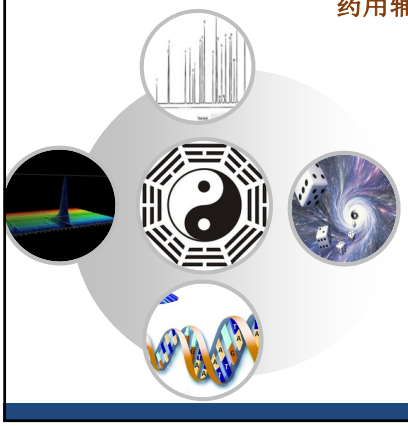
Risks, classifying management and technical requirements for pharmaceutical excipients

药用辅料的风险、分级管理和技术要求



National Institutes for Food and Drug Control (NIFDC), CFDA
中国食品药品检定研究院
Institute for Packaging Materials and Pharmaceutical Excipients Control
包装材料与药用辅料检定所
Director & Professor, Huimin Sun
孙会敏

Sep.18, 2018 France, EDQM

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About NIFDC

- NIFDC was founded in 1950.It is a subordinate agency of China Food and Drug Administration(CFDA) and there are 29 Internal institutions within NIFDC.
- Currently, there are more than 1326 employees, around 50% employees with higher education background of Master or PhD degree, 70 experts entitled to take the Government Special Allowance.
- There are more than 13754 modern testing instruments and equipment in NIFDC.

In September 2015, NIDFC moved to new site with the area of 100,383 square meters.

But some institutes are still on the old site, including the Institute for Packaging Materials and Pharmaceutical Excipients Control (my institute).

Missions

1. To undertake relevant registration testing of drug and medical devices and technical evaluation, and for the testing of healthy food, cosmetics apply for approving, and for the testing and specification evaluation of imported drugs.

药品、医疗器械的注册审批检验及其技术复核，保健食品、 化妆品审批所需的检验检测，进口药品注册检验及其质量标准复核

2. To carry out the post market surveillance testing, contract testing, sampling testing, and safety evaluation of drug, medical devices, healthy food, cosmetics, and restaurant food, and responsible for the drug testing at port of entry. 监督检验、委托检验、抽查检验以及安全性评价检验检测，药品进口口岸检验

3. To organize the Re-testing and technical evaluation of drug and medical devices 复验及技术检定

4. Be responsible for the lot release of biological products. 生物制品批签发

5. To undertake the technical review and verification of the specification, guidelines and testing procedures regarding with drug, medical devices and restaurant food.

药品、医疗器械和餐饮服务食品安全相关标准、技术规范及要求、检测方法制修订的技术复核与验证，保健食品、化妆品技术规范、技术要求及检测方法的制修订

6. To carry out the registration testing, post market surveillance testing, contract testing, sampling testing, and re-testing of pharmaceutical excipients, primary packaging materials and container. And be responsible for the technical review and verification of specification of pharmaceutical excipients and packaging materials.

药用辅料、直接接触药品的包装材料及容器的注册检验、监督检验、委托检验、复验及技术检定，相关国家标准制修订的技术复核与验证

7. To take charge of research, development, testing, distribution and administration of the National Reference Standards of drug and medical devices. 国家标准物质研究、制备、标定、分发和管理

8. To take charge of the testing of bacterial (viral) strains, take charge of collection, identification, preservation, distribution and management of medical standard bacterial (viral) strains and cell strains. 生产用菌毒种、细胞株的检定，医用标准菌毒种、细胞株的收集、鉴定、保存、分发和管理

Missions

9. To take charge of the preservation, breeding and supplying of experimental animals and the quality control of experimental animals.
实验动物质量检测和实验动物保种、育种和供种

10. To take charge of the technical supervision of advertisements regarding drugs, medical devices and healthy products and internet information related with drugs.
药品、医疗器械和保健食品广告以及互联网药品信息服务的技术监督

11. Be responsible for providing technical assistance and guidance regarding laboratory testing technology for the food and drug quality control institutes nationwide; also be responsible for organizing the activities to provide technical assistance to the scientists within the drug quality control institute around the nation.
全国食品药品监管系统检验检测机构的业务指导、规划和统计，药品研究、生产、经营相关单位以及医疗机构中的药品检验检测机构及人员的业务指导

12. To organize the specification research and new method/technology research regarding the drug, medical devices, healthy food, cosmetics and restaurant food.
药品、医疗器械、保健食品、化妆品和餐饮服务食品安全相关标准研究以及安全监测和质量控制新方法、新技术研究

13. Be responsible for the technical administrative affair of China Food and Drug Administration (CFDA), be responsible for the routine work of the experts committees related with healthy food, cosmetics, and restaurant food safety.
国家药品监督管理局科技管理日常工作，保健食品、化妆品和餐饮服务食品安全相关专家委员会的日常工作

14. Be responsible for the research and lab investigation of the server side effect (ADR) regard with drug and medical devices.
承担严重药品不良反应或事件以及医疗器械不良事件原因的实验研究

15. To organize the international collaboration and cooperation in the field of testing and analysis of drug, medical devices, healthy food, cosmetics, and restaurant food safety.
药品、医疗器械、保健食品、化妆品和餐饮服务食品安全相关检验检测工作的国际交流与合作

16. Undertake others tasks assigned by CFDA.
国家药品监督管理局交办的其他事项

Organization Structure

14 Institutes

- Institute for Food Control
- Institute for Cosmetics Control
- Institute of Chemical Drug Control
- Institute for Biological Product Control
- Institute for Medical Devices Control
- Institute for Control of Chinese Traditional Medicine and Ethnic Medicine
- **Institute for Control of Packaging Material and Pharmaceutical Excipients**
- Institute for Laboratory Animal Resources
- Institute for Reference Standard and Standardization
- Institute for Food and Drug Safety Evaluation
- Institute for In Vitro Diagnostic Reagents
- Institute for Medical Device Standardization Administration, NIFDC
- Food and Drug Technical Supervision Center
- Generic Drugs Quality Research Center

15 Administration departments (……)

Missions of Institute for Control of Packaging Material and Pharmaceutical Excipients

- To carry out the registration testing, post market surveillance testing, contract testing, imported testing, and re-testing of packaging materials and pharmaceutical excipients related with drugs.
- Be responsible for the National Standard and technical review and verification of specification of excipients and packaging materials and container.
- To take charge of researching and Standardisation of Reference Substances of excipients, packaging materials and container.
- To organize testing, quality control, new method/technology research and compatibility testing regarding excipients, packaging materials and container.
- Undertake others tasks assigned by CFDA.

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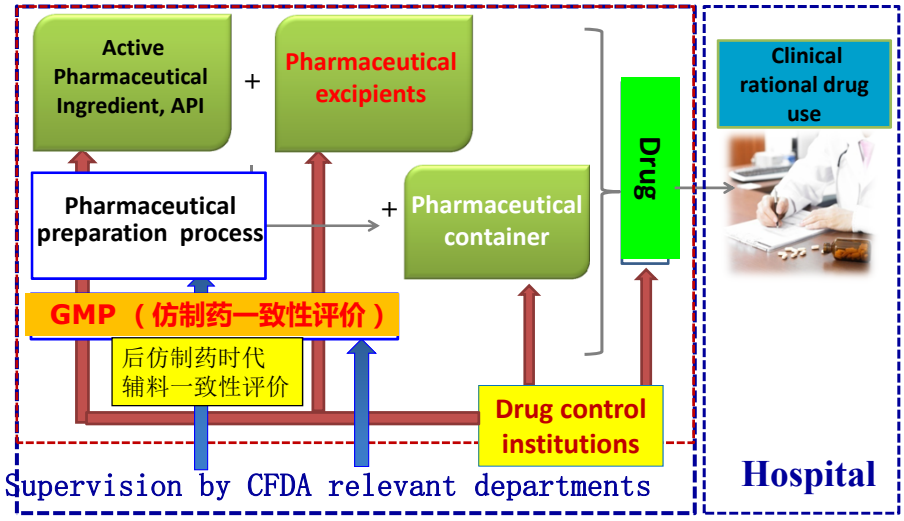
Background of pharmaceutical excipients
药用辅料的背景情况

Pharmaceutical excipients



Pharmaceutical excipients are important material foundations for ensuring the production, development and application of pharmaceutical preparations.

Definition of pharmaceutical excipients
药用辅料的定义

药用辅料 惰性 (Inert)/ 活性 (Active)/风险(Risk)?
药辅同源：甘露醇，乙醇，卵磷脂

Drug Administration Law, CFDA

The excipients and additives used in the drugs and preparations.
辅料指生产药品和调配处方时所用的赋形剂和附加剂

Ch.P 2015 edition

The excipients and additives used in the drugs and preparations, which has been evaluated in terms of safety in addition to the active ingredient or the precursor, and is contained in the pharmaceutical preparation.
药用辅料系指生产药品和调配处方时使用赋形剂和附加剂，是除活性成分或前体以外，在安全性方面已进行了合理评价，并且包含在药物制剂中的物质。

FDA

Inactive ingredients other than API in the preparation.
制剂中除主药(API)以外的非活性成分

IPEC (国际辅料协会)

Excipients play a critical role in the manufacture of medicines by helping to preserve the efficacy, safety, and stability of active pharmaceutical ingredients (APIs), and helping to ensure that they deliver their promised benefits to patients. Optimal use of excipients provides pharmaceutical manufacturers with drug development cost-savings, enhanced functionality capability and can also assist in drug formulation innovation.

EP/《欧洲药典》

Any constituent of a medicinal product that is not an active substance. Adjuvants, stabilisers, Antimicrobial preservatives, diluents, antioxidants are excipients.
除活性成分外，药物产品的其它构成成分。例如：辅助剂、稳定剂、防腐剂、抗氧化剂等均属于赋形剂。

JP/《日本药局方》

Pharmaceutical excipients are substances other than active substances contained in preparations, and they are used to increase the utility of the active substance(s) and preparation, to make formulation process easier, to keep the product quality, to improve the usability, and so forth.

