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Review of the Development of General Chapters in the 2020 Edition of the Chinese Pharmacopoeia

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ABSTRACT

In July 2020, the National Medical Products Administration and the National Health Commission of China approved the 2020 edition of the Chinese Pharmacopoeia, which was officially enacted on December 30, 2020. The general chapters serve as the foundation for drug standards, detailing common testing procedures and implementation guidelines. Compared to previous editions, the 2020 version demonstrates notable enhancements, emphasizing scientific validity, broad applicability, practical operability, and sustainable development. This edition expands the use of sophisticated analytical technologies, strengthens methods for detecting external contaminants in traditional Chinese medicines, and aligns technical criteria more closely with global standards. By providing updated methodological and technical guidance, it supports the safe and effective regulation of pharmaceuticals in China, promotes adoption of advanced technologies, improves quality control, and reinforces regulatory measures. This review offers a thorough summary of the main updates and characteristics of the general chapters in the 2020 edition, aiming to facilitate accurate understanding and proper application.

Keywords: Review, Development, General chapter, 2020 edition, Chinese pharmacopoeia

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Introduction

Approved in July 2020 by the National Medical Products Administration (NMPA) and the National Health Commission of China, the 2020 edition of the Chinese Pharmacopoeia officially took effect on December 30, 2020. As a legally binding technical standard, it governs all aspects of drug development, production, usage, and regulation within China. The general chapters are central to ensuring the Pharmacopoeia's consistent and accurate application. This edition contains a total of 360 general chapters, comprising 23 newly added and 83 revised entries, reflecting both the current state of China's pharmaceutical technology and alignment with international standards for drug quality control.

Broader use of advanced analytical methods

The 2020 edition introduces and updates numerous analytical methods to improve accuracy and safety. Method 0451, "X-ray Fluorescence Spectroscopy," provides protocols for analyzing elemental impurities qualitatively and quantitatively [1–9]. Oscillating transducer density meters were incorporated into method 0601, "Determination of Relative Density" [10, 11]. Method 0713, "Tests of Fat and Fatty Oil," was revised to include melting range, saponification value, and iodine value, along with additional parameters such as unsaponifiable matter, fatty acid composition, alkaline impurities, anisidine value, sterols, and trans fatty acids [12–16].

Modern molecular techniques were added, including polymerase chain reaction (method 1001), bacterial DNA identification (method 1021), and DNA sequencing (method 9108), enhancing precision in drug identification and clinical safety [17–22]. Consistent with the 3Rs principle of animal testing, many in vitro, instrument-based methods now replace in vivo biological tests. Biological assay methods were expanded, with anti-factor IIa and

anti-factor Xa tests included in method 1208, "Biological Assay of Heparin" [23–27] and heparin-binding capacity testing added to method 1213, "Biological Assay of Protamine Sulfate" [28–32]. Sterilization procedures were updated in method 1421, introducing vapor-phase and liquid-phase techniques to ensure sterility in production [33–36], while the monocyte activation test was incorporated in guideline 9301, "Application of Safety Tests for Injection" [37–42]. Guidelines 9099 and 9100 were added to guide verification and transfer of analytical procedures in accordance with standards from the United States Pharmacopoeia (USP) and the American Association of Analytical Chemists [43–49].

Analytical methods were further refined for broader applicability. Method 1105, "Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests," now includes improved aerosol sample preparation and specific guidance for testing small-dose, low-content, and limited-batch samples. Method 1107, "Microbiological Acceptance Criteria of Nonsterile Pharmaceutical Products," updated acceptance criteria for semisolid preparations to match the strictness required for liquids. Method 1121, "Antimicrobial Effectiveness Testing," revised definitions and scope for antimicrobial preservatives and adjusted recovery rates for suitability tests, aligning with method 1105 [50]. Additional newly introduced and revised testing methods are summarized in **Table 1**.

