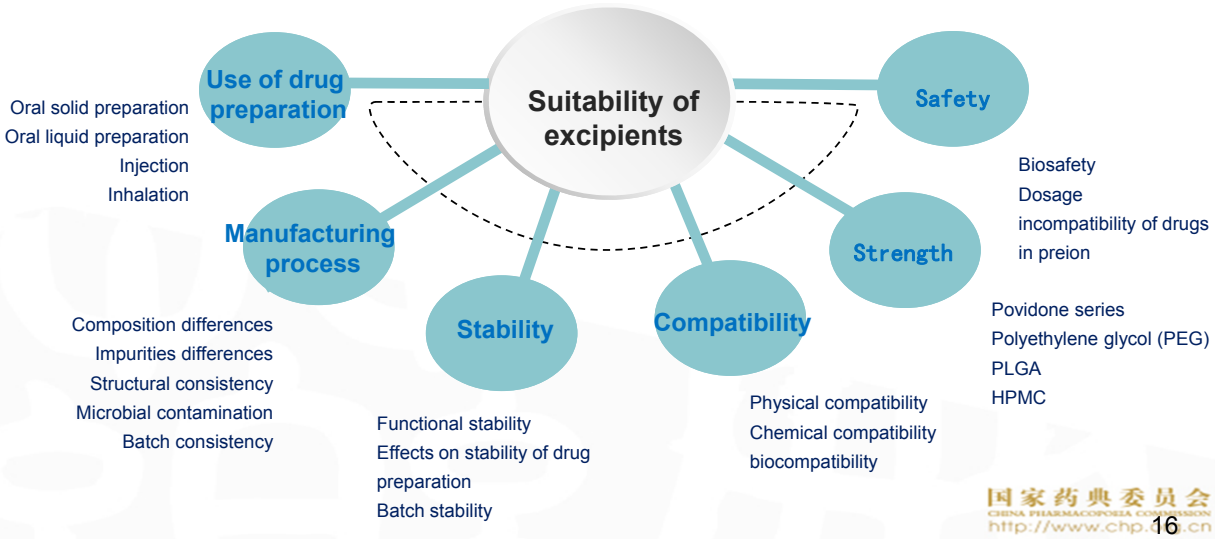
Guideline draft for suitability of excipients (drafted)



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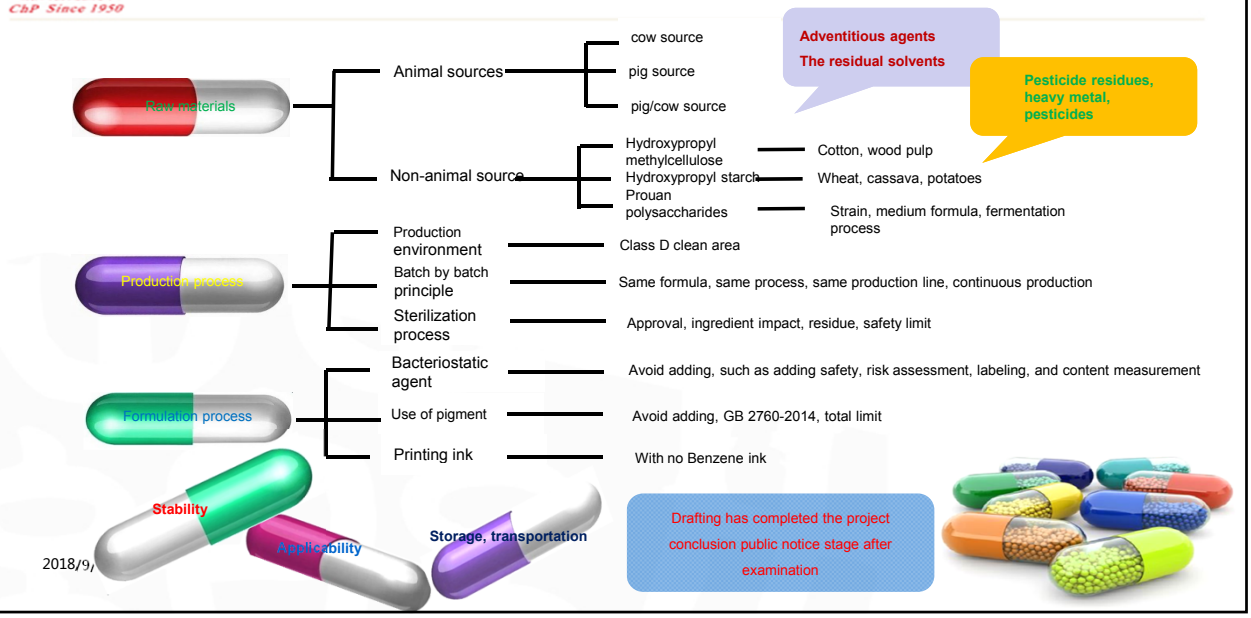
Finished the draft on general charpter of hollow capsules



