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The New Chemistry, Manufacturing, and Controls (CMC) Regulations in China

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Abstract

An overview of the revised drug regulations, application process, and the requirements for the post-approval CMC amendments in China is presented in this article. The National Medical Products Administration (NMPA) is the regulatory authority in China that is responsible for evaluation of the new drug registration applications and the amendments during the life cycle of the drug. NMPA launched the revised Drug Registration Regulations (DRR) from July 2020 through 2024. This is the first major revision of the drug regulations in China since 2007 and has significant impact on how the new drug registration applications and life cycle amendments are filed and evaluated by the NMPA. China's adaptation to ICH and a comparison with US FDA, EMA, and PMDA regulations is discussed.

Introduction

The National Medical Products Administration, NMPA (1), previously known as the China State Food and Drug Administration (CFDA), is the regulatory authority in China that is responsible for evaluation of the new drug registration applications and the amendments thereof during the life cycle of the drug. The NMPA works closely with the Centre for Drug Evaluation (CDE) for safety, efficacy, and quality based on the recently revised drug registration regulations (DRR), prevailing laws, and existing scientific knowledge. The DRR, effective July 1, 2020, is the first major revision of the drug regulations in China since 2007 and has significant impact on how the new drug registration applications and life cycle amendments are filed and evaluated by the NMPA (2-5).

Authors discuss the revised drug regulations in China for Chemistry, Manufacturing, and Controls (CMC) post-approval change amendments in light of the International Conference on Harmonization (ICH) guidances, the US FDA (6), European Medicines Agency (EMA) (7), and Japan's PMDA (8) Regulations.

National Medical Products Administration (NMPA) Organization

The NMPA is incharge of the overall administration of drug registrations nationwide and is responsible for establishing the systems, policies, guidances, and streamline practices. It provides supervision of its subordinate bodies in accordance with the law. The NMPA affiliate organizations include, Centre for Drug Evaluation (CDE), National Institutes for Food and Drug Control (NIFDC), Centre for Medical Device Standards Management, Centre for Drug Re-evaluation (CDR), Centre for Medical Device Evaluation (CMDE), The Centre for Administrative

Services and Complaints & Reports, The Centre for Information(NMPAIC), National Institute for Drug Control (NIDC), Chinese Pharmacopoeia Commission (CPC), and Centre for Food and Drug Inspection (CFDI). Amongst these CDE is responsible for evaluating clinical trial applications, marketing authorization applications (MAA), post-approval change applications, and registration renewal applications of drugs manufactured domestically and outside the country.

Revised Drug Registration Regulations (DRR) for the Post-approval Changes

Subsequent to the revised drug regulations, the NMPA issued a series of guidances in 2021-2024 to facilitate implementation of the new DRR provisions that govern drug manufacturing, cGMPs, GCPs, and post-approval management of drugs & amendments (2-5). These include interim regulatory guidelines in June 2022 termed as "Articles" for managing and evaluating the post-approval change applications based on the revised DRR.

The 35 Articles are divided into 5 chapters as below:

- **Chapter I General Provisions (Articles 1-6)**
- **Chapter II Circumstances of Change (Articles 7-20)**
  - **Section 1 Change Management of MAHs (Articles 7 – 11)o Section 2 Change Management of Drug Manufacturing Sites (Articles 12-16)**
  - **Section 3 Change of Other Drug Registration Management Items (Articles 17-20)**
- **Chapter III Confirmation and Adjustment of Change Management Categories (Articles 21-23)**
- **Chapter IV Procedures, Requirements, Supervision, and Administration of Changes (Articles 24 -31) Chapter V Supplementary Provisions (Articles 32-35)**

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The above articles provide necessary framework for effective life-cycle management of drugs in China.

The revised drug registration regulations (DRR) provide three registration categories, viz., innovative drugs, improved new drugs, or genetic drugs for chemical or biologic products. This is a significant improvement from 2007 regulations which consisted of a complex system of 15 registration categories. Similarly, proposed revisions in regulations differentiate the drugs that are manufactured domestically or outside China. MAH should note that the manufacturing of drugs within or outside China plays a crucial role in review, approval, implementation timelines, and subsequent market supply.

