Chinese Pharmacopeia (ChP 2020) and China Excipient Regulation Changes since 2015 – Path Forward

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Presentation Outline

Recent changes in government structure and developments concerning registration requirements

Evolution of excipient regulations in China
- Bundling Review
- Registration
- Joint Review

Chinese Pharmacopeia (ChP) challenges for global companies
- Requirements
- General Chapters
- New ChP initiatives
2018 Changes in China Pharmaceutical Regulatory Agency Structure

Old version

New version Mar. 2018

• 26 Departments
• 10 Subordinate Agency

• CFDA changed to NMPA, no more food responsibility
• NMPA reports to SMRA
• SAMR reports State Council
• SAMR is responsible to food safety

CFDA: China Food and Drug Administration
SAIC: State Administration for Industry and Commerce of the People’s Republic of China
AQSIQ: General Administration of Quality Supervision, Inspection and Quarantine

reschuffle

NMPA (National Medical Product Admin.)
• Oversight of registration & surveillance of drug, cosmetics, medical device

SAMR (State Admin. for Market Regulation)
• Consolidated role of market supervision, fair competition and quality control (merge related function from other ministries)

GAC (General Admin. of Custom)
• Oversight of import/export (merge CIQ from AQSIQ)

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Evolution of Excipient Regulations in China

2001
Drug Administration Law (No. 45)
Excipient used in drugs must meet requirement for pharmaceutical application

2004
Administration approval list decision (No. 412, The State Council)
Excipient needs to be approved by CFDA or local FDA

2005
Excipients Registration Documents Requirement (No. 61)
Domestic excipients with national standard – Local CFDA, imported excipients & New Excipient – CFDA

Aug. 18, 2015
Reform of Drug and Medical Devices Review and Approval System (No. 44, The State Council)

Aug. 10, 2016
Announcement on Excipient bundling reviewed and Approved with drug application (No. 134, CFDA)
As of 8/10/16 excipient is transferred from separate approval to bundling review/approval w/ drug application

Nov. 28, 2016
Dossier requirements of Excipient for bundling reviewed & Approval (No.155, CFDA)
Evolution of Excipient Regulations in China

- **Oct. 8, 2017**
  - Dossier Requirements of Excipient for Bundling Review & Approval (No.155, CFDA)
  - API/excipient/packaging joint-reviewed with drug application

- **Nov. 30, 2017**
  - Adjusting the Review and Approval Matters of the Drug Substance, Excipients and Packaging Materials (No. 146)
  - API/excipient/packaging joint-reviewed w/ drug application. Dossier requirement is CFDA 2016 No.155

- **Dec. 4, 2017**
  - Joint-review management regulation for API/Excipient/Packaging with finished drug
  - Joint review process begins

*Imported drugs are included in the scope*
Evolution of Excipient Regulations in China

June 5, 2018
Requirement on the Registration Documentation for Pharmaceutical Excipients (Exposure Draft)
Draft dossier requirements for joint review registration – Classification of different types of excipients

June 29, 2018
IPEC China and IPEC Federation submitted detailed comments
Requested significant changes regarding the level of detail needed for manufacturing process, validation, stability, etc.

April 2019
Announcement on Further Improving the Bundling Review and Approval with Drug Product and its Related Supervision Matters (Draft for Comment) (NMPA)

July 16, 2019
Announcement of the National Medical Products Administration on Further Improving the Bundling Review and Approval with Drug Product and its Related Supervision Matters (No. 56)
Enforcement Aug. 15, 2019
November 2019

Technical Guideline for Making Post-Approval Changes to Chemical Drug Products – Draft for Comment

- Approved drugs must be re-registered every 5 yr
  - Provincial MPA – domestically produced drugs
  - CDE – imported drugs
- Considers level of risk and impact of changes on safety, efficacy and quality of the drug product
  - Post-marketing evaluation & studies of the drug
  - Adverse reactions
- Major, moderate, minor changes defined
  - Includes changes in excipients
Old vs New Drug Approval Process

**Before 2016**

- APIs, excipients & packaging materials
  - Reviewed & approved separately
  - Individual licenses (domestic) or Import Drug License (IDL)

**Before 2017**

- Imported drugs
  - APIs, excipients & packaging materials were included in the drug product submission package
  - API information was provided in a CTD type document
  - Excipient & packaging materials – only basic information provided

**2017**

- Joint review – applies to all domestic & imported drugs
  - APIs, excipients & packaging materials each have separate dossiers submitted by supplier
  - Joint review of these dossiers with finished drug dossier
China Dossiers:
Two-step Registration Process for Suppliers