Animal source materials and accessories contained in the ChP 2015 edition

Serial No.	Species	Source	Serial No.	Species	Source
1	Taurine	Separated from bezoar; Terrestrial mammals have higher levels of liver and bile; marine animals such as cuttlefish, octopus, fish, and shellfish such as oysters and clams	11	shellac	Animal-derived fatty resin
2	Lanolin-free lanolin	Wool	12	Sodium caseinate	Cow, sheep
3	shellac	Animal-derived fatty resin	13	Sulfuric acid fish egg	Fish
4	Egg yolk lecithin	Egg	14	Lactose for inhalation	Animal milk
5	Cetyl	Whale	15	Heparin sodium	Pig
6	Egg yolk lecithin (for injection)	Wool	16	glycerin	Natural animal and vegetable fat refining
7	Cholic acid, sodium cholate	Pig bile	17	Lactic acid	Fermentation
8	cholesterol	Fresh animal offal, bone marrow and brain, wool grease	18	Capsule gelatin	Bovine bone, pork bone
9	Squalane	Shark liver (botanical)	19	Squalane	Shark liver (botanical)
10	Bovine serum	Fetal calf, newborn calf	20	Human albumin	Human plasma

General rules for the production and preparation of pharmaceutical excipients of animal sources

Starting materials control

- Animal species, population health status
- Feeding facilities and environment, pathogen monitoring
- Organ extraction, collection, storage and transportation
- Screening before putting into production
- Exogenous factor screening
- Strengthen auditing of suppliers

Technical process control

- Process validation, stability, batch-to-batch consistency
- Determine process parameters and process effects
- Strengthen the inspection of exogenous factors pollution of intermediate products
- Production process trend analysis
- Good Manufacturing Practice (GMP) for Excipients
- Prevention and control of pollution, external pollution factors

Virus inactivation process

- Virus inactivation verification
- Evaluation of virus inactivation effect
- Establishment of evaluation method for virus inactivation effect
- The effect of virus elimination process on ingredients

Test method

- Method validation
- Applicability
- Sensitivity
- Specificity
- Comprehensive evaluation

Composition control

- Impurities, residual substances, residual reagents
- Prohibition of addition of toxic and hazardous substances
- Control of risky substances
- Safety limit

Stability control

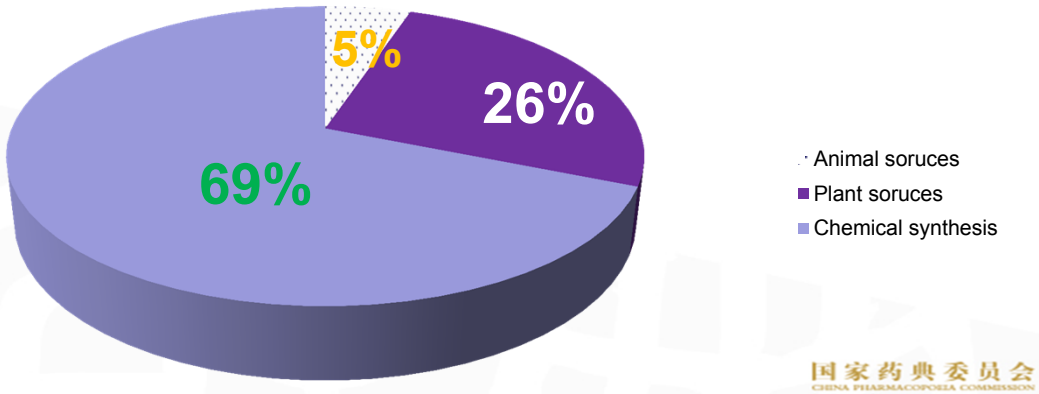
- Packaging, storage, transportation
- Use period
- Possible impact assessment during use
- Batch stability and consistency