The NMPA also formulated the "Provisions for Change Management of the Post-approval Drugs (Interim)," effective February 10, 2021. NMPA expects MAHs shall assess the changes to the approved chemical drugs, according to relevant technical guidelines and then choose the change type following the guidance, "Requirements on Change Items and Declaration Materials for Approved Chemical Drugs" [3-5].

Post Approval Changes

As per revised DRR the changes to already approved drugs are categorized as Major, Moderate, or Minor ((Article 76 – 81 of the Provision of Drugs (5). The technical guidelines further provide examples of these categories.

Major changes

These may include CMC or clinical changes involving major process changes, equipment changes, batch size changes beyond 2X, and change in the MAH and/or the commercial product name (2). These changes cannot be implemented until approved by the CDE. Note, the significant difference with EMA and FDA regulations wherein batch size change below 10X is considered as a minor change and may be reported in an annual report, unless there are formulation or process changes involved.

Moderate changes

These include changes involving addition of a test in the specification, tightening a specification or making a non-technical change such as changes in the local registration agent or certain packaging changes for imported drugs. These must be filed with the CDE before implementation.

Minor changes

These include CMC or clinical changes related to the excipient vendor (without lowering the grade or specification) or change in the package size. These do not require CDE approval but should be reported in the annual report.

Table 1 below summarizes and compares change type, filing categories, HA approval, implementation timelines, and application fees with other major regions.

Table 1. Overview of the post approval change categories, review/approval times and fees as per revised DRR and comparison with the US FDA, EMA, and PMDA regulations

Change Type	China Filing Category	FDA/EMA/PMDA Filing Category (6-8)	Implementation	CDE Review Time (China)	Fees
Major change/s	Prior Approval Application	US FDA – PAS EMA - Type II Variation Japan (PMDA) – PCA	After approval by CDE	80 Working Days (Domestically manufactured)	99,600 RMB
				200 Working Days (Imported drug)	2,83,600 RMB
Moderate change/s	Notification to CDE	US FDA - CBE-30 EMA - Type IA/IB Japan (PMDA) – PCA	Tell & Do	Implement after	30 Days review
Minor change/s	Annual Report	US FDA - Annual report EMA - Type 1A Japan (PMDA) – MCN	Do & Tell	No approval required	No fees

RMB - Chinese Yuan; FDA – Food and Drug Administration; EMA – European Medicines Agency; PMDA – Pharmaceuticals and Medical Devices Agency; PCA (Japan) – Pharmaceutical Change Application; MCN (Japan) - Minor Change Notification

ICH Implementation in China

On June 2, 2017 China officially joined the ICH and began to integrate procedures and regulatory guidances into the Chinese drug regulatory system. In June 2018, NMPA became a member of the ICH Management Committee to further participate in the international drug development and registration process. NMPA on its website states that it wants to fully draw on the guidelines of developed regulatory agencies in Europe (EMA), the US (FDA), and Japan (PMDA) to ensure that China aligns with international standards. Implementation of ICH M4Q Common Technical Document (CTD) in 2018 allowed Chinese marketing registration applications to align with the US FDA and EMA's new drug application format and technical content. As of May 2021, China had fully implemented all three ICH Tier 1 guidelines (ICH Q1, Q7, and E6) and implemented the five ICH Tier 2 guidances (ICH M1, M4, E2A, A2B, and E2D) by 2022.

To further align with the international standards, the NMPA has adopted the ICH guideline, "Q12: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management" on August 25, 2023 (5). The ICH Q12 guideline provides a new approach and regulatory tool for managing post-approval changes for the medicinal products (PACMP). NMPA, however, expects MAH to fully evaluate and inform the Agency whether it has adequate research and development foundation data and implementation conditions as recommended in the ICH guidance (NMPA CDE Notice No. 48 of 2020). A transition period of 24 months up to August 2025 is estimated for the full implementation of ICH Q12 guidance or may be extended further, as necessary.