Table 1. Additions and revisions in the general testing methods of the Chinese Pharmacopoeia 2020 edition

General chapter	Additions and revisions
0421, Raman Spectroscopy	Introduced transmittance, tip-enhanced Raman spectroscopy, and imaging methods; broadened their uses in physics, chemistry, process monitoring, and related analytical areas.
0512, High-Performance Liquid Chromatography	Provided comprehensive updates on recent HPLC advances and applications. Incorporated details on multidimensional HPLC, charged aerosol detection, modified chromatographic parameters, and standard qualitative techniques.
0661, Thermal Analysis	Added a thermogravimetry-mass spectrometry approach to enable qualitative and quantitative determination of crystallization solvents (including water) or other volatile substances in samples.
0981, Crystallinity	Included differential scanning calorimetry for assessing crystallinity via sharp endothermic peaks in crystalline substances or dispersed (or absent) peaks in amorphous ones. This technique can also distinguish crystal forms when endothermic peak positions differ among solid-state polymorphs of the same compound.
0991, Determination of Specific Surface Area; 0992, Determination of the Density of Solids	Supplied fundamental definitions and terms for specific surface area and solid density, along with descriptions of instruments and measurement procedures.
1143, Test for Bacterial Endotoxins; 9251, Guideline for the Application of the Bacterial Endotoxin Test	Established traceability to international reference standards and addressed false-positive outcomes with handling strategies to prevent misjudgment from β-glucans. Updated the gel-clot technique by eliminating the initial lysate-filling step before endotoxin addition. Standardized interference experiment design, execution, and limit criteria for consistency and quality; included guidance on endotoxin limits, method selection, and sample pretreatment amid lysate shortages. Introduced the recombinant factor C assay, appropriate for samples with β-glucans, factor B, or prothrombin, to alleviate resource constraints in amoebocyte lysate.
1146, Test for Histamines; 9301, Guideline for the Application of Safety Tests for Injections	Added procedures for preparing histamine test solutions, method suitability verification, and minimum valid concentration assessment.
9015, Guideline for Studies and Quality Control of Drug Polymorphisms	Incorporated solid-state nuclear magnetic resonance spectroscopy. Variations in the chemical environment of identical nuclei across polymorphs produce distinct chemical shifts, coupling constants, and relative intensities, facilitating crystal form identification.

Enhanced methods for detecting exogenous contaminants in traditional chinese medicines (TCMs)

The 2020 edition of the Chinese Pharmacopoeia introduced significant improvements in detecting exogenous pollutants in TCMs. Method 2341, "Determination of Pesticide Residues," was updated to include both qualitative screening and quantitative analytical approaches, such as gas chromatography-tandem mass spectrometry (GC-

MS/MS) and high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS). Qualitative screening allows rapid assessment, risk monitoring, and early-warning testing of pesticide residues, while pesticides with specific requirements can be directly measured using quantitative methods. The total number of pesticides monitored in this edition has increased to 592, with 88 pesticides analyzed via GC-MS/MS and 523 via HPLC-MS/MS. For compounds amenable to both techniques, the preferred analytical method is specified, and the maximum number of characteristic ions is recommended [51–56].

Method 2351, "Determination of Mycotoxins," now includes highly sensitive, low-detection-limit techniques for mycotoxin analysis, such as HPLC-MS/MS for aflatoxin and patulin; HPLC and HPLC-MS/MS for ochratoxin A, zearalenone, and vomitoxin; and multi-mycotoxin detection via HPLC-MS/MS. However, these methods require complex sample preparation, specialized instruments, and trained personnel, limiting their widespread application in routine TCM quality control. To address this, a rapid, sensitive, straightforward, and cost-effective ELISA method for aflatoxin detection has been introduced as a practical tool for quality assurance of TCMs in China **(Table 2)** [57–63].

Table 2. Comparison of immunological and chemical methods for the determination of aflatoxins.

Item	Pretreatment	Sensitivity	Type	Percent recovery (%)				Equipment	Speed	Cost (RMB/test)	Personnel	Refs.
				Hordei Fructus Germinatus	Ziziphi Spinosae Semen	Persicae Semen	Coicis Semen					
ELISA	Direct dilution or extraction, 20–60 min	ng/mL	AFB_1	82.8–95.9	74.7–88.5	94.1–101.9	84.0–89.1	Fluorophotometer (10,000–30,000 RMB)	60 min/test	30–50	Ordinary personnel can operate	[58]
			AFTs	98.4–110.4	87.0–98.6	104.0–112.0	86.8–103.3					
HPLC	Immunoaffinity column, 4–8 h	ng/mL	AFB_1	61.3–70.9	57.0–61.8	68.1–78.5	63.9–69.7	HPLC (<100,000 RMB)	3 h/test	200–300	Requires trained personnel to operate	[58]
			AFTs	62.5–78.5	58.1–67.8	69.2–84.0	65.1–74.5					

AFB1: aflatoxin B1; AFTs: total aflatoxin.