Homology of medicine and pharmaceutical excipients
药辅同源

Name	API	Pharmaceutical excipients
VE (for injection)	Improve Blood Circulation, Anti-aging, etc 改善血液循环、抗衰老等	Anti-oxygen 抗氧剂
VC (for injection)	Reduce the incidence of cancer, etc. 降低癌症发病等	Anti-oxygen 抗氧剂
Mannitol (for injection)	Diuretic, dehydrant, etc. 利尿剂、脱水药等	Solubilizer, flavoring agents, disintegrating agent, etc. 增溶剂、矫味剂、崩解剂等
Ethanol (for injection)	Sterilize 消毒	Solvent, sanitizer, etc. 溶剂；消毒剂
Sorbitol (for injection)	Treat encephaledema and glaucoma 治疗脑水肿及青光眼	Plasticizer, emulgator, filling agent 增塑剂；乳化剂；填充剂
Lecithin (for injection)	Protect liver, Anti-aging, etc. 保护肝脏、延缓衰老等	Emulgator, solubilizer, stabilizer, etc. 乳化剂；增溶剂；稳定剂等

Pharmacological effect 药理作用

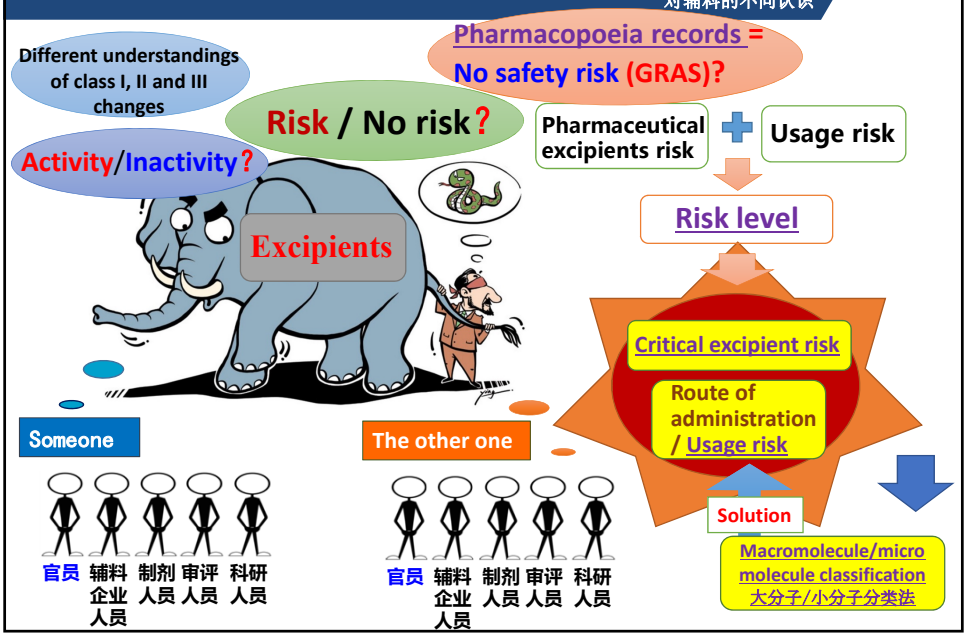
指药物与机体细胞间的作用机制，是分子反应机制，有其特异性，是机体对药物反应的表现。是药物分类的依据，**又是临床用药时指导用药和拟定治疗剂量的依据。** 1

Interaction

Toxic effect 毒性作用

是指药物引起身体较重功能紊乱和组织病理变化，一般是由于病人的个体差异，病理状态或合用其它药物引起敏感性增加而引起的。**用药剂量>治疗剂量时，易产生毒性作用。** 2

Different understanding of pharmaceutical excipients
对辅料的不同认识



Polyethylene glycol (PEG)

Sergio Canavero used PEG(聚乙二醇) as adhesive (粘合剂) in human head trans plantation (换头术). It has been reported that PEG can promote nerve growth in spi nal cord in animal experiments. (PEG在动物实验中,有促使脊髓的神经生长的作用)

Polyethylene glycol (PEG)

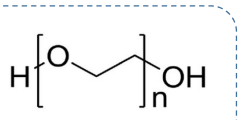
- **PEG**，是由环氧乙烷与水或乙二醇逐步加成制得，根据分子量不同可以分为PEG300、PEG400、PEG600、PEG1000、PEG1500、PEG6000等。

Liquid → **Solid**

PEG300、PEG400、PEG600、PEG1000、PEG1500、PEG6000

➢ Characteristics of PEG

- 广泛的溶解范围
- 兼容性
- 成膜性
- 增塑性
- 分散性
- 不挥发性
- 生理惰性
- 润滑性



PEG Chemical formula

➢ Usage of PEG

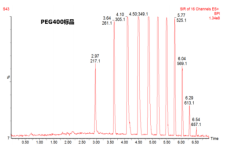
- **Biomedical (生物医学领域)**：促细胞融合、医用高分子材料表面改性剂、牙科固定剂
- **Food additives (食品添加剂)**：被膜剂
- **Pharmaceutical and Cosmetic (制药和化妆品领域)**：软化剂、保湿剂、润滑剂、软膏基质、粘合剂、药物载体、稳定剂和增塑剂与致孔剂。
- **Low molecular weight PEG (低分子量)：是水溶性药物和一些有机药物良好的溶剂**

PEG400 measured by UPCC-MS

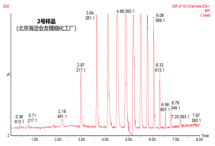
UPCC-MS

Content limit set-up of polymerization degree distribution by UPCC-MS

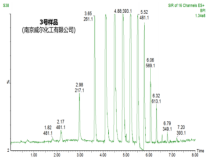
Polymerization (n)	Content limit
≤4	≤5%
5≤n≤12	≥90%
13≤n≤18	≤5%



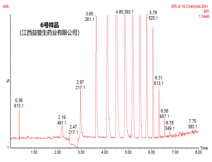
PEG400 Standard



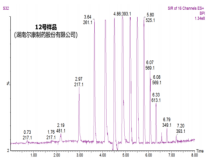
Sample 1



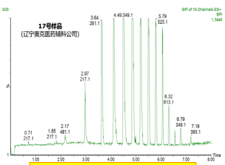
Sample 2



Sample 3



Sample 4

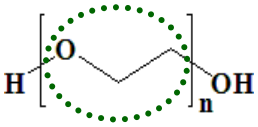


Sample 5

UPCC-MS spectra of PEG400 from different manufacturers

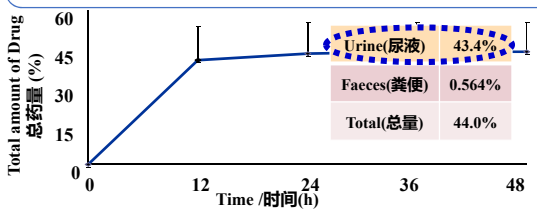
- **Relative deviations of average molecular weights of PEG400 samples were all less than 4.0%**
- **Degree of polymerization of PEG400 and its distribution can be accurately measured by UPCC-MS**

Polyethylene glycol (PEG)



- PEG polymers
  - compound of repeating units of ethylene glycol,
  - is generally considered biologically inert and safe in humans.
- PEGylation of drugs
  - is extensively used to improve their PK properties
  - increase therapeutic efficiency
  - diminish the potential for immunogenicity and toxicity.
- lead to significant PEG accumulation in tissues
  - with chronic administration
  - potentially result in adverse effects.

➢ LC-MS/MS based on MRM scanning mode has excellent performance in quantitative analysis
➢ Gold standard for analysis of limited and definite drugs



The cumulative excretion of PEG4000 after intravenous administration accounted for the percentage of the dose.

◎ The drug(MW > 400Da) usually excreted by bile.
◎ Interesting, PEG-4k excrete mainly by renal excretion.
◎ PEG may be a flexible molecular.
◎ PEG can excrete through kidney.

源于顾景凯老师ppt

Anal. Chem. 2017, 89, 5193-5200----SCI 6.32

Risk level of pharmaceutical excipients

药用辅料风险关注度

- Risks of pharmaceutical excipients themselves and risks of their use should be considered together.

把辅料本身风险级别和使用风险合并一起考虑才可有效地确定辅料的风险高低，确定其关注度。

Risk level: High, Medium, Low

Risk level	High risk of their use	Medium risk of their use	Low risk of their use
High risk of excipients	**High risk** (Excipients for injection from animals/Lactose 动物来源的注射用辅料/乳糖)	**High risk**	Medium risk
Medium risk of excipients	**High risk**	Medium risk	Low risk
Low risk of excipients	Medium risk	Low risk	**Low risk** (GRAS/Common use, Oral, Less dosage)

(Characteristics: Oral solid preparations, low dosage, low safety risk)

十一、2016年第134号公告附件1中规定的不纳入关联审评审批的药用辅料有哪些？

（一）矫味剂（甜味剂）：如[糖]、木糖醇、麦芽糖醇等。该类品[种]

（二）香精、香料：如桔子香[精]准 食品添加剂使用标准》、GB 306[0]则》等相关要求。

（三）色素（着色剂）：如氧[化]家标准 食品添加剂使用标准》等相[关]

（四）pH调节剂（包括注射剂[中]石酸、氢氧化钠、浓氨溶液、盐酸、硫酸、磷酸、乳酸、磷酸二氢钾、磷酸氢二钾、磷酸氢二钠、磷酸二氢钠等。

（五）仅作为辅料使用、制备工艺简单、理化性质稳定的无机盐类（包括注射剂中使用的无机盐类）：如碳酸钙、碳酸钠、氯化钾、氯化钙、氯化镁、磷酸钙、磷酸氢钙、硫酸钙、碳酸氢钠等。

（六）口服制剂印字使用的无苯油墨。

上述药用辅料，现行版《中国药典》已收载的，应符合现行版《中国药典》要求；现行版《中国药典》未收载的，应符合国家食品标准或现行版USP/NF、EP、BP、JP药典标准要求；其他辅料，应符合药用要求。

药品注册申请人在药品注册申请时，应至少在药品注册申报资料中提供药用辅料的生产企业信息、产品基本信息、生产工艺信息、产品质量标准、检验报告书等相关资料。上述辅料完成关联审评后不核发核准编号。

食品药品监管总局将根据工作需要对不纳入关联审评审批范围的药用辅料进行调整和完善。

- This is from Announcement on Associated Review and Approval of Pharmaceutical Packaging Materials and Pharmaceutical Excipients with Drugs ([2016] No.134).
- In this slide, some **sweetening agent, flavors, colorant, pH adjusters** and **other pharmaceutical excipients used in preparations** that may not be reviewed and approved according to the requirements of Announcement No.134, **because of their usage and characteristics**.

FDA——DMF

What is critical excipients?
It is dependent on their characteristics, functions, usages and dosage.