Evaluation and Approval Process for CMC Post-Approval Change Applications

Once a prior approval application or notification of change/s is submitted to the CDE it is evaluated as per the guidance in a timely manner. The CDE review and approvaltimelines are illustrated in Figure 1.

Figure 1. Post-Approval Change Application Review and Approval Process by CDE

CDE receives application/notification form for the changes (Major/Moderate)

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Formal screenings by CDE - 5 Working days

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Payment of fees per submission category

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CDI issues notice of supplement receipt, correction of Notice of Inadmissibility

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CDI issues any questions/additional information request during review

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MAH responds to questions/additional information request

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CDE issues acceptance notice after further review

Documentation for the Post-Approval CMC Submissions

There is great emphasis on documentation and compilation of these in certain format required by the CDE. While applicable Module 3 CTD sections are required as per ICH guidance M4Q and Q12 there are several regional documents required to be included in Module 1 for the major and moderate change amendments. These are listed below.

Module 1 Documentation Requirements

- Justification and Rationale for the change/s
- European Medicines Agency (reference country) approval for the change/s (mandatory requirement if the product is marketed in the European Union)
- Quality control specifications registered with the Agency should be confirmed and verified with the proposed change
- Revised drug specification document (if change in specification).
- Summary of Packaging Components (SmPC), if product label is impacted by the proposed changes along with copies of sample labels.
- CMC study reports, if relevant (e.g. process validation, comparative dissolution)
- Process validation samples batch listing document (major changes)
- Any other data specified by CDE.
- Certificates of analysis for the pre- and post-change drug substance and/or drug product, as applicable
- Process validation (PV) batch samples with at least 12 months before expiry for major post approval changes
- Manufacturing Process Information Sheet (MPIS) - Drug substance
- Manufacturing Process Information Sheet (MPIS) - Drug product
- Registered Quality Standard (RQS)
- Justification and Rationale document should be provided in Module 1 to include a comparison of current and proposed changes, manufacturing process description, critical process parameters, equipment list for each unit operation, and comparison of pre- and post-change stability data.
- The chromatograms of relevant drug substance and/or drug product batches placed on stability for the assay and related substances test parameters. Often CDE may request chromatograms of the pre-change stability batches as well during review of the application.
- The Registered Quality Standard (RQS) document is issued by the CDE after drug product registration is completed. RQS consists of a summary of the product details, such as product name, dosage form, manufacturer name, site details, quality control specifications and test methods in Chinese language. MAH should get it translated in appropriate language (e.g. English) and ensure information is consistent with the Module 3 dossier. The RQS document should be available at the drug product manufacturing site and MAH regulatory department. If there is any discrepancy, MAH should contact CDE and resolve the issue.

Manufacturing Process Information Sheet (MPIS)

China does not require Module 2 Quality Overall Summary. Instead, it incorporates a summary of Module 3 in Manufacturing Process Information Sheet (MPIS) and RQS documents.

The drug substance and drug product MPIS documents in Module 1 are mandatory requirements in all CMC applications. These comprise product information and a comparison of the currently approved (pre-change) and the proposed (post-change) information. If there is no change in a parameter, no detailed information of approved content is expected by CDE. The detailed information expected in MPIS - drug substance and MPIS - drug product is illustrated in Figure 2a and Figure 2b, respectively.