Variety and use of plant-derived pharmaceutical excipients contained in the ChP 2015 edition

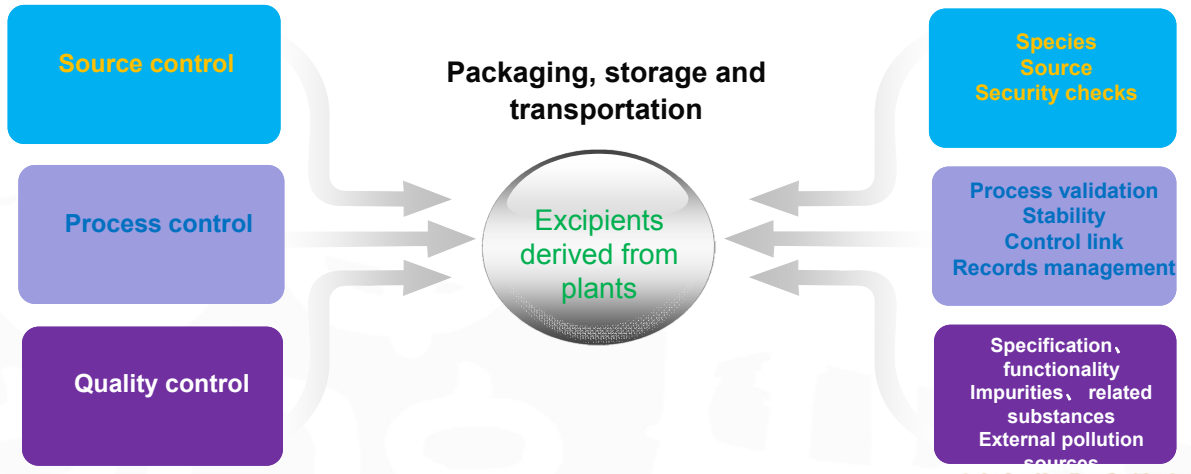
Serial No.	Species	Use	Serial No.	Species	Use	Serial No.	Use	Serial No.	Species	Use	Serial No.
1	Ethyl cellulose	Coating material, release retarder	17	Xylitol	Sweetener	33	Alginic acid	Alginic acid	49	Sodium oxymethylcellulose	Blocking, coating material
2	Ethyl cellulose aqueous dispersion	Coating material	18	Corn borer	Coating material, release retarder	34	Sodium alginate	Sodium alginate	50	Sodium hydroxymethyl starch	Filling and disintegrating agent
3	Ethyl cellulose aqueous dispersion type B	Coating material, release retarder	19	corn starch	Filling and disintegrating agent	35	Trehalose	Trehalose	51	Polysorbate 80 (for injection)	Solubilization, emulsifier
4	Methylcellulose	Bonding, suspending agent	20	Coco fat	Lubricant, suppository matrix	36	Pregelatinized hydroxypropyl starch	Pregelatinized hydroxypropyl starch	52	sucrose	Flavor, adhesive
5	West yellow gum	Bonding, suspending, emulsifying	21	Compressible sucrose	Dilution, flavoring agent	37	Pregelatinized starch	Pregelatinized starch	53	Sucrose pellet core	Carrier material
6	Clove leaf oil	Bonding, suspending, emulsifying	22	Soluble starch	Dilution, disintegrant	38	Xanthan gum	Xanthan gum	54	Refined corn oil	Solvent, dispersant
7	Clove oil	Corrigent	23	Cross-linked sodium carboxymethyl cellulose	Disintegration, filler	39	Hypromellose phthalate	Hypromellose phthalate	55	olive oil	Solvent, dispersant
8	Eugenol	Corrigent	24	Maltodextrin	Filling, flavoring agent	40	Hydroxyethyl cellulose	Hydroxyethyl cellulose	56	dextrin	Filling, bonding agent
9	Soybean oil	Flavoring agent	25	maltose	Filling, flavoring agent	41	Hydroxypropyl cellulose	Hydroxypropyl cellulose	57	Menthol	Flavor, fragrance
10	Soybean oil (for injection)	Dispersant, solvent	26	Chitosan	Disintegration, thickener	42	Silicified microcrystalline cellulose	Silicified microcrystalline cellulose	58	Sodium starch phosphate	Adhesive
11	Hydrogenated soybean oil	Dispersant, solvent	27	Low substituted hydroxypropyl cellulose	Disintegration, filler	43	Hydroxypropyl cellulose	Hydroxypropyl cellulose	59	Thymol	Bacteriostatic agent
12	Soy lecithin	Lubricating and retarding agent	28	Arabinogalactan	Suspension, adhesive	44	Hydroxypropyl beta cyclodextrin	Hydroxypropyl beta cyclodextrin	60	Carnauba wax	Coating material, retarder
13	Soybean phospholipid (for injection)	Emulsification, solubilization	29	Gum arabic	Suspension, thickener	45	Hydroxypropyl starch hollow capsule	Hydroxypropyl starch hollow capsule	61	Fractal cellulose	Bonding, filling, disintegration
14	wheat starch	Emulsification, solubilization	30	Pectin	Thickening, release retarder	46	Starch hydrolysate	Starch hydrolysate	62	Hydroxymethyl cellulose calcium	Filling and disintegrating agent
15	Potato starch	Dilution, bonding	31	Hydrogenated castor oil		47	Agar	Agar	63	D-xylose	
16	Cassava starch	Filling and disintegrating agent	32	Cyclodextrin	Inclusion, stabilizer	48	Microcrystalline cellulose	Microcrystalline cellulose			