Pharmaceutical excipients/Packaging Material Manufacturers provide DMF application
辅料/药包材生产企业提交DMF申请

FDA accept and carry out formal examination
FDA接受申请，进行基本的形式审查

Approve: receive DMF number
审查合格：发给DMF号

Disapprove: return, tell the reason
审查不合格：退回，告知原因

DMF holder send Authorized value
DMF持有者发出授权值

Drug Manufacturers provide IND, NDA, ANDA applications
药品生产企业提交IND、NDA、ANDA申请

Update/Charge Activate DMF
更新/收费
激活DMF

Associated reviewed by CDER
CDER进行关联性审评

Proposed Pharmaceutical excipients /Packaging Material defect with preparations
与制剂一起提出辅料/药包材缺陷

TYPES OF DMFs

The types of DMFs are:

- **Type II Drug Substance, Drug Substance Intermediate and Material Used in Their Preparation, or Drug Product**
  II类 药物，药物中间体、制剂中使用的关键辅料或者药品
- **Type III Packaging Material**
  III类 药包材
- **Type IV Excipient, Colorant, Flavor, Essence, or Material Used in Their Preparation**
  IV类 辅料，色素、香料，制剂中使用的辅料

Type III Packaging Material

There appears to be some confusion regarding when a Type III DMF (packaging material) should be submitted. It is not required that packaging information be submitted to the FDA in a DMF. The responsibility for providing information about packaging components rests foremost with the applicant of an NDA, ANDA or BLA, or the sponsor of an IND. This information may be provided to the applicant by the manufacturer of a packaging component or material of construction and may be included directly in the application. Any information that a manufacturer does not wish to share with the applicant or sponsor (i.e., because it is

Colorant, Flavor, Essence, or Material Used in Their Preparation

ted Reference Information

Characteristics and risks of pharmaceutical excipients
药用辅料的特点及风险

Diverse sources 来源多样

From animals(TSE, Infectious microbial infections, viral inactivation, etc.), plants(pesticide residue, Biotoxin contamination, Transgenic species, etc.), Minerals, Chemical synthesis
动物（TSE、传染性微生物感染、病毒灭活）、植物（农药残留、生物毒素污染、转基因物种）、矿物质，化学合成

Complex production process 生产工艺复杂

Extraction, Synthesis (focus on the mass of monomer, initiator, catalyst), Semi-synthesis (focus on naturals), Purification, etc.
提取、合成(关注单体、引发剂、催化剂的质量)、半合成(关注起始天然物)、纯化

Different routes of administration 给药途径不同

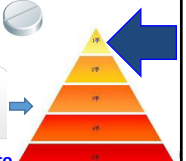
Oral, injection, topical, ophthalmic, nasal, otic, venous, etc. (High-risk: injection, inhalation, ophthalmic)
口服用、注射用、外用、眼用、鼻用、耳用、腔道用……（高风险等级如注射级、吸入级、眼用级等的纯度、安全性指标高于其他的级别）

Different dosage 处方用量

Oral tablet(Compound Aspirin Tablets: over 90% excipients), Injection (Intravenous fat emulsion: about 19% excipients)
口服片（复方阿司匹林片：含辅料53.4%;硝酸甘油片：含辅料90%以上）注射剂（静脉注射用脂肪乳：含辅料19%）

Classifying management 分级别管理

Risk control should be carried out according to the route of administration and the amount of prescription. Pay attention to high-risk pharmaceutical excipients.(Solubilizer, preservative in injection)
根据给药途径和处方用量不同应进行风险控制，尤其应重视高风险的药用辅料质量控制（关注注射剂中增溶剂、防腐剂）



Different cognition 认识不同

Excipients are inert, non-toxic/safety risks; suppliers are free to change and there is the risk from quality differences.
辅料惰性无毒/安全性风险；供应商随意改变，存在质量差异风险。

Classification of pharmaceutical excipients
药用辅料的分类

Country	Actual use	Pharmacopoeia records
China	543 kinds	270 kinds
USA	1500 kinds	525 kinds
pe	3000 kinds	280 kinds
Japan	1000 kinds	131 kinds

Ch.P

Classified by source	天然产物、半合成物和全合成物
Classified by formulation for preparation	片剂、注射剂、胶囊剂、颗粒剂、眼用制剂、鼻用制剂、栓剂、丸剂等
Classified by usage	可分为溶媒、抛射剂、增溶剂、助溶剂、乳化剂、着色剂、黏合剂、崩解剂、填充剂、润滑剂、润湿剂、渗透压调节剂、稳定剂、助流剂、抗结块剂、助压剂、矫味剂、抑菌剂等
Classified by route of administration	口服、注射、黏膜、经皮或局部给药、经鼻或吸入给药和眼部给药等

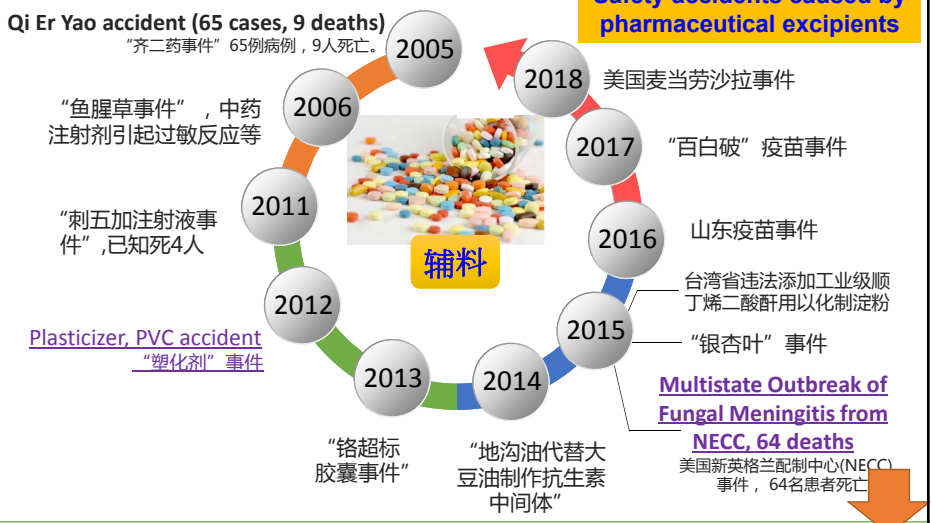
According to the classification method of macromolecular excipients and micromolecule excipients, the quality status of domestic pharmaceutical excipients can be evaluated objectively from the application and quality control of excipients

从大分子辅料和小分子辅料分类的方法看，能够客观评估国内药用辅料的质量状况，可以把握辅料应用和质量控制。

Classified by difficulty level of quality control 按质量控制的难易程度分类	Macromolecule/micromolecule classification 药用大分子辅料和药用小分子辅料

Safety accidents
药用辅料质量风险引起的安全性事件

Safety accidents caused by pharmaceutical excipients



Pharmaceutical excipients are important for drug safety and quality.

近年来发生的药害事件说明了药用辅料对药品安全与质量的重要性。

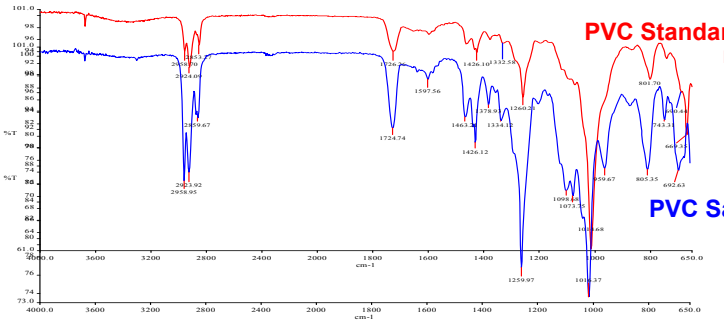
Amoxicillin Clavulanate Potassium Dry Suspension (Libatin)

阿莫西林克拉维酸钾干混悬剂（立百汀）

On Jun 21, 2011

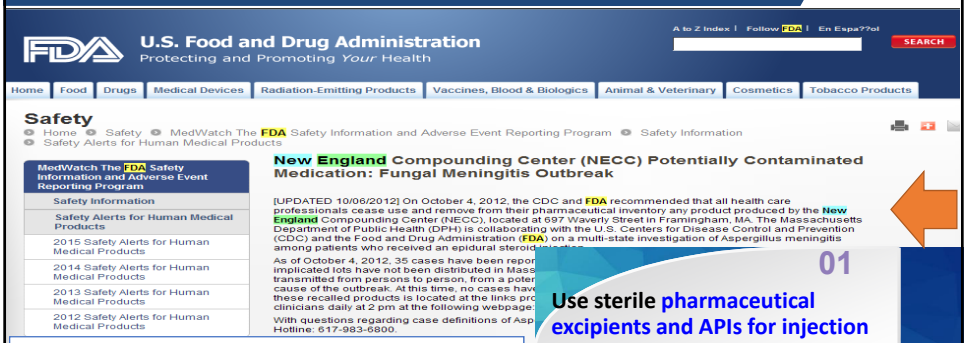
- The plasticizer diisodecyl phthalate (DIDP) in the Libatin (for children's preparation) PVC cap volatilizes and spreads into the drug.
- Qualitative Analysis of Libatin PVC Caps by IR

立百汀(**儿童制剂**)瓶盖内垫PVC内垫中增塑剂**邻苯二甲酸二异癸酯（DIDP）**挥发扩散到立百汀药物表面。力百汀瓶盖内垫成分定性（红外光谱法）分析。



New England Compounding Center accident

美国新英格兰配制中心（NECC）事件



In September 2012, fungal meningitis broke out in USA, which resulted in 64 deaths in 9 states. The reason was that they received methylprednisolone acetate (MPA) steroid injections contaminated by fungal from the New England Compounding Center (NECC) in Framingham. In January 2015, The United States Department of Justice has decided to sue 14 employees of NECC for second-degree murder.

2012年9月，美国爆发了严重的脑膜炎事件，事件导致9个州的64名患者死亡，事故原因为新英格兰配制中心生产甲泼尼龙醋酸酯(MPA)被真菌污染。2015年1月，美国司法部决定以二级谋杀罪起诉新英格兰配制中心的14名员工。

01 **Use sterile pharmaceutical excipients and APIs for injection without production instructions**
未按照生产指令使用无菌的注射用药用辅料和原料

02 **Workshop contaminated**
无菌车间污染

03 **Sterilizers contaminated**
灭菌柜污染

04 **Methylprednisolone acetate (MPA) contaminated by fungal**
最终导致甲泼尼龙醋酸酯被严重染菌

Risk Summary
药用辅料风险分析小结

The quality risks of pharmaceutical excipients exist throughout the production, distribution and usages. Mainly in the following aspects:

Pharmaceutical excipients

- **Safety**
  - Source and Method (animals, plants, minerals, chemical synthesis)
  - Manufacturing process (Extraction, Synthesis, Semi-synthesis, Purification)
  - Detrimental impurity
- **Functionality**
  - Batch stability (sustained-release preparations)
  - Supplier quality variance
  - Route of administration(Oral, injection, topical, ophthalmic, nasal, otic, venous, etc.)
  - Macromolecule: composition, molecular weight and its distribution, degree of polymerization, catalyzer, monomer

http://www.nicpbp.org.cn

Content/目录

Comparison of Pharmaceutical Excipients Review & Approval System in China and ICH Excipient Management Systems

Regulation Management

	USA	EU		Japan	China
Pharmaceutical excipient management system	DMF	CEP certification	Provide dossiers with preparations	MF	Review & Approval
Review & Approval	Dependent, review & approval with preparations, Pharmaceutical excipient unapproved	Independent (EDQM)	Dependent, review & approval with preparations, Pharmaceutical excipient unapproved	Dependent, review & approval with preparations, Pharmaceutical excipient unapproved	Dependent, associated review & approval with preparations, receive approval number
Range	Critical excipient	Excipients collected in EP, COS certification	Excipients not collected in EP	New excipients, generic drug and coprocessed excipient	Excipients used in newly declared domestic preparations, regardless of whether the Chinese Pharmacopoeia contains

Type II DMF

EDMF&COS: EDMF applies to all APIs. COS certification can handle substances collected in EP, including APIs and pharmaceutical excipients.

Only after the MF registration information is replaced with a formal registration number, the review of drug marketed applications will start.

FDA——DMF

What is critical excipients?
It is dependent on their characteristics, functions, usages and dosage.