1st step: Obtain tentative register number (not published):
- name
- local vs. imported
- packaging size
- administrative route

2nd step: Submit dossier via compact disk to CDE

Submit additional/revised documentation

Completeness assessment by Agency

Publish formal registration number*

Documentation ready for Joint Review, triggered by drug product submission

* Registration number published along with material name, manufacturer name and address, local vs imported, packaging size, registration date and joint review status publicly visible under [http://www.cde.org.cn/yfb.do?method=main](http://www.cde.org.cn/yfb.do?method=main)
Drug MAH needs to evaluate excipient changes on their products and then file a supplement or filing based on the results.
Format of LOA → Similar to LOA for U.S. DMF

- **Excipient Information**
  - Excipient (or authorized) company
  - Excipient product name
  - Administration route usage of the excipient
  - Excipient registration no.

- **Drug Information**
  - Name of MAH holder
  - Drug name with dosage form
Key Information on CFDA No. 146

Establishment of the platform for obtaining a Registration No. is still on-going

- Excipient company completes general information on CDE website
- Excipient company sends dossier to CDE (in CD-ROM)
  - Completeness assessment by CDE
    - Within 5 working days
    - YES: Information public (in table format)
    - NO: Information supplement notification

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Joint Review Registration Dossier requirements
No. 155 (2016)

- Detailed information required
  - Manufacturing process, equipment, process controls, process development, validation, site-specific stability testing
  - Specific process conditions, model & serial #s for every piece of equipment, etc.
  - More information than required in any other market!

- Most global excipient manufacturers have not provided this level of detail in their dossiers
  - Intellectual property considerations

- Do not know what is deemed acceptable until these dossiers are reviewed as part of a bundled drug product review process
Announcement No. 56

- Issued July 16, 2019
- Enforcement August 15, 2019
- Improvement based on Announcement No. 146 (2017) Joint Review Process
- **Replaces** No. 155 with Announcement No. 56 Appendix 1. Requirements for Registration Information of Pharmaceutical Excipients

*Result: Simplifies the document requirements of the Bundling Review filing with the information in Appendix 1*

- States that on-site inspection for manufacturing of excipients shall be carried out in accordance with the GMP for Pharmaceutical Excipients (Safety Document [2006] No. 120 issued by NMPA)

*Result: Local FDA will have responsibility for on-site GMP inspections*
CDE will transfer approval information of the API, excipients & packaging materials to the registration platform and assign registration numbers

- Exceptions: those banned from using, eliminated or annulled by the State

- Registration status of excipients & packaging materials will be identified on the registration platform as:
  - “A” (Active): Accepted and certified or approved with drugs for bundling review
  - “I” (Inactive): Accepted but not certified or not approved with drugs for bundling review

Result: All approved IDLs or local excipient licenses certified will be identified as “A” in the CDE platform
Announcement No. 56

Appendix 4. Annual Report

- Applicant must submit an Annual Report in the 1st quarter of every year via the CDE platform.
- Report must include a summary of any API, excipient and packaging materials changes from the previous year.
- If no changes were made, a statement must be provided to that effect including information regarding the relevant drug product, such as the name of the pharmaceutical company, the drug product name, etc.

Result: Change control records and LOA information
Announcement No. 56  Appendix 1

Classification of Excipients

Excipients **having not been used** in any drug products marketed both domestically & overseas, including

1.1 Excipients with new molecular structure and excipients not belonging to 1.2 and 1.3
1.2 Simple chemical structure changes (e.g. salt base, hydrate, etc.) to excipients which have history of use
1.3 The excipients obtained from the co-processing of the two or more excipients which have history of use
1.4 Excipients having a history of use but the route of administration changed

Excipients **having been used in any drug products marketed both domestically and overseas and**

2.1 Excipients not included in ChP/USP/EP/BP/JP
2.2 Excipients that have been included in one of USP/EP/BP/JP, but not used in domestically marketed drugs
2.3 Excipients that have been included in one of USP/EP/BP/JP, but not included in the ChP
2.4 Excipients already included in the ChP

Excipients **having been used in any foods or cosmetics and**

3.1 Excipients for oral preparations with national food safety standards
3.2 Excipients used in topical drugs with national or industrial standards for cosmetics
Announcement No. 56 Appendix 1
Requirements for Registration Documentation

+ Need to provide the information as required
- Do not need to provide the information
± Provide the information depending on reviewer’s need

According to the different classification of excipients, either of the registration data between 3.2.1 and 3.2.2, between 3.4.1 and 3.4.2, and between 4.1.1 (1) and (2) could be selected to provide

**High Risk Excipients Include**

- animal or human-derived excipients
- excipients for injection
- ophthalmic preparations
- inhalation preparations
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Chinese Pharmacopeia 2020

Issues impacting industry

Expected publication
July 2020
Chinese Pharmacopeia (ChP) Requirements

- All excipients in the registration dossier that have a ChP monograph **should** meet the ChP requirements at time of submission for use in **new drug product** joint reviews (certain exemptions exist which must meet the GB stds)

- A number of commonly used global excipients cannot meet the ChP 2015 requirements (limits and/or test methods)!

