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REVIEW

Evolving drug regulatory landscape in China: A clinical pharmacology perspective

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Abstract

In order to encourage innovative medicine to address Chinese unmet medical needs, China has changed its drug regulatory landscape to speed up access to new medicines. In order to understand the fast-changing landscape and to enable planning of more global drug development programs and study designs in China, we reviewed 15 published clinical pharmacology-related guidances by the National Medical Products Administration (NMPA), and compared them with reference guidances from the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), or the International Conference on Harmonization (ICH), to understand the similarities and differences, especially any China-specific requirements, such as ethnic sensitivity analysis. Overall, by reviewing these clinical pharmacology-related NMPA guidances, it is clear that NMPA guidances are very similar to FDA, EMA, and ICH guidances. There are no relevant differences in the major principles, but some differences in structure, contents, and focus were noted. The NMPA is adapting flexibility statements into newly published guidances. Ethnic sensitivity analysis needs to be implemented early in drug development plans. The NMPA encourages sponsors to conduct early clinical trials in China or include China early in multiregional clinical trials, and to obtain safety, efficacy, and pharmacokinetic data for ethnic sensitivity analysis. Depending on the stage of development, ethnic sensitivity analysis can be conducted using in vitro or literature data, other Asian clinical data, or Chinese clinical data.

INTRODUCTION

In order to encourage innovation to address unmet Chinese medical needs, China has changed its drug regulatory landscape to speed up access to new drugs. Publication of "State Council Circular No. 44" on August of 2015 marked the beginning of China drug regulatory reform.[1] In the following years, new guidances have been published and old guidances have been updated, especially after China joined the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) as its regulatory member in 2017. Starting from the beginning of 2020 to the end of September of 2020, more than 60 draft guidances have been published on the

National Medical Products Administration (NMPA) website (http://www.cde.org.cn) to solicit public comments and opinion, indicating the rapid process of drug regulation standardization in China.

All guidances published in NMPA websites are Chinese and there are no official English versions. In order to evaluate the fast changing landscape and to enable us to better plan drug development programs and study designs in China, we reviewed published clinical pharmacology-related guidances (draft and final) by the NMPA, compared them with reference guidances from the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the ICH, to understand the similarities and differences, especially any China-specific requirements, such as ethnic sensitivity analysis.

Along with drug regulatory reform, the China drug regulatory agency name has been changed several times, State Drug Administration (SDA), 1998–2003, State Food and Drug Administration (SFDA), 2003–2013, China Food and Drug Administration (CFDA), 2013–2018, and NMPA, 2018–present. To be consistent in this analysis, as the guidances we selected to review cover the period from SDA to NMPA, we will use the latest name, NMPA, in this publication when describing China's regulatory agency for drugs.

OVERVIEW OF NMPA CLINICAL PHARMACOLOGY GUIDANCE DOCUMENTS

A group of AstraZeneca Clinical Pharmacologists and Pharmacometricians who are fluent in both English and Chinese reviewed the website of the NMPA Center for Drug Evaluation (http://www.cde.org.cn), guidance page. Key guidances related to clinical pharmacology topics, including first time in man, pharmacokinetics (PK) and pharmacodynamics (PD), drug-drug interaction (DDI), special population PK, bioavailability (BA) and bioequivalence (BE), etc. are selected to include in the analysis. The guidances that were reviewed are listed in Table 1. Each guidance was reviewed by two assessors separately. The information in each guidance was compared with the comparable guidances published by the FDA, the EMA, or the ICH to identify major differences in principles, especially the China-specific requirements. As China guidances usually cover both chemical drugs and Chinese medicine, this review is focused on chemical drugs.

Ethnic sensitivity is usually assessed by PK comparison between Chinese versus non-Chinese participants to support clinical trial conduct and registration in China. The importance of ethnic sensitivity is highlighted and discussed in two recently NMPA published guidances, about how to evaluate overseas clinical data and how to evaluate drugs that are approved overseas but not in China yet. Therefore, ethnic sensitivity analysis for China is discussed and summarized in this paper without comparison to guidances of other regions.

COMPARISON OF NMPA GUIDANCES VERSUS COMPARABLE GUIDANCES FROM FDA, EMA, OR ICH

The Technical Guideline of New Drug Phase I Clinical Study Application[2] was published by the NMPA in 2018. It referenced FDA guidance (1995): Content and Format of Investigational New Drug (IND) applications for Phase I Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products,[3] and Questions and Answers published in 2000.[4] This NMPA guidance is very similar to the FDA guidance in overall content. Both guidances describe what should be included in submission. In addition, the NMPA guidance has sections to cover "biologics" and "overseas data," and states that the format and content of IND can directly reference ICH common technical document for preparation. EMA guidance (2017): guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products,[5] had a markedly different focus and it was not fully reflected in this NMPA guidance.