Pharmaceutical excipients/Packaging Material Manufacturers provide DMF application
辅料/药包材生产企业提交DMF申请

FDA accept and carry out formal examination
FDA接受申请，进行基本的形式审查

Approve: receive DMF number
审查合格：发给DMF号

Disapprove: return, tell the reason
审查不合格：退回，告知原因

DMF holder send Authorized value
DMF持有者发出授权值

Drug Manufacturers provide IND, NDA, ANDA applications
药品生产企业提交IND、NDA、ANDA申请

Update/Charge Activate DMF
更新/收费
激活DMF

Associated reviewed by CDER
CDER进行关联性审评

Proposed Pharmaceutical excipients /Packaging Material defect with preparations
与制剂一起提出辅料/药包材缺陷

TYPES OF DMFs

The types of DMFs are:

➢ Type II Drug Substance, Drug Substance Intermediate and Material Used in Their Preparation, or Drug Product
II类 药物，药物中间体、制剂中使用的关键辅料或者药品

Type III Packaging Material

➢Type III Packaging Material
III类 药包材

There appears to be some confusion regarding when a Type III DMF (packaging material) should be submitted. It is not required that packaging information be submitted to the FDA in a DMF. The responsibility for providing information about packaging components rests foremost with the applicant of an NDA, ANDA or BLA, or the sponsor of an IND. This information may be provided to the applicant by the manufacturer of a packaging component or material of construction and may be included directly in the application. Any information that a manufacturer does not wish to share with the applicant or sponsor (i.e., because it is

➢Type IV Excipient, Colorant, Flavor, Essence, or Material Used in Their Preparation
IV类 辅料，色素、香料，制剂中使用的辅料

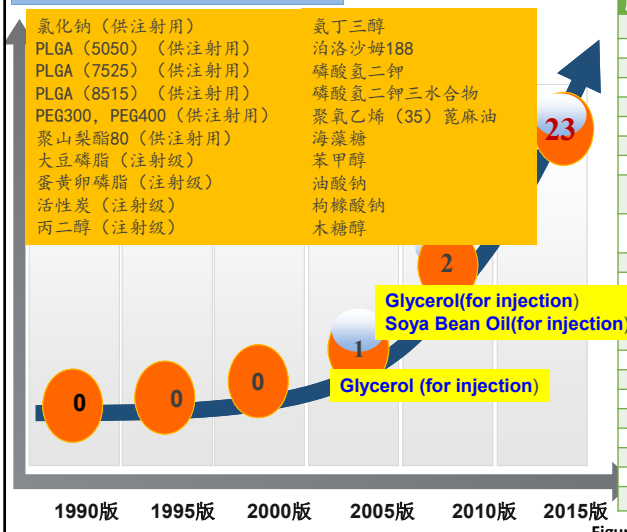
Colorant, Flavor, Essence, or Material Used in Their Preparation

ted Reference Information

Situation of standards of pharmaceutical excipients for injection in Ch.P 2015 edition

中国药典注射用药用辅料标准现状

Monograph Management



中国药典收录注射用药用辅料标准数

序号	名称	用途
1	氯化钠	渗透压调节剂
2	甘油	溶剂
3	PLGA(50/50)	载体材料
4	PLGA(75/25)	载体材料
5	PLGA(85/15)	载体材料
6	PEG300	溶剂
7	PEG400	溶剂
8	聚山梨酯80	乳化剂
9	大豆磷脂	乳化剂、脂质体膜材
10	蛋黄卵磷脂	乳化剂、脂质体膜材
11	活性炭	吸附剂
12	丙二醇	溶剂
13	氨丁三醇	PH调节剂
14	大豆油	溶剂
15	泊洛沙姆188	乳化剂
16	磷酸氢二钾	酸碱调节剂
17	磷酸氢二钾三水合物	酸碱调节剂
18	聚氧乙烯(35)蓖麻油	溶剂
19	海藻糖	稳定剂
20	苯甲醇	溶剂
21	油酸钠	表面活性剂
22	枸橼酸钠	酸碱调节剂
23	木糖醇	渗透压调节剂

Figure 1. 23 kinds of pharmaceutical excipients for injection recorded in Ch.P 2015

Pharmaceutical excipients for injection in Ch.P 2015 edition

2015版中国药典注射用药用辅料

- **Compared with the global pharmacopoeia, Pharmaceutical excipients for injection in Ch.P 2015 edition is up to 23. But it still can not reach the number of injectable excipients (about 140 kinds)**

现状：虽然在全球药典标准中，中国药典注射用标准是最多达23个，但是还是不能满足国内注射剂常用辅料的要求(约140多种)

Pharmaceutical excipients used in injections

名称	用途
丙二醇	抗菌剂;防腐剂; 消毒剂; 润湿剂; 增塑剂;溶剂; 乳化剂; 溶剂
氢氧化钠	碱化剂; 缓冲剂
甘油	溶剂;助悬剂
聚山梨酯80	表面活性剂;乳化剂;增溶剂;润湿剂
EDTA二钠	螯合剂
乙醇	抗菌防腐剂;消毒剂;皮肤渗透促进剂;溶剂
无水乙醇	溶剂
PEG400	软膏基质;增塑剂;溶剂;栓剂基质;片剂和胶囊剂的润滑剂
苯甲酸钠	抗菌剂;防腐剂; 润滑剂
氯化钠	填充剂; 张度剂
氯化钾	治疗剂; 张度剂
无水亚硫酸钠	抗氧剂
浓氨溶液	缓冲剂;ph调节剂
硫酸	酸化剂;
焦亚硫酸钠	抗菌剂;防腐剂; 抗氧剂
枸橼酸	酸化剂; 抗氧剂; 缓冲剂; 螯合剂;香料增强剂; 防腐剂
氯化钙	抗菌防腐剂;治疗剂;吸水剂
葡甲胺	有机碱
碳酸氢钠	碱化剂; 治疗剂
甘露醇	稀释剂; 增塑剂; 甜味剂; 填充剂;治疗剂; 张度剂
磷酸氢二钠	缓冲剂;螯合剂
胆固醇	润肤剂; 乳化剂
无水醋酸钠	pH值调节剂;缓冲剂
甘氨酸	崩解剂;pH调节剂;缓冲剂;填充剂;矫味剂;助溶剂;稳定剂
硫酸钠	抗氧剂
羧甲基纤维素钠	崩解剂;片剂黏合剂;稳定剂;助悬剂;增黏剂;吸水剂

名称	用途
聚山梨酯20	表面活性剂;乳化剂;增溶剂;润湿剂
亚硫酸氢钠	抗氧剂
硫酸镁	填充剂
枸橼酸钠	缓冲剂;pH调节剂;矫味剂;稳定剂;螯合剂;防腐剂
谷氨酸	矫味剂
磷酸氢二钾	pH值调节剂
乳酸	酸化剂; 酸化剂
苯酚	抗菌防腐剂;消毒剂
十二烷基硫酸钠	污剂;乳化剂;皮肤穿透剂;片剂和胶囊剂润滑剂;润湿剂
甲硫氨酸	缓冲剂
苯甲醇	抗菌剂;防腐剂; 消毒剂; 溶剂
乙二胺	助溶剂
大豆卵磷脂	乳化剂;增溶剂
乳糖	填充剂;稀释剂
硫代硫酸钠	抗氧剂;洗涤剂
苹果酸	酸化剂
氢氧化钾	碱化剂
稀盐酸	pH值调节剂;缓冲剂;矫味剂;PH调节剂;溶解剂;助溶剂
蛋黄卵磷脂	分散剂;润湿剂;乳化剂;稳定剂
硫柳汞	抗菌剂;防腐剂; 消毒剂;
蔗糖	赋形剂;矫味剂; 包衣剂; 制粒剂; 混悬剂; 甜味剂; 填充剂;片剂填充剂; 治疗剂; 增粘剂
磷酸二氢钠	缓冲剂;螯合剂
山梨醇	润湿剂; 增塑剂; 乳化剂; 甜味剂;填充剂
三氯叔丁醇	抗菌剂;防腐剂; 增塑剂
磷酸	酸化剂
右旋糖酐	保护剂
大豆油	油脂性基质; 溶剂

Ch.P 2015/USP40-NF35/EP 9.0/JP 16
Excipients for injection (注射用辅料收载情况)

	Ch.P 2015 edition	USP40-NF35	EP 9.0	JP 16
Variety number	23	1	6	2
	Ch.P 2015	USP40-NF35	EP 9.0	JP 16
磷酸氢二钾三水合物	Egg Yolk Lecithin for injection (蛋黄卵磷脂)	Egg Yolk Lecithin for injection (蛋黄卵磷脂)	Egg Yolk Lecithin for injection (蛋黄卵磷脂)	Water for Injection 注射用水
大豆磷脂	磷酸氢二钾		Cholesterol for Parenteral Use (胆固醇)	Sterile Water for Injection in Containers 注射用无菌水
活性炭	氯化钠		Soyabean lecithin for injection (大豆磷脂)	
氨丁三醇	甘油		Dextran 1 for injection (葡聚糖1)	
大豆油	PLGA(50/50)		Water for Injection (注射用水)	
泊洛沙姆188	PLGA(75/25)		Sterile Water for Injection (注射用无菌水)	
聚氧乙烯(35)蓖麻油	PLGA(85/15)			
海藻糖	PEG300			
苯甲醇	PEG400			
油酸钠	聚山梨酯80			
枸橼酸钠	丙二醇			
木糖醇				

Content/目录

Technical Requirements for pharmaceutical excipients standards for injection
注射级药用辅料标准技术要求

Items of pharmaceutical excipient monograph
药用辅料标准控制项目

23(in Ch.P 2015) / 270(Total)

Name	辅料名称
Structure	结构式
Molecular formula	分子式
CAS number	[CAS]号
Source&Method	来源与制法
Characteristic	性状
Identification	鉴别
Test	检查
Content	含量
Type	类别
Storage	储藏

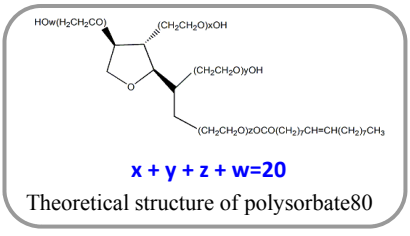
Items that should be paid attention to in pharmaceutical excipients for injection monograph
注射级药用辅料标准中应关注的项目

- **Source** 来源
- **Manufacturing Process** 生产工艺
- **Impurities** 杂质
- **Macromolecule** 大分子:分子量及分布、聚合度、催化剂;残留单体;聚合物
- **Route of administration (for injection)** 给药途径(注射用)
- **Excipients absorption and Potential toxicity** 辅料吸收及潜在毒性
- **Bacterial endotoxin/Sterility** 细菌内毒素(热原)/无菌
- **Abnormal toxicity** 异常毒性
- **Osmotic pressure** 渗透压
- **Depressor substances or Pressor substance** 降压物质或升压物质

For example, Polysorbate80(for injection), Lactose, Lecithin, Activated carbon, Hydroxypropyl - β – cyclodextrin, Povidone, Benzalkonium chloride.