Raw material sources for pharmaceutical excipients production

Proportion of excipients from different sources



Quality control considerations for excipinets derived from plants



Chinese herbal medicine processing excipients

Chinese herbal medicine processing is considered to change the drug effect

- Yellow wine, white wine, vinegar, salt water, refined honey, ginger juice, licorice juice, black bean juice, evodia rutaecarpa juice, sesame oil, rice bran water, radish juice, Chinese honeylocust fruit juice
- Lime water, river sand, talcum powder, sulfur, cinnabar, terra flava usta(focal subsoil)
- Bile, sheep fat, animal blood, cow's milk, wheat bran, rice, white peony, glutinous rice, tofu, pollen typhae

General rules of excipients for processing

Definition:

The excipients for processing Chinese herbal medicines refer to the additional materials added in addition to the main medicine in the process of processing Chinese herbal medicine, which have the effect of supporting the main medicine to achieve the purpose of processing. After excipients are added to the Chinese herbal medicine and processed, they can play a role in alleviating or changing the performance of the drug, reducing or eliminating the toxic side effects of the drug, enhancing the curative effect, flavoring and odor, and introducing the drug into the menstruation.

- Safety
- Controllability
- Raw materials
- Production process
- Home made processing excipients

- Plants, animals
- Stable quality
- Species identification
- Stable process
- Guarantee period

Principles for selection of pharmaceutical excipients

- Excipients have been approved domestically and used in preparations
- Commonly used excipients for domestic marketed preparations
- Foreign imported excipients are widely used in domestic preparations and have a long history of use.
- The national drug regulatory authorities consider it necessary to develop national standards for pharmaceutical excipients.