- All **existing drug** products **should** contain excipients which meet the ChP requirements when they come up for renewal (every 5 years) – no clear policy at this time

- Global pharma companies are currently trying to provide various types of justifications when ChP compliance is not possible – **outcomes uncertain at this time**!
Recent ChP 2020 Proposed General Chapters

Guideline for Applicability Study of Pharmaceutical Excipients (FRCs)
- Non-mandatory FRCs (tentative confirmation)

Nomenclature of Pharmaceutical Excipients in China
- Recommended ChP follow WHO Good Pharmacopoeial Practices

Pre-mixed/Co-processed Pharmaceutical Excipient Production and Quality Control Guidelines
- Includes lists of [possibly mandatory] specific FRC tests
- Recommended removing pre-mixed excipients

Guidelines for Production of Control Quality of Animal-Derived Pharmaceutical Excipients
- Extensive controls
Recent ChP 2020 Proposed General Chapters

**Genotoxic Impurities**
- Recommended to align with ICH M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceutical Limit Potential Carcinogenic Risk Step 4 Guideline

**Residual Solvents**
- Recommended to align with ICH Q3C

**Elemental Impurities**
- Recommended to align with ICH Q3D
- Will not be implemented in ChP 2020

**Change Control**
- Still in draft – IPEC China recommending IPEC Significant Change principles

- Recommended following ICH guidelines

Proposed Announcement Regarding Sterility Test for Pharmaceutical Excipients

- Proposing to replace “sterility” check in monographs with a General Chapter
• Encourage and regulate drug MAH’s, excipient manufacturers, inspection agencies, educational and research institutions, social groups, etc. to undertake or participate in national pharmaceutical excipient standard research, and clarify the qualifications, responsibilities and work processes of the drafting and review units of the ChP standards for excipients.

• **Improved guidelines on the types and number of samples that should be collected when drafting a monograph** – states that samples from both domestic and foreign excipient manufacturers should be collected whenever possible.
Non-Harmonized Example - Hypromellose

**Assay:**
Changed Type 2910 % hydropropoxyl from 27.0-30.0 to 28.0-30.0 - aligned with other compendia

**Acidity/Alkalinity (pH):**
Change from a 1% to 2% solution – aligned with other compendia
According to GLP, the range for the temperature of the test solution should vary $\pm 0.2^\circ$C, not $\pm 2^\circ$C
When to take the measurement - read the pH value after the probe has been immersed for $5 \pm 0.5$ min

**Loss on Drying (LOD):**
Regarding the change from 1 hr. to 2 hr. drying there should be no difference in test results between 1 and 2 hr. Other compendia use a 1 hr. drying time.

**Heavy Metals:**
Change from NMT 20 to NMT 10 ppm.
ChP requires testing of each attribute on each lot the testing requirement is a serious issue for manufacturers. Not implementing ICH Q3D EIs.
Non-Harmonized Example - Hypromellose

**Methanol, Propylene Oxide, Isopropanol, Toluene, Dichloromethane, Trichloromethane, Trichloroethylene, Dioxane and Benzene:**
- Recommended removing residual solvents requirements and chromatographic methods in the monograph, place in a General Chapter & harmonize with ICH Q3C
- Propylene oxide is not a solvent

**Arsenic Salt:**
Unnecessary, As is included in the heavy metals test

**Insoluble Substances in Water:**
Unnecessary, the test is unreliable, not reproducible and should be removed

**Formate Ion (HCOO-), Acetate Ion (CH3COO-) and Chloride Ion (Cl-):**
- No reason for the inclusion of these specifications
- Formic acid and acetic acid are part of ICH Q3C
- Chloride ion test is unnecessary

**Labeling: Molecular Weight and Molecular Weight Distribution and Particle Size “should be labeled”:**
- Add definitions for label and labeling in the General Notices
- These are all FRCs
Acknowledgements

- Colin Li – Former Chair of IPEC China
- Suming Cissy Wang – Current Chair of IPEC China
- Andy Peng – DuPont
- Martin Tao - DuPont