Polysorbate80 (for injection)

Polysorbate80（Tween80）**聚氧乙烯脱水山梨醇单油酸酯**，属于亲水型非离子型表面活性剂，可广泛应用于药品、食品、化妆品等。



x + y + z + w=20

Theoretical structure of polysorbate80

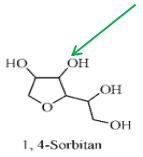
◆ 中药注射剂：鱼腥草注射液、香丹注射液、脉络宁注射液等；

Pharmaceutical excipient: Tween80

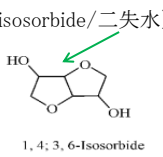
2006年6月1日鱼腥草注射液系列药品由于发生严重不良反应，被国家食品药品监督管理总局紧急叫停。

Complex ingredient 组分复杂性:

① parent nucleus(sorbitan/一失水；isosorbide/二失水)



1, 4-Sorbitan



1, 4; 3, 6-Isosorbide

② fatty acids(oleic acid, linoleic acid, palmitic acid , Stearic acid, etc.油酸、亚油酸、棕榈酸、硬脂酸等)

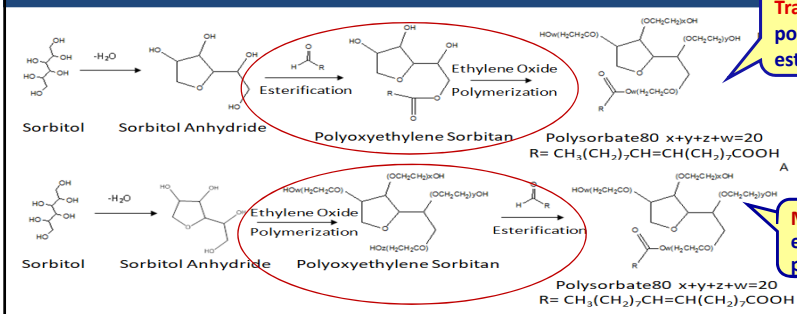
③ esterification of oleic acid (monoeaster, diester, triester, tetraester单、二、三、四酯)

④ polymerization of ethylene oxide

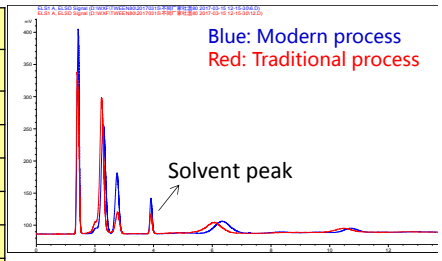
中药注射剂的溶剂大部分是吐温80
弄清楚结构有助于其质量提升

Comparison of production process of polysorbate80

聚山梨酯80生产工艺比较



序号	Traditional process	Modern process
1	聚山梨酯80成品中的聚乙二醇含量高	聚山梨酯80聚乙二醇含量未检测出
2	成品色度是APHA≤400#	成品色度是APHA≤60#
3	选用的油酸含量≥70%	选用的油酸含量≥90%
4	生产过程较难控制，指标波动大	生产过程容易控制，指标稳定
5	成品中含有油酸聚氧乙烯醚	成品中有微量的油酸聚氧乙烯醚
6	环氧乙烷，二氧六环杂质超标	环氧乙烷，二氧六环杂质减少
7	乙二醇、二甘醇杂质多	乙二醇、二甘醇杂质少



Comparative chromatogram of polysorbate80 products from different manufacturing processes

Polysorbate80 for injection monograph in 2015 Ch.P

注射用辅料聚山梨酯80的质量标准

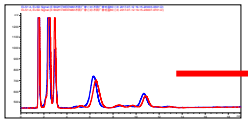
项目	Ordinary-grade (2015 Ch.P)	For injection (2015 Ch.P)
性状	本品为淡黄色至橙黄色的黏稠液体;微有特臭,味微苦略涩,有温热感	
相对密度	在20℃时应为1.06-1.09	
黏度	在25℃时（毛细管内径为2.0~2.5mm）为350~550mm²/s	在25℃时（毛细管内径为2.0~2.5mm）为350~450mm²/s
酸值	不得过2.0	不得过1.0
皂化值	45~55	
羟值	65~80	
碘值	18~24	
过氧化值	不得过10	不得过3
鉴别	（1）取本品的水溶液（1→20）5ml，加氢氧化钠试液5ml，煮沸数分钟，放冷，用稀盐酸酸化，显乳白色浑浊。 （2）取本品的水溶液（1→20），滴加溴试液，溴试液即褪色。 （3）取本品6ml，加水4ml混匀，呈胶状物。 （4）取本品的水溶液（1→20）10ml，加硫氰酸钴铵溶液（取硫氰酸钴铵17.4g与硝酸钴2.8g，加水溶解成100ml）5ml，混匀，再加三氯甲烷5ml，振摇混合，静置后，三氯甲烷层显蓝色。	
酸碱度	pH5.0~7.5	
颜色	取本品10ml,与同体积的黄色2号标准液比较（附录IX A），不得更深	
乙二醇、二甘醇	均不得过0.01%	
TEG	--	NMT 0.01%
环氧乙烷和二氧六环	环氧乙烷不得过1ppm，二氧六环不得过10ppm	
冻结试验	取本品，置玻璃容器内，于冰浴中放置24小时，不得冻结。	取本品,置玻璃容器内,于5℃±2 ℃放置24小时,不得冻结。
水分	水分不得过3.0%	不得过0.5%
炽灼残渣	不得过0.2 %	不得过0.1%
重金属	不得过10ppm	
砷盐	不得过2ppm	
Fatty Acid Composition	NLT 58.0%,含肉豆蔻酸、棕榈酸、棕榈油酸、硬脂酸、亚油酸与亚麻酸分别不得大于5.0%、16.0%、8.0%、6.0%、18.0%与4.0%	NLT 98.0%，其中肉豆蔻酸、棕榈酸、棕榈油酸、硬脂酸、亚油酸、亚麻酸含量均不得过0.5%
Bacterial endotoxin	--	每1mg聚山梨酯80中含内毒素的量应小于0.012EU
Sterility	--	取本品，依法检查（附录XI H），应符合规定

Aldehydes?

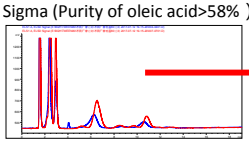
Composition differences of Polysorbate80 from different manufacturers

不同厂家聚山梨酯80产品的组成差异分析

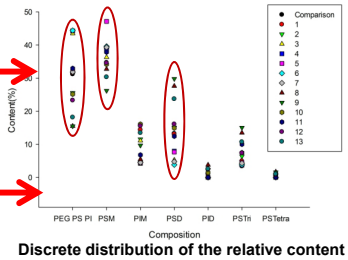
➢ Composition of polysorbate80 synthesized from different oleic acid purity



Sigma (Purity of oleic acid>58%)



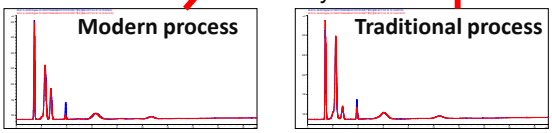
Sigma (Purity of oleic acid >70%)



Discrete distribution of the relative content (%) of polysorbate80 components from different manufacturers

- 不同厂家产品在组分1（PEG/PS/PI），组分2（PSM）和组分4（PSD）的含量离散程度较大；
- 厂家2~7的聚山梨酯80各组分的色谱峰面积总和均远小于对照各组分的峰面积之和。说明这些厂家的聚山梨酯80除了已知的7类主要组分外，仍**含有其他未知的物质或杂质。**

➢ Composition of Polysorbate80 from the different batches of the same factory



Comparative chromatogram of polysorbate80 products from different manufacturing processes

● Conclusion

The composition of Polysorbate80 produced by different factories and different processes is obvious different, which indicates that its functional and biological effects are also different.

不同厂家、不同工艺生产的聚山梨酯80组成上有较大的差异，由此预示了其功能性和生物学效应也有区别。

Allergic impurities in injectable excipients ——protein in lactose

乳糖的生产工艺流程图：

牛奶发酵(Fermentation)后得到乳清（Whey）（干物质、乳糖、脂肪、灰分）→脱脂→ 去除蛋白→蒸发浓缩→冷却晶体→分除母液→洗涤结晶→分除洗水→干燥→粗制乳糖→溶解→压滤→结晶→分除母液→洗涤→干燥→粉碎→筛选→包装

Lactose
乳糖的结构式

原料乳清中的残留蛋白(Residual protein)是注射用乳糖过敏源：

乳糖中还可能含有三聚氰胺

residual protein in lactose	%
α-Lactalbumin (α-牛乳清蛋白)	19.7%
β-Lactoglbulin (β-牛乳球蛋白)	43.6%
BSA (牛血清白蛋白)	4.7%
Ig (免疫球蛋白)	3%
Other proteins (其他蛋白)	29%

Allergology International. 2009;58:137-139
DOI: 10.2332/ allergolint.C-07-59

CASE REPORT

Acute Allergic Reaction due to Milk Proteins Contaminating Lactose Added to Corticosteroid for Injection

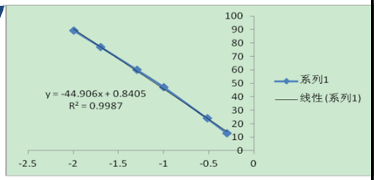
Asuka Eda[1], Kazuko Sugai[2], Hiromi Shioya[1], Asako Fujitsuka[2], Setsuko Ito[4], Tsutomu Iwata[2] and Tetsunori Funabiki[3]

The residual protein in lactose is a risk factor for the safety of injections.