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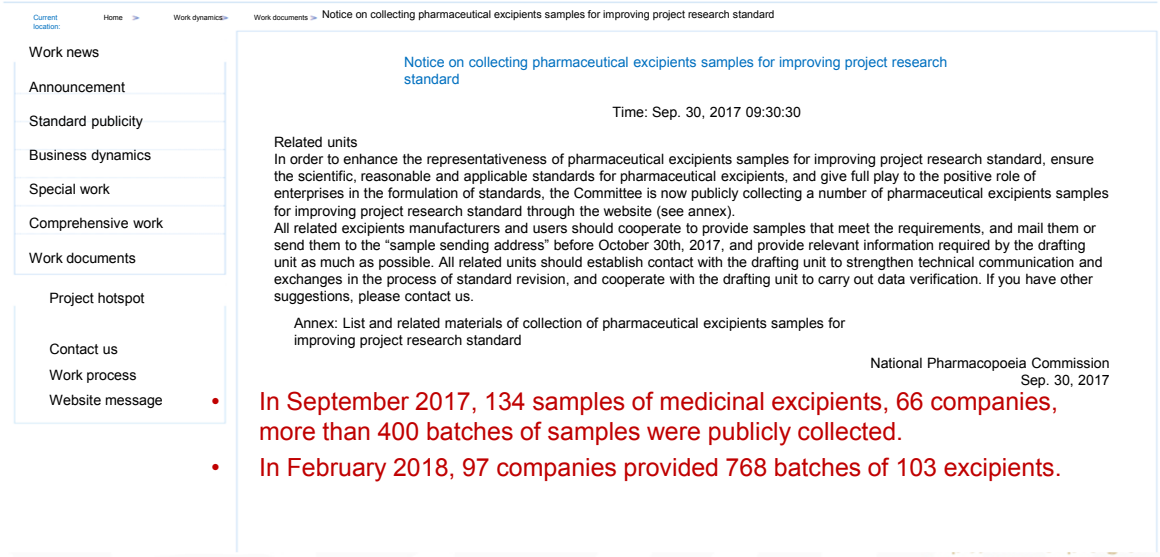
Collection of pharmaceutical excipients samples



Current location: Home > Work dynamics > Work documents > Notice on collecting pharmaceutical excipients samples for improving project research standard

Work news
Announcement
Standard publicity
Business dynamics
Special work
Comprehensive work
Work documents
Project hotspot
Contact us
Work process
Website message

Notice on collecting pharmaceutical excipients samples for improving project research standard

Time: Sep. 30, 2017 09:30:30

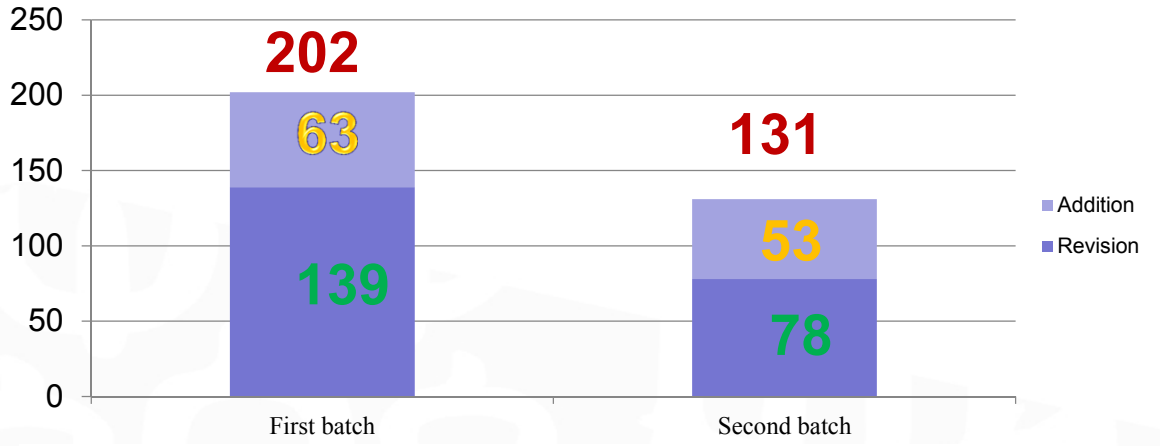
Related units
In order to enhance the representativeness of pharmaceutical excipients samples for improving project research standard, ensure the scientific, reasonable and applicable standards for pharmaceutical excipients, and give full play to the positive role of enterprises in the formulation of standards, the Committee is now publicly collecting a number of pharmaceutical excipients samples for improving project research standard through the website (see annex).
All related excipients manufacturers and users should cooperate to provide samples that meet the requirements, and mail them or send them to the "sample sending address" before October 30th, 2017, and provide relevant information required by the drafting unit as much as possible. All related units should establish contact with the drafting unit to strengthen technical communication and exchanges in the process of standard revision, and cooperate with the drafting unit to carry out data verification. If you have other suggestions, please contact us.