The establishment of acceptable microbiological criteria for TCM decoction pieces marked a significant advancement, leading to the introduction of tailored strategies and methods for controlling microbial contamination in TCMs based on their intended use. Unlike pharmaceuticals manufactured under good manufacturing practices, TCM decoction pieces harbor a higher microbial load, with greater species diversity and uneven distribution. Additionally, microbial testing requirements vary depending on the type of medicinal material. To address these challenges, method 1108, "Microbiological Examination of Traditional Chinese Medicine Decoction Pieces," was introduced. This method specifies enumerated microbial parameters, including total aerobic microbial counts, total combined yeast and mold counts, and heat-resistant bacteria counts, as well as parameters for specific microorganisms such as bile-tolerant gram-negative bacteria, Escherichia coli, and Salmonella. The procedure also defines the sample quantity, preparation of the test solution, and suitability testing of the counting method, recognizing that result interpretation for TCMs may carry greater uncertainty compared with other products.

In method 2322, "Determination of Mercury and Arsenic Speciation and Valence States," improvements were made to the preparation of test solutions to overcome challenges in analyzing arsenic and mercury valence states in marine- and animal-derived TCMs. The updated method provides detailed instructions on test solution preparation, sample quantity selection, and the principles underlying the method's application.

Alignment of technical requirements with ICH guidelines

Since joining the International Council for Harmonisation (ICH) in 2017, the NMPA has strengthened the integration of international standards in compiling the 2020 edition of the Chinese Pharmacopoeia **(Table 3)** [64–67]. The newly introduced general technical requirements reflect the current landscape of drug production, quality control practices, and the applicability of products on the Chinese market, while the revised requirements have

been harmonized with ICH guidelines wherever feasible, promoting greater alignment with global pharmaceutical standards.

Table 3. Implementation status of the ICH Q4B in the Chinese Pharmacopoeia 2020 edition

ICH No./Chinese Pharmacopoeia No.	Testing method	Implementation status	Main differences	Refs.
Annex 1/0841	Residue on ignition/sulfated ash	Under implementation	Amount of sulfuric acid added, ignition temperature, and criteria for experiment completion	[64-66]
Annex 2/0102, 0942	Test for extractable volume of parenteral preparations	Under implementation	Sampling procedure, procedural details, and interpretation of results	[64-66]
Annex 3/0903	Test for particulate contamination: subvisible particles	Under implementation	Calibration of instruments for light obscuration particle counting, requirements for environmental water sample testing, sampling procedure, and evaluation criteria for injections labeled with 100 mL volume	[64-66]
Annex 4A/1105	Microbiological examination of nonsterile products: microbial enumeration tests	Under implementation	Microbial strains, culture media, and procedural details	[64, 66]
Annex 4B/1106	Microbiological examination of nonsterile products: test for specified microorganisms	Under implementation	Microbial strains, culture media, procedural details, and result interpretation	[64, 66]
Annex 4C/1107	Microbiological examination of nonsterile products: acceptance criteria for pharmaceutical preparations and substances for pharmaceutical use	Under implementation	Applicability scope, Salmonella detection methods, microbial limits for low- and micro-dose forms such as transdermal patches, and criteria for traditional Chinese medicines (herbal drugs)	[64, 66]
Annex 5/0921	Disintegration test	Under implementation	Equipment specifications and result evaluation	[64-66]
Annex 6/0941	Uniformity of dosage units	Under implementation	Testing procedures and result evaluation	[64-66]
Annex 7/0931	Dissolution test	Under implementation	Testing procedures and result evaluation	[64-66]
Annex 8/1101	Sterility test	Under implementation	Microbial strains, quantity of items tested, filtration frequency, and volume of rinse fluid	[64, 66]
Annex 9/0923	Tablet friability	Under implementation	Equipment and additional notes	[64-67]
Annex 10/0541	Polyacrylamide gel electrophoresis	Under implementation	Procedural details	[64-66]
Annex 11/0542	Capillary electrophoresis	Under implementation	Procedural details	[64-66]
Annex 12/0982	Analytical sieving	Under implementation	Chinese Pharmacopoeia includes the manual sieving method; the ICH guideline includes the sonic-sifter sieving method	[64-66]

Annex 13/0993	Bulk density and tapped density of powders	Under implementation	No changes	[64-66]
Annex 14/1145	Bacterial endotoxins test	Under implementation	Method description	[64, 66]