乳糖中的残留蛋白对注射剂的安全构成一定风险

Allergic impurities in injectable excipients ——protein in lactose

序号	生产厂家	检品编号	批次	氮含量（ppm）
1	A	EC0601201206524	10620352	19.1
2		EC0601201208983	10600315	16.7
3	B	EC0601201206263	647653	43.6
4	C	EC0601201206515	BU100017	28.3
5		EC0601201206243	10578109	49.9
6		EC0601201206265	10549374	38.9
7		EC0601201206272	10587945	56.3
8	D	EC0601201206266	L1142	18.9
9		EC0601201206270	L1201	59.4
10		EC0601201207635	L1145	20.4
11		EC0601201207681	L1134A4004	29.2
12		EC0601201209464	L1142	45.2
13	E	EC0601201206599	20110802	38.0
14		EC0601201206600	20110405	52.4
15		EC0601201207682	20120318	41.1
16	F	EC0601201206521	8511102114	17.8
17		EC0601201206523	8511022714	99.3
18		EC0601201206526	8511102314	50.9
19		EC0601201208458	8511111614	20.6
20	G	EC0601201207683	1201002	22.7
21		EC0601201207660	1205006	12.2
22		EC0601201207647	1204002	11.7
23		EC0601201208977	1202004	25.6
24		EC0601201207658	1204005	14.1
25	H	EC0601201207645	20120303	11.5
26		EC0601201207674	20111219	14.8
27		EC0601201208982	20120526	12.3
28		EC0601201208981	20120506	30.4
29		EC0601201208980	20120522	46.3
30		EC0601201208979	20120508	38.5
31		EC0601201208978	20120521	34.3
32		EC0601201208984	20120605	20.5
33		EC0601201209455	20120131	14.3
34	I	EC0601201207644	120314	14.7
35		EC0601201209453	20120605	25.4
36		EC0601201209454	20120520	29.6
37	J	EC0601201206225	20120302	25.8
38		EC0601201206228	20120301	23.3
39		EC0601201206232	20120101	20.8



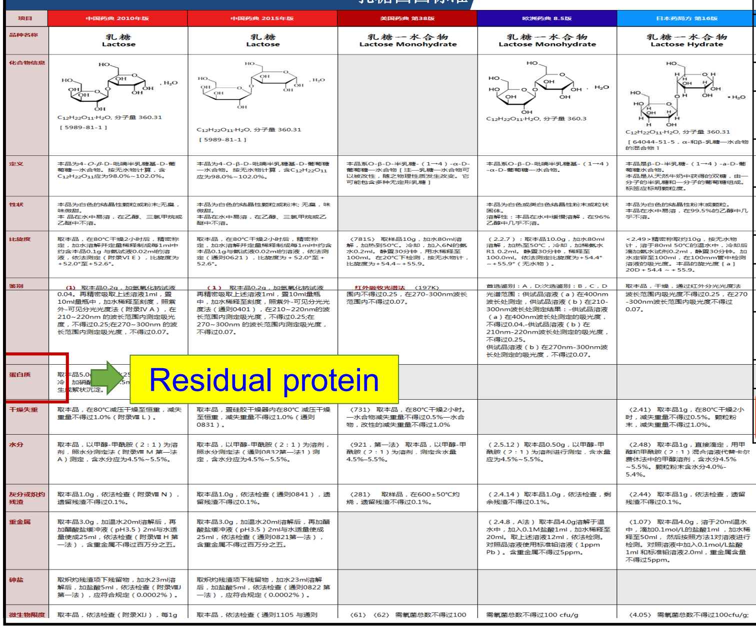
Y=-44.906+0.8405 (r=0.9994) 10ppm-500ppm

39批乳糖中残留蛋白氮含量在11.5ppm-99.3ppm之间，按照口服级标准，39批样品都合格，由于本次抽样39批乳糖样品大多来自注射剂生产厂家，这些批次的乳糖用在注射剂中，则会有一定的风险。

国内外尚无注射级乳糖的法定标准，国外肺部给药吸入级乳糖的残留蛋白氮含量规定为32ppm，国家食品药品监督管理局在《新药用辅料非临床安全性评价指导原则》中将注射用辅料与肺部给药辅料的安全性归为一类，故本次抽验注射级乳糖残留蛋白氮含量限量定为32ppm,按此标准，39批样品中有14批不合格，不合格率为36%，值得关注的是并不是所有国外产品的残留蛋白氮含量都合格，提示企业不能完全迷信国外产品的质量，如果乳糖是用于注射，买回原料后，企业应先提纯降低残留蛋白后再使用。

Lactose monograph

乳糖四国标准



Lactose (for injection)	Lactose (for inhalation)
Definition	Definition
Identification	Identification
Water	Water
Specific rotation	Specific rotation
Bacterial endotoxins	Bacterial endotoxins
Microbial limits	Microbial limits
pH	pH
Residue on ignition	Residue on ignition
Heavy metal	Heavy metal
Sterility	Particle shape and morphology
Residual protein	
	Content of alpha and beta anomers
	Assay

Different sources of lecithin has different compositions
不同来源的卵磷脂组成不同

Soya Lecithin

Ingredient	%
PC/磷脂酰胆碱	**57.8%**
PE/磷脂酰乙醇胺	**13.3%**
PI/磷脂酰肌醇	2.2%
LPC/溶血磷脂酰胆碱	3.2%
LPE/溶血磷脂酰乙醇胺	0.6%
Others/其它	22.9%

大豆磷脂
Daodu Linzhi
Soya Lecithin

Oral/口服
For injection/
注射用

[8030-76-0]

大豆磷脂系从大豆中提取精制而得的磷脂混合物。以无水物计算，含磷量应不得少于2.7%；含氮量应为1.5%～2.0%；含磷脂酰胆碱应不得少于45.0%，含磷脂酰乙醇胺应不得过30.0%，含磷脂酰胆碱和磷脂酰乙醇胺总量不得少于70%。

Different fatty acid ester chains

Measure: Establish four monographs (different sources and routes of administration) separately
分别建立两个来源，给药途径不同的四个标准

Egg Yolk Lecithin

Ingredient	%
PC/磷脂酰胆碱	**73.0%**
PE/磷脂酰乙醇胺	**15.0%**
SM/鞘磷脂	2.5%
PI/鞘脂酰肌醇	0.9%
LPC/溶血磷脂酰胆碱	5.8%
PE/溶血磷脂酰乙醇胺	2.1%
Others/其它	0.9%

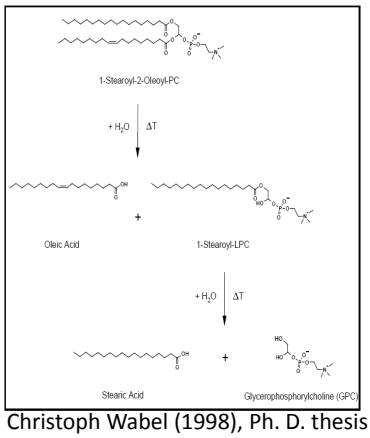
蛋黄卵磷脂
Danhuang Luanlinzhi
Egg Yolk Lecithin

Oral/口服
For injection/
注射用

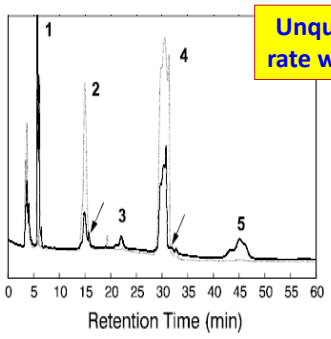
[93685-90-6]

本品系以鸡蛋黄或蛋黄粉为原料，经适当溶剂提取精制而得的磷脂混合物。以无水物计算，含氮(N)应为1.75%～1.95%，含磷(P)应为3.5%～4.1%，含磷脂酰胆碱不得少于68%，含磷脂酰乙醇胺不得过20%，含磷脂酰胆碱和磷脂酰乙醇胺总量不得少于80%。

Substances cause Haemolysis or agglutination
——lysophosphatide in lecithin



Christoph Wabel (1998), Ph. D. thesis



HPLC chromatograms of native 1.2% w/w Lipoid E80® dispersion [pH ≅6.2] (·····) and after autoclaving for 5 h (—) without prior pH adjustment:

1-FFA 2-PE 3-LPE 4-PC 5-LPC

Unqualified rate was 22%

18批**卵磷脂**国家抽验样品中共有**4批样品不符合规定，溶血磷脂酰乙醇胺**的不合格率为22%----2013年抽验

http://www.nicpbp.org.cn

Activated carbon (For injection)
活性炭（供注射用）

About 1.5 billion bags of activated carbon are used each year.
每年115亿袋的大输液使用量/其他吸附工艺

中国药典 2015 年版　　活性炭（供注射用）

活性炭（供注射用）
Huoxingtan（Gongzhusheyong）
Activated Charcoal（For Injection）

[7440-44-0]

本品系由木炭、各种果壳和优质煤等作为原料，通过物理和化学方法对原料进行破碎、过筛、催化剂活化、漂洗、烘干和筛选等一系列工序加工制造而成具有很强吸附能力的多孔疏松物质。

【性状】本品为黑色粉末，无臭、无味，无砂性。

【鉴别】取本品 0.1g，置耐热玻璃管中，在缓缓通入压缩空气的同时，在放置样品的玻璃管处，用酒精灯加热灼烧（注意不应产生明火），产生的气体通入氢氧化钙试液中，即生成白色沉淀。

【检查】酸碱度　取本品 2.5g，加水 50ml，煮沸 5 分钟，放冷，滤过，滤渣用水洗涤，合并滤液与洗液使成 50ml，滤液应澄清，遇石蕊试纸应呈中性反应。

氯化物　取酸碱度项下的滤液 10ml，加水稀释成 200ml，摇匀，分取 20ml，依法检查（通则 0801），与标准氯化钠溶液 5.0ml 制成的对照液比较，不得更浓（0.1%）。

硫酸盐　取酸碱度项下的余下的滤液 20ml，依法检查（通则 0802），与标准硫酸钾溶液 5.0ml 制成的对照液比较，不得更浓（0.05%）。

未炭化物　取本品 0.25g，加氢氧化钠试液 10ml，煮沸，滤过，滤液如显色，与对照液（取比色用氯化钴液 0.3ml、比色用重铬酸钾液 0.2ml、水 9.5ml 混合制成）比较，不得更深。

碳化锌　取本品 0.5g，加水 20ml 与盐酸 5ml，煮沸，蒸气不能使醋酸铅试纸变黑。

氯化物　取本品 5g，至高温炽灼，加水 50ml 与碳石酸 2g，振摇，滤出液用置于冰水浴的吸收液吸收，吸收液为氢氧化钠试液 2ml 和水 10ml，蒸馏出约 25ml 馏出液，加水稀释至 50ml，加入 12 滴硫酸亚铁试液，加热至几乎沸腾，放冷，加盐酸试液 1ml，溶液应不变蓝。

乙醚中溶解物　取本品 2.0g，加乙醇 50ml 煮沸回流 10 分钟，立即滤过，滤液用乙醇稀释至 50ml，取滤液 40ml，105℃干燥至恒重，遗留残渣不得过 8mg。

荧光物质　取本品 10.0g，至高温炽灼，加入 100ml 环己烷，振摇 2 小时，滤出液用环己烷稀释至 100ml，作为供试品溶液。取蒽宁，精密称定，加 0.005mol/L 的硫酸溶液溶解并定量稀释制成每 1ml 中含蒽宁 83ng 的对照溶液，照紫外-可见分光光度法（通则 0401），在 365nm 波长处分别测定吸光度，供试品溶液的吸光度应小于对照溶液的吸光度。

重金属　取本品 1.0g，加稀盐酸 10ml 与蒸馏水 5ml，煮沸 5 分钟，滤过，滤渣用热水 10ml 洗净，合并滤液与洗涤液，加硫酸 1ml，蒸干后，炽灼至恒重。遗留残渣不得过 4mg。

干燥失重　取本品，在 120℃干燥至恒重，减失重量不得过 10.0%（通则 0831）。

炽灼残渣　取本品约 0.50g，加乙醇 2～3 滴湿润后，依法检查（通则 0841），遗留残渣不得过 3.0%。

铁盐　取本品 1.0g，加 1mol/L 盐酸溶液 25ml，煮沸 5 分钟，放冷，滤过，用热水 30ml 分次洗涤残渣，合并滤液与洗液加水至 100ml，摇匀；精密量取 5ml，置 50ml 纳氏比色管中，依法检查（通则 0807），与标准铁溶液 1.0ml 制成的对照液比较，不得更深（0.02%）。