Annex: List and related materials of collection of pharmaceutical excipients samples for improving project research standard

National Pharmacopoeia Commission
Sep. 30, 2017

- In September 2017, 134 samples of medicinal excipients, 66 companies, more than 400 batches of samples were publicly collected.
- In February 2018, 97 companies provided 768 batches of 103 excipients.

The new excipients monograghs developing plan in ChP 2020



The list of new excipinets monogrphs under development have be publiced in the ChP website

Publicity Status of Standard for Pharmaceutic Excipients

Serial No.	Product name	Serial No.	Product name
1	桉油 Eucalyptus Oil	11	磷酸二氢钠一水合物 Sodium Dihydrogen Phosphate monohydrate
2	八角茴香油 Star Anise Oil	12	硫酸钠 Sodium Sulfate
3	扁桃仁油 Almond Oil	13	硫酸钠十水合物 Sodium Sulfate Decahydrate
4	冰片（合成龙脑） Borneolum Syntheticum	14	麦芽糖醇 Maltitol
5	二甲基甲酰胺 Dimethylformamide	15	松节油 Turpeniine Oil
6	肌醇 Inositol	16	无水磷酸二氢钠 Anhydrous Sodium Dihydrogen Phosphate
7	聚苯乙烯磺酸钠 Sodium Polystyrene Sulfonate	17	香草醛 Vanillin
8	聚葡萄糖 Polydextrose	18	油酸聚烃氧（5~6）酯 PolyoxylOleate(5~6)
9	可可脂 Cocoa Butter	19	油酸聚烃氧（10）酯 PolyoxylOleate(10)
10	磷酸二氢钠二水合物 Sodium Dihydrogen Phosphate dihydrate	20	月桂酸 lauricacid

Expanded verification time: 2017-9-15; Standard publicity time: 2017-11-5

Publicity Status of Standard for Pharmaceutic Excipients

Serial No.	Product name	Time	Serial No.	Product name	Time	SerialNo.	Product name	Time
1	冰片(合成龙脑) Borneolum Syntheticum	2018-2-2	12	肉豆蔻醇 Myristyl alcohol	2018-4-8	23	椰 子 油 **Coconut Oil**	2018-4-8
2	丙烷 Propane	2018-2-2	13	肉豆蔻酸 Myristic Acid	2018-4-8	24	硬脂酸钙 **Calcium Stearate**	2018-4-8
3	氮气 Nitrogen	2018-2-2	14	肉豆蔻酸甲酯 **Methyl Myristate**	2018-4-8	25	硬脂酸铝 Aluminium Stearate	2018-4-8
4	丁烷 Butane	2018-2-2	15	肉豆蔻酸异丙酯 Isopropyl Myristate	2018-4-8	26	硬脂酸钠 Sodium Stearate	2018-4-8
5	二甲醚 Dimethyl Ether	2018-2-2	16	肉豆蔻油 **Nutmeg Oil**	2018-4-8	27	月桂醇 Lauryl Alcohol	2018-4-8
6	异丁烷 Isobutane	2018-2-2	17	糖二酸钙 **Calcium Saccharate**	2018-4-8	28	月桂油 Laurel oil	2018-4-8
7	白陶土 Kaolin	2018-4-8	18	甜菊素 **Steviosin**	2018-4-8	29	棕 榈 酸 **Palmitic Acid**	2018-4-8
8	对氯苯酚 Parachlorophenol	2018-4-8	19	脱氢醋酸 Dehydroacetic Acid	2018-4-8	30	棕榈核油 Palm Kernel Oil	2018-4-8
9	伽马环糊精 **Gamma Cyclodextrin**	2018-4-8	20	脱氢醋酸钠 Sodium Dehydroacetate	2018-4-8	31	N-甲基-吡咯烷酮 **Methylpyrrolidone**	2018-4-8
10	己 二 酸 **AdipicAcid**	2018-4-8	21	小茴香油 **Bitter-Fennel Fruit Oil**	2018-4-8			
11	玫瑰油 **Rose Oil**	2018-4-8	22	柠檬油 **LemonOil**	2018-4-8			