Stability and quality control innovations

Stability remains a crucial factor affecting the competitiveness of pharmaceutical products and represents a key area for technological advancement. In the 2020 edition, guideline 9001, "Stability Testing of Drug Substances and Preparations," was updated in line with ICH Q1A [68], introducing a definition for "significant changes" to help manufacturers focus on critical quality attributes. The guideline also clarified requirements for transporting temperature-sensitive drugs and identified key stability parameters for special dosage forms, including sustained- and controlled-release preparations and inhalation products. Guideline 9101, "Validation of Analytical Methods," was revised according to ICH Q2 [69], with adjustments to methods for assessing accuracy and precision and removal of correction factor content. Guideline 9102, "Analysis of Impurities in Drugs," incorporated ICH Q3A and Q3B frameworks, detailing reporting, identification, and qualification thresholds for drug impurities, along with decision-making flowcharts [70, 71]. In guideline 0861, "Determination of Residual Solvents," cumene and methyl isobutyl ketone were reclassified from class 3 to class 2 solvents, and triethylamine, a class 3 solvent, was newly added to align with ICH Q3C [72]. Method 0931, "Dissolution and Drug Release Test," was expanded to include the flow-through cell and reciprocating cylinder methods. Additionally, instruments, methods, and interpretation approaches consistent with ICH Q4B Annex 7 [73–82] were introduced, with examples including compound ketoconazole cream and lithium carbonate sustained-release tablets. Method 1101, "Sterility Tests," was revised based on ICH Q4B Annex 8 [83] to provide more practical guidance, including updates on environmental monitoring, culture media and strain handling, incubation and observation procedures, and sample testing requirements. Recognizing the functional importance of powder characteristics, method 0993, "Bulk Density and Tapped Density of Powders," was added, reflecting ICH Q4B Annex 13 [84–86]. Furthermore, guideline 9306, "Genotoxic Impurities Control," was introduced following ICH M7 [87], establishing principles, assessment approaches, and calculations for acceptable intakes and limits.

Despite these efforts, some general testing methods in the 2020 edition still differ from ICH Q4B standards **(Table 3)**. Many of the Chinese Pharmacopoeia's methods were originally based on the British Pharmacopoeia and WHO standards, with long-standing applications in China. However, the current global harmonization trend relies on the ICH and the Pharmacopoeial Discussion Group. Limitations in information availability and regulatory complexity have sometimes delayed updates, yet the Chinese Pharmacopoeia Commission (ChPC) continues to actively promote harmonization. In October 2018, an ICH Q4 symposium in Beijing brought together over 20 experts from the ICH Expert Working Group and ChPC to discuss implementation strategies in China. By 2020, the status of the Chinese Pharmacopoeia's ICH Q4B implementation was officially added to the ICH website [64].

Summary and future directions

The general chapters of the 2020 Chinese Pharmacopoeia emphasize scientific rationale, risk management, and practical applicability, while referencing ICH guidelines. Recent advances and updated requirements provide methodological support to ensure the safety, efficacy, and quality control of pharmaceuticals in China. This edition will actively facilitate the adoption of advanced technologies, strengthen regulatory oversight, and improve drug quality management.

As evidenced by the evolution of other pharmacopoeias, drug standards develop progressively due to the inherent limitations of scientific understanding. The 2025 edition of the Chinese Pharmacopoeia is expected to expand implementation of quality-by-design and lifecycle management concepts [88–96], incorporating analytical procedure lifecycle guidelines, process analytical technologies, and enhanced use of statistical tools for method development, validation, transfer, and verification. Microbiological control systems will increasingly be risk-based.

Well-established analytical techniques such as HPLC, GC, and atomic spectroscopy will undergo further refinement, while new, scientifically robust, and practical methods will be added. Personalized microbiological testing for specific preparations and rapid microbiological methods will be further developed [97–101]. Methods for analyzing active ingredients, toxic substances, exogenous contaminants in crude TCMs, and microbial evaluation of TCM decoction pieces will continue to improve.

The ICH initiated a revision of Q4B guidelines in 2020, and the ChPC will maintain active participation in harmonization efforts, promoting alignment with ICH Q4 standards. Additional guidelines, including ICH Q3D, will also be integrated, and the general chapter on "Elemental Impurities Limits and Procedures" will be further developed to strengthen control and assessment of elemental impurities in Chinese pharmaceuticals.

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