锌盐　取本品 1.0g，加水 25ml，煮沸 5 分钟，放冷，滤过，用热水 30ml 分次洗涤残渣，合并滤液与洗液，加水至 100ml，摇匀；精密量取 10ml，置 50ml 纳氏比色管中，加抗坏血酸 0.5g，加盐酸溶液（1→2）4ml 与亚铁氰化钾试液 3ml，加水稀释至刻度，摇匀，加锌生荧指示液与标准锌溶液[精密称取硫酸锌（$ZnSO_4 \cdot 7H_2O$）44mg，置 100ml 量瓶中，加水溶解并稀释至刻度，摇匀，精密量取 10ml，置另一 100ml 量瓶中，加水稀释至刻度，摇匀，即得，每 1ml 相当于 10μg 的 Zn]0.5 方法制成的对照液比较，不得更浓（0.005%）。

重金属　取本品 1.0g，加稀盐酸 10ml 与蒸馏水 5ml，煮沸 5 分钟，滤过，滤渣用热水 35ml 洗涤，合并滤液与洗液至 50ml，摇匀，分取 20ml，加醋酸盐缓冲液 1 滴，溶液显玫瑰红色，加醋酸盐缓冲液（pH3.5）2ml 与 25ml，加抗坏血酸 0.5g 溶解后，依法检查（通则 0821 5 分钟时比色，含重金属不得过百万分之三十。

吸着力　（1）取干燥至恒重的本品 1.0g，加 0.12% 蒽宁溶液 100ml，在室温不低于 20℃下，用力振荡 1 立即用干燥的中速滤纸滤过，分取续滤液 10ml，滴与硫化汞指试液 3 滴，不得发生浑浊。

（2）取两个 100ml 具塞锥形瓶，一份加干燥至恒重的 0.25g，再分别精密加入 0.1% 蒽宁溶液各 50ml，振摇不低于 20℃下，振荡频率 5 分钟，将两瓶中的溶液分别用干燥的中速滤纸滤过，精密量取续滤液各 25ml，分别置 250ml 量瓶中，各加 10% 醋酸钠溶液 50ml，摇匀后，加水稀释至刻度，摇匀，精密加碘滴定液（0.05mol/L）35ml，密塞，振摇 10 分钟[振荡频率为每分钟 1 次，50 分钟后，用水稀释至刻度，摇匀]，放置 10 分钟，分别用干燥滤纸滤过，精密量取续滤液 100ml，分别用硫代硫酸钠滴定液（0.1mol/L）滴定，[并用空白试验校正]，[消耗滴定液（0.05mol/L）]的差数不得少于 1.4ml。

微生物限度　取本品，依法检查（通则 1105），每 1g 供试品中需氧菌总数不得过 1000cfu，霉菌和酵母菌总数不得过 100cfu。不得检出大肠埃希菌，试品中不得检出沙门菌。

细菌内毒素　活性炭所含内毒素本底值　称取活性炭，加入约 5ml 细菌内毒素检查用水配置成悬浊液，加入约 5% 蒽宁溶液（1.5g/100ml）的混合溶液，振荡混合 9 分钟，然后 1500 转离心 5 分钟，离心后，取上清液用 0.22μm 无热原

滤膜过滤，取续滤液按照通则 1143 检测，样品细菌内毒素应小于 2EU/g。

活性炭对细菌内毒素吸附力　取细菌内毒素国家标准品 1 支，按使用说明书配制成浓度为 200EU/ml，20EU/ml 的标准内毒素溶液备用，称取约 75mg 活性炭两份，分别加入约 5ml 浓度为 200EU/ml 和 20EU/ml 的标准内毒素溶液配制成活性炭浓度为 1.5%的混合溶液，漩涡混合 9 分钟，1500 转离心 5 分钟，离心后，取上清液用 0.22μm 无热原滤膜过滤，取续滤液按照通则 1143 检测，应能使 200EU/ml，20EU/ml 的标准内毒素溶液内毒素含量均下降 2 个数量级（吸附率达到 99%）。

无菌（供无菌菌工艺的无菌制剂用）　取本品，依法检查（通则 1101），应符合规定。

【类别】药用辅料，吸附剂等。

【贮藏】密封保存。

ttp://www.nicpbp.org.cn

Activated carbon (For injection)
活性炭（供注射用）

Adsorption is the CMA of activated carbon. The requirement in Ch.P 2015 edition is higher than in 2010 edition, which is consistent with that in the USP.
吸着力是主要功能性指标，2015版标准比2010版标准高，但与USP标准一致

检查项目		2010 版 药 典 标 准（化学药品）	2015版拟定活性炭（供注射用）标准	GB/T13803.4-1999（针剂用性炭）		
	吸着力	（1）0.12%硫酸奎宁溶液100 ml，不得发生浑浊。（2）消耗碘滴定的	（1）0.12%硫酸奎宁溶液100 ml，不得发生浑浊。（2）消耗碘滴定液（0.05mol/L）的差数不得少于1.4ml。	（1）0[illegible]硫酸奎[illegible]溶液100 [illegible]不得发生浑浊。（2）所消耗的亚[illegible]毫[illegible]11[illegible]	奎宁溶液50ml，不得发生浑浊。（2）消耗碘滴	每100g活性炭至少吸附
	活性炭所含内毒素本底值	——	细菌内毒素应小于2EU/g			
	活性炭对细菌内毒素吸附力	——	应能使其内毒素含量下降2个数量级（吸附率达到99%）			
	微生物限度	——	应符合规定	——	应符合规定	应符合规定
	无菌	——	应符合规定	——	——	——

USP use strychnine sulfate (poison, expensive). Japan use Quinine.
USP使用硫酸士的宁;/毒/贵;日本用奎宁

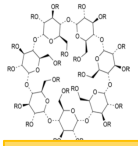
Function: To adsorb endotoxin, which is not allowed to contain in activated carbon. Otherwise it will pollute drugs.
作用是吸附内毒素，但本身不允许含有，否则会污染药品

Adsorption is the critical function attribute of activated carbon.
吸附力是活性炭的主要功能性和质量评价指标

Quality control research is being carried out for the risk control of nanoparticles below 200nm that cannot be filtered in activated carbon.
对于活性炭中无法过滤的200nm以下纳米微粒的风险控制。正在进行质控研究

Hydroxypropyl - β - cyclodextrin

羟丙基-β-环糊精



Solubilizer

Item	Year	Acceptability (%)	Pharmacopoeia Criterion
Propylene oxide(PO)	2016	66.7	USP, 1ppm
Residual protein		58.3	Nitrogen content≤0.01%

Renal toxicity may comes from Hydroxypropyl - β - cyclodextrin

◆ **Risks**

- Not set Bacterial endotoxin, Microbial limit and Sterility items
- No restrictions on propylene oxide residues
- No residual protein control

No.	Manufacturers	Inspection number	Batch number	PO
1	A	EC0601201609123	160401	27ppm
2		EC0601201609122	160801	33ppm
3	B	EC0601201608770	20151031	未检出
4		EC0601201607301	20150525	1ppm
5		EC0601201609750	20151120	1ppm
6		EC0601201610287	20150114	4ppm
7		EC0601201610288	20151202	1ppm
8		EC0601201610289	20160329	1ppm
9		EC0601201610308	20160325	1ppm
10	C	EC0601201607299	20160303	未检出
11		EC0601201607300	20160319	未检出
12	D	EC0601201610410	E001C	14ppm

◆ **Measures**

- It is recommended to add bacterial endotoxin, microbial limit, sterility, propylene oxide, residual protein, conductivity, etc.
  建议增加细菌内毒素、微生物限度、无菌、环氧丙烷、残留蛋白、电导率
- It is recommended to measure the degree of substitution by NMR.
  建议采用NMR法测定取代度的方法

Povidone——2-pyrrolidone

Disintegrant, adhesive,etc

Comparison of N-vinylpyrrolidone, aldehyde and hydrazine in povidone from different national pharmacopoeia

聚维酮中N-乙烯基吡咯烷酮、醛和肼在各国药典中的标准对比

		Ch. P 2010	USP35/NF30	BP2013/EP7. 0	JP16
N-Vinyl-2-pyrrolidone	Limit	≤0.2%（200 times）	≤0.001%	≤0.001%	≤0.001%
	Results	100%	54. 2%（其中超标的样品都是国产样品）		
Aldehyde	Limit	≤0.2%（40 times）	≤0.05%	≤0.05%	≤0.05%
	Results	100%	68. 7%（超标的样品也都是国产样品）		
Hydrazine	Limit	未规定	≤0.0001%	≤0.001%	≤0.001%
	Results	_	2批国产样品超标		

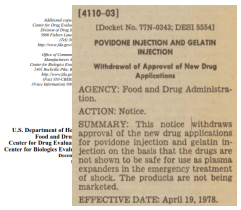
Manufacturing process of povidone to remove 2-pyrrolidone 聚维酮去除2-吡咯烷酮生产工艺	Advantage	Disadvantage
Ultra-filtration membrane filtration 超滤膜过滤去除法	Low material loss and short time 物料损失低,工艺用时短	High cost and more polluted water 成本高，废水较多
Adsorption 吸附法	Simple equipment 设备简单	Time consuming and large material loss 耗时，物料损失较大

Toxicity of 2-pyrrolidone impurities

聚维酮——2-吡咯烷酮杂质的毒性

Guidance for Industry

Q3C Impurities: Residual Solvents


[4110-03]

[Docket No. 77N-0343; DESI 5554]

POVIDONE INJECTION AND GELATIN INJECTION

Withdrawal of Approval of New Drug Applications

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: This notice withdraws approval of the new drug applications for povidone injection and gelatin injection on the basis that the drugs are not shown to be safe for use as plasma expanders in the emergency treatment of shock. The products are not being marketed.

EFFECTIVE DATE: April 19, 1978.

➢**According to the European Chemicals Agency (ECHA), the no Observed Adverse Effect Level (NOAEL) of 2-pyrrolidone is 207mg/kg/d. And based on ICH Q2C, the acceptable daily intake (ADI) of 2-pyrrolidone is calculated to be 41.4mg/d.**

参考欧洲化学品管理局(ECHA)的毒理学数据库，2-吡咯烷酮的无明显损害水平(NOAEL)为207mg/kg/d。依据ICH Q3C指南方法计算2-吡咯烷酮的每日允许摄入量为41.4mg/d。

◆ Risks

① In the FDA's 1978 announcement, all products used in intravenous injection or containing PVP were recalled. Because PVP interferes with the coagulation process and affects the identification of blood type in blood transfusion or distribution.

FDA于1978年颁布通告，将用于静脉注射剂中使用或含有PVP的产品全部召回，原因是PVP妨碍凝血过程，在输血或配血中的影响血型的鉴定。

② The limit of 2-pyrrolidone is an urgent problem

2-吡咯烷酮的限度是个急需关注的问题

◆ Measures

The limit of 2-pyrrolidone is NMT 0.5% in Copovidone monograph from USP, EP and BP. Both povidone and co povidone are water-soluble substances with similar uses and the routes of administration, so the limit of 2-pyrrolidone should be the same,' NMT 0.5%'.