Publicity Status of Standard for Pharmaceutic Excipients

Serial No.	Product name	Time	Serial No.	Product name	Time	Serial No.	Product name	Time
1	右旋糖酐 20 **Dextran 20**	2018-4-27		四氟乙烷（外用气雾剂） **Tetrafluoroetnone**	2018-4-27		维生素 Vitamin C	2018-7-3
2	右旋糖酐 40 **Dextran 40**	2018-4-27		七氟丙烷（外用气雾剂） **Heptafluoropropane**	2018-4-27		薄荷素油 Peppermin Oil	2018-7-3
3	瓜尔胶 **Guar Gum**	2018-4-27		甜菊素 **Steviosin**	2018-8-13		酪蛋白酸钠 Sodium Caseinate	2018-7-3
4	卡拉胶 **Carrageenan**	2018-4-27		花生油 **Peanut Oil**	2018-8-13		维生素 Vitamin C	2018-7-3
5	松香 **Rosin**	2018-4-27		棕榈酸 **Palmitic Acid**	2018-8-13		薄荷素油 Peppermin Oil	2018-7-3
6	盐酸半胱氨酸 **Cysteine Hydrochloride**	2018-4-27		肉豆蔻酸异丙酯 Isopropyl Myristate	2018-8-13		酪蛋白酸钠 Sodium Caseinate	2018-7-3
7	桉油 **Eucalyptus Oil**	2018-4-27		磷酸二氢钠二水合物 **Sodium Dihydrogen Phosphate dihydrate**	2018-7-20		盐酸氯己定 **Chlorhexidine Dihydrochloride**	2018-7-3
8	乳酸 **Lactic Acid**	2018-4-27		磷酸二氢钠一水合物 **Sodium Dihydrogen Phosphate monohydrate**	2018-7-20			
9	甘露醇 **Mannitol**	2018-4-27		无水磷酸二氢钠 **Anhydrous Sodium Dihydrogen Phosphate**	2018-7-20			
10	山梨醇 **Sorbitol**	2018-4-27						

Establishment of standard database for pharmaceutic adjuvant

Challenge

- Industry level is not high
- Weak research base
- Lack exchange of supply and demand information
- Management model needs to be changed
- Establish evaluation criteria
- Product intrinsic quality
- Set up the testing method
- 。。。。

Problems with standards development

- Variety (what the industry needs)
- Sample (what industry uses)
- Project (what is the industry concerned about)
- Limits (what industry does)
- Process (what is used in the industry)
- Source (what industry uses)
- Specification (what does the enterprise need)

Next steps…..

- ✓ Clarify positioning, make up the short board, fill the blank, strengthen the association
- ✓ Strengthen the establishment of the drug standard system
- ✓ It is suggested to review and approve the standard system by using associated evaluation
- ✓ Perfect the test method establishment, method transformation, test result analysis and evaluation platform
- ✓ Improve the establishment of digital drug standards
- ✓ Perfect the establishment of drug standards and resource database

Summary

- Material safety control
- Identification of production materials
- Formulation process control
- Specification of detection method
- Establishment of test items
- Establishment the whole process, life-cycle control system
- Establishment of considerations, strategies, and methods for the study of associations with preparations
- Establishment the whole process, life-cycle control system
- Strengthen the general chapter draft on the compability, suitibility and stablity of the excipients

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Thank you for your attention