Figure 2a: Contents of MPIS - Drug Substance

- Chemical drug substance name, structure, manufacturer name, address, responsibilities, and registration number / status
- List of starting materials, supplier name, compendial grade, chemical formula, structure and chemical name
- Manufacturing process flow chart and process controls*
- List of equipment used in the manufacturing process*
- Specifications ant test methods of critical starting materials, intermediates, drug substances and related substances (e.g. impurities)*
- Packaging component specification and test methods*

Figure 2b: Contents of MPIS - Drug Product

- Chemical drug product generic name, manufacturer/s, MAH holder name and registration no. of the drug product
- List of drug substances, excipients, unit & batch composition, supplier name, compendial grade, DMF approval no. and active/inactive status.
- List of packaging materials, supplier name, DMF approval no. and active/inactive status
- Manufacturing process flow chart, description, critical process steps & controls*
- List of equipment used in the manufacturing process unit operation*
- Specification and test methods - API, excipients, critical intermediates (if any) and drug product (release and shelf life). Detailed information should be provided for all inhouse specifications and test methods.*
- Packaging component specification and test methods*

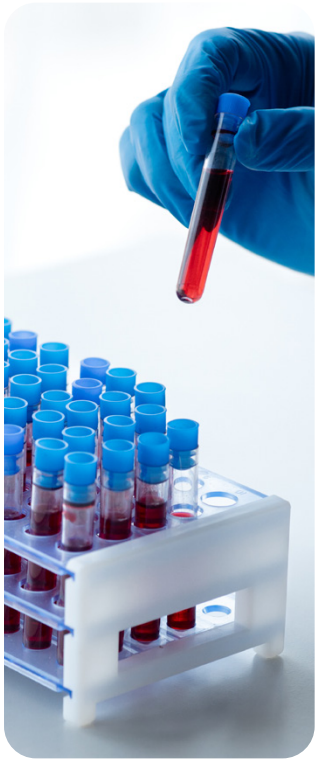
Administrative Changes

The revised drug registration regulations also include guidance on the administrative changes. The new Drug Manufacturing Certificates are numbered as an abbreviation - [Province + 4-digit year + 4-digit sequence number]. When company information (such as name or address) is updated or the license is re-issued, the original Drug Manufacturing Certificate number remains the same. In the event of a company separation, new numbers will be assigned while the original Drug Manufacturing Certificate number remains unchanged. During a company merger, one of the original Drug Manufacturing Certificate numbers will be retained. Drug approval numbers will remain the same in the case of post-marketing changes to registration items.

Unique Post-Approval Application Requirements in China

The new revised DRR provides much needed clarity in Chinese regulations and overall alignment with the ICH, and major regulatory agencies such as US-FDA, EMA and PMDA. The revised regulations also offer guidance on the lifecycle management of CMC and clinical information, based on a robust change control system in accordance with widely accepted cGMPs and GCPs.

However, information that is redundant to Module 3 CTD sections such as in the MPIS documents, Justification and Rationale, quality declarations in Module 1, comparative chromatograms and other raw data including stability data, seems to add complexity to application process. It is imperative CDE will need additional resources for reviewing these redundant data and/or documents. Some elements of these additional requirements could possibly be included into ICH recommended Quality Overall Summary (QOS), cGMPs, or verified at the time of site inspection. This could make regulatory documentation less cumbersome and confusing to the MAH and the Agency equally. Additionally, translating submission documents into Chinese presents its own challenges, particularly concerning technical study reports and the accuracy of the conclusions drawn.



2025 Policy Document

On December 30, 2024, China's General Office of the State Council issued an "Opinion" document committing to substantially improve the quality and efficiency of review and approval processes for innovative drugs and medical devices, while also significantly strengthening lifecycle oversight. The goal is to advance drug and medical device regulations, as well as review and approval efficiency and quality, by 2027. The agency envisions a modernized regulatory system by 2035 that will promote a strong and innovative pharmaceutical industry.

Partner with Syner-G for Regulatory Success in China

Navigating China's evolving CMC regulatory landscape demands precision, foresight, and deep technical expertise. At Syner-G, our team brings decades of hands-on experience in regulatory CMC strategy, dossier preparation, and post-approval change management—ensuring compliance with NMPA requirements while aligning with ICH, US FDA, EMA, and PMDA standards. Whether you are preparing your first China submission, managing complex life-cycle changes, or optimizing your global regulatory strategy, Syner-G can help you streamline processes, mitigate risk, and accelerate approvals. Contact us today to discuss how we can guide your products from development through successful commercialization in China and beyond.

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