美国药典、欧洲药典及英国药典中"共聚维酮" 要求"2-吡咯烷酮"限度不得过0.5%。聚维酮与共聚维酮均为水溶性物质，用途和给药途径相似，其中的2-吡咯烷酮限度也应该相同，都应为"不得过0.5%"。

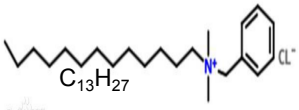
In summary, it is scientific and reasonable that 2-pyrrolidone limit is NMT 0.5%.

综上所述，聚维酮中"2-吡咯烷酮限度不得过0.5%"更科学合理。

Ophthalmic excipient——Benzalkonium chloride

眼用辅料——苯扎氯铵

- 苯扎氯铵：是氯化二甲基苄基烃铵的混合物(C8-C18)，含烃胺盐$C_{22}H_{40}CL_N$应为95.0%-105.0%。
- 主要成分含有C_{13}与苯扎氯铵同系物（C_{14}, C_{16}），不同的碳原子数，抑菌效力不同，C_{12}为苯度氯胺。



Benzalkonium chloride

No.	Batch No.	Manufactures	Proportion of composition		
			n-C_{12} (%)	n-C_{14} (%)	n-C_{16} (%)
Y1	20150618	A	100	-	-
n-C_{14} monomer	C1520084	B	-	100	-
n-C_{16} monomer	D1514040		-	-	100

《消毒技术规范》（2002版）的规定进行实验

样品名称	MIC（最小抑菌浓度）			
	金黄色葡萄球菌	大肠埃希菌	白色念珠菌	黑曲霉
C_{12}单体	1.53	48.83	24.41	3.05
C_{14}单体	3.05	6.10	6.10	12.21
C_{16}单体	3.05	24.41	3.05	6.10

每种单体和不同烷基组成比例的样品，对金黄色葡萄球菌、大肠埃希菌、白色念珠菌和黑曲霉等4种细菌的MIC明显不同。

Home ▸ Human regulatory ▸ Marketing authorisation ▸ Product information ▸ Reference and guidelines ▸ Excipients labelling

Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use'

Email Print Help Sh

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Benzalkonium chloride	09/10/2017	Ocular	Zero	Benzalkonium chloride may be absorbed by soft contact lenses and may change the colour of the contact lenses. You should remove contact lenses before using this medicine and put them back 15 minutes afterwards. Benzalkonium chloride may also cause eye irritation, especially if you have dry eyes or disorders of the cornea (the clear layer at the front of the eye). If you feel abnormal eye sensation, stinging or pain in the eye after using this medicine, talk to your doctor.	From the limited data available, there is no difference in the adverse event profile in children compared to adults. Generally, however, eyes in children show a stronger reaction for a given stimulus than the adult eye. Irritation may have an effect on treatment adherence in children. Benzalkonium chloride has been reported to cause eye irritation, symptoms of dry eyes and may affect the tear film and corneal surface. Should be used with caution in dry eye patients and in patients where the cornea may be compromised. Patients should be monitored in case of prolonged use.
Benzalk				Benzalkonium chloride may cause irritation or swelling inside the nose, especially if used for a long time.	Long-term use may cause oedema of the nasal mucosa.
Benzalkonium chloride	09/10/2017	Inhalation	Zero	Benzalkonium chloride may cause wheezing and breathing difficulties (bronchospasm), especially if you have asthma.	
Benzalkonium chloride	09/10/2017	Cutaneous	Zero	Benzalkonium chloride may irritate the skin. You should not apply this medicine to the breasts if you are breast-feeding because the baby may take it in with your milk.	Use during pregnancy and lactation is not expected to be associated with harmful effects to the mother as cutaneous absorption of benzalkonium chloride is minimal. Not for application to mucosa.

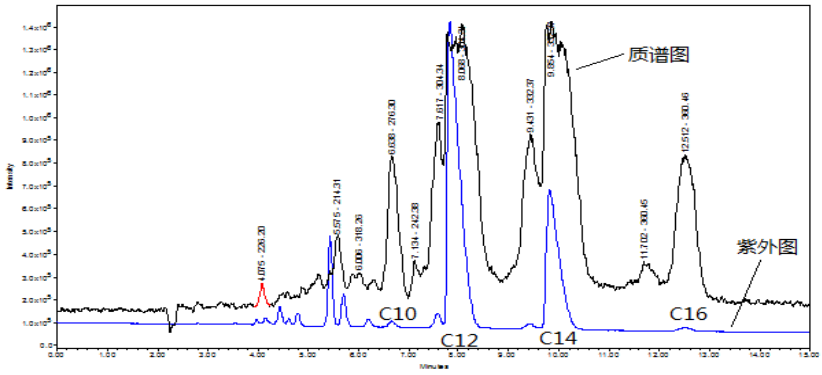
Benzalkonium chloride may also cause eye irritation, especially if you have dry eyes or disorders of the comea (the clear layer at the front of the eye). If you feel abnormal eye sensation stinging or pain in the eye after using this medicine, talk to your doctor.
苯扎氯铵可能会引起眼睛刺痛，尤其是眼睛干涩或者患有眼部疾病时。用药后一旦感觉到眼睛不适、肿胀或者疼痛，应咨询医生后再用药。

C_{10} determined by HPLC-MS

HPLC-MS法检测C 10

HPLC-MS can separate C_{10}, C_{12}, C_{14} and C_{16}, and analyze them accurately and quantitatively.
HPLC-MS法可以分离C_{10}、C_{12}、C_{14}和C_{16}，并分别对其准确定量分析

苯扎氯铵



- HPLC-MS: ACQUITY UPLC H-Class PDA-QDa system; Column: Intersil CN column, 3um, 4.6X100 mm; Temperature: 35℃; Injection volume: 5-8uL; Detection wavelength: 215nm; QDa detection: ESI+, Scan, SIR mode; Mobile Phase A: acetonitrile; mobile phase B: 100 mM NH4Ac in water (pH = 5.0); Flow rate: 1.00 ml/min; Isocratic elution: A/B = 50:50

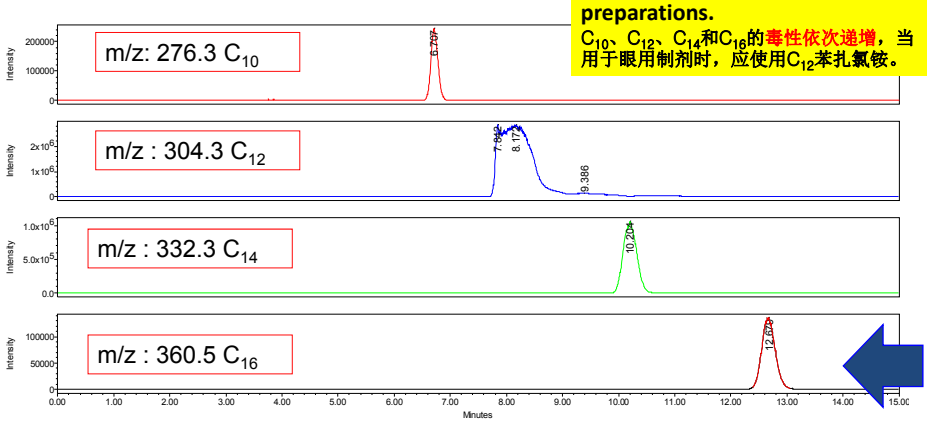
仪器系统:ACQUITY UPLC H-Class PDA_QDa 系统;色谱柱:Intersil CN柱, 3um,4.6X100 mm;温度:35℃;进样量:5-8uL ;检测波长:215nm;QDa检测:ESI+, Scan, SIR模式;流动相 A:乙腈;流动相 B:100mM NH4Ac 水溶液(pH=5.0);流速: 1.00ml/min;等度洗脱:A/B = 50:50

C_{10} determined by HPLC-MS

HPLC-MS法检测C $_{10}$

The toxicity of C_{10}, C_{12}, C_{14} and C_{16} increased in turn, and C_{12} should be used when used in eye preparations.

C_{10}、C_{12}、C_{14}和C_{16}的毒性依次递增，当用于眼用制剂时，应使用C_{12}苯扎氯铵。



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Technical requirements of pharmaceutical excipients in Ch.P

药用辅料的技术要求

Name	
1. Guidelines for sustained release, controlled release and delayed preparations	缓释、控释和迟缓制剂指导原则
2. General rules for capsules (Empty/Vacant) capsules)	胶囊（空心胶囊）通则
3. Principles of generic designation of pharmaceutical excipients in China	中国药用辅料通用名称命名原则
4. Guidelines for general requirements for pharmaceutical excipients of Chinese Medicinal Herbs Preparation	中药炮制辅料通用要求指导原则
5. Guidelines for production and quality control of pharmaceutical excipients (premix / co-processing)	药用辅料（预混/共加工）生产和质控技术指导原则
6. Study on general principles for the production and quality control of animal source pharmaceutical excipients	动物来源药用辅料生产和质量控制通则研究
7. Establishment of functional evaluation methods for pharmaceutical excipients	药用辅料功能性相关评价方法的建立
8. Determination of molecular weight and molecular weight distribution of macromolecular pharmaceutical excipients	大分子药用辅料分子量及分子量分布测定
9. Guidelines for evaluation of biological safety of pharmaceutical excipients	药用辅料生物安全性评价方法指导原则
10. Guidelines for research on compatibility between pharmaceutical excipients and drugs	药用辅料与药物相容性指导研究原则
11. Guidelines for research on the applicability of pharmaceutical excipients	药用辅料适用性研究指导原则
.....	

Content/目录

Conclusion 总结

Pharmaceutical excipients are important components of drugs, which quality could affect the quality and safety of drugs directly, especially the pharmaceutical excipients for injection. A quality problem with a drug can only affect one point, but if a quality problem with a kind of excipient affects all drugs that use the excipient, then drug will be affected in whole.

For many years, China attaches great importance to the quality of excipients and implement review and approval management, which guarantees overall quality of excipients.

Furthermore, on the one hand, the quality and safety of excipients for injection, interaction with API, influence of preparations on absorption and effectiveness ought to be paid more attention. On the other hand, it is necessary to strengthen the study of Critical Quality Attributes of excipients, which could help manufactures find out the difference between domestic excipients and original excipients and guide them to select excipients scientifically. It could enhance the quality of domestic excipients and promote the industrialization level fundamentally in order to improve the safety of drugs.

药用辅料是药品重要的组成部分，其质量直接影响着所有药品的质量安全，尤其是注射用辅料。一个药品出现质量问题只会影响一个点，但若一个辅料出现质量问题就会影响所有使用此辅料的药品，就会影响一个面。

多年来，我国在药用辅料的管理和质量上高度重视，采取关联审评审批的管理模式，保障了药品研发的辅料整体质量。

一方面，我们更应该关注注射用辅料的质量和安全，以及与API的相互作用，对制剂的吸收和有效性的影响。同时加强对药用辅料关键质量属性的研究，从而找出国产辅料和原研辅料的差异，以及指导国内药用辅料企业和制剂企业科学的选择辅料，指导国内药用辅料企业切实提高国产辅料质量，根本上提升行业工业化水平，为提高人民安全用药。

Thank You !

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