Estimating the Maximum Recommended Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers[6] was published by the NMPA in 2012. It outlines approaches to calculate maximum recommended starting dose (MRSD) for first-in-human clinical trials of new molecular entities in adult healthy volunteers, and recommends a standardized process by which the MRSD can be selected. This NMPA guidance is very similar to the FDA guidance (2005): Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers.[7] In addition, the NMPA guidance discussed two additional approaches to estimate MRSD, (1) estimation of MRSD based on systemic exposure level and allometric scaling approach, and (2) estimation of MRSD based on minimum anticipated biological effect level. The constant (K_m) that is used to convert dose in mg/kg to dose in mg/m^2 is slightly different between the NMPA guidance and the FDA guidance. For example, for a human adult, the K_m was 36.88 and 37 in the NMPA and the FDA guidance, respectively. For child with 20 kg body weight, the K_m was 26.47 and 25 in the NMPA and the FDA guidance, respectively. Therefore, the calculated human equivalent doses may be slightly different when using different K_m values from the two guidances. The clinical impact of the differences is expected to be minimum but should be evaluated on a case-by-case basis.

TABLE 1 Listing of NMPA clinical pharmacology-related guidances reviewed

NMPA guideline[a]	Date of publication	Key recommendations or major differences from the FDA/EMA
Technical Guideline of New Drug Phase I Clinical Study Application[2]	Jan 2018	Similar to FDA. NMPA guidance covers "biologics" and "overseas data," and states that the format and content of IND can directly reference ICH CTD for preparation.
Estimating the Maximum Recommended Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers[6]	May 2012	Similar to FDA. NMPA discusses allometric scaling and minimum anticipated biological effect level approaches. The constant to convert dose in mg/kg to dose in mg/m^2 is slightly different.
Technical Guideline of Clinical Pharmacokinetic Study for Chemical Drugs[8]	Mar 2005	Similar to FDA guidances. FDA bioanalysis guidance also discusses ligand-binding assays, endogenous compounds, biomarkers, and diagnostic tests.
Technical Guideline on Pharmacokinetics and Pharmacodynamics Study in the Development of Antibacterial Drugs[10]	Aug 2017	Similar to EMA. NMPA guidance covers post antibiotics effects, animal studies, PK studies, metabolites, and analysis methods (e.g., Monte Carlo Simulation) in more detail.
Technical Guideline of Pharmacokinetics in Patients with Impaired Hepatic Function[12]	May 2012	Similar to FDA (direct translation)
Technical Guideline of Pharmacokinetics in Patients with Impaired Renal Function[14]	May 2012	Similar to FDA (direct translation)
Technical Guideline of Drug Interaction Studies (draft)[16]	Sep 2020	Similar to FDA
Technical Guideline of Safety Testing of Drug Metabolites[20]	May 2012	Similar to FDA
Technical Guideline of Bioavailability and Bioequivalence Studies[22]	Mar 2005	NMPA recommends BA/BE studies be conducted in Chinese populations. Otherwise, similar to FDA.
Technical Guideline for Human Bioequivalence Studies with Pharmacokinetic Endpoints for Chemical Drug Generics[25]	Nov 2015	Similar to FDA. NMPA does not cover sprinkle BE, BE in specific beverages, and complex active ingredient mixtures.
Guideline of Waiver of In Vivo Bioequivalence Studies[27]	May 2016	Similar to FDA and EMA. NMPA asks for BE studies in Chinese, sponsor should discuss with NMPA early.
Guideline of Statistical Approaches to Establishing Bioequivalence[30]	Oct 2018	Similar to FDA. Definition of "BE set" differs potentially requiring larger sample size for China BE studies.
Technical Guideline of Bioequivalence of highly variable drugs[32]	Oct 2018	States that wider BE criteria can be considered for drugs with good tolerability and large safety margin but does not specify.

Abbreviations: BA, bioavailability; BE, bioequivalence; CTD, common technical document; EMA, European Medicines Agency; FDA, US Food and Drug Administration; ICH, International Conference on Harmonization; IND, Investigational New Drug; NMPA, National Medical Products Administration; PK, pharmacokinetic.

[a]All guidances published in NMPA websites are Chinese. The English title was translated by the authors.

Technical Guideline of Clinical Pharmacokinetic Study for Chemical Drugs[8] was published by the NMPA in 2005. The NMPA guidance includes two parts, (1) bioanalytical method establishment and validation and (2) PK study. For bioanalytical methods, the NMPA guidance focused on chromatographic assays and has only one paragraph to summarize microbiology and immunology method validation. The FDA guidance on bioanalysis issued in 2001 was also primarily focusing on chemical assay, with some discussion on microbiologic and ligand binding assays. The FDA guidance was updated in 2018[9] and has extended the scope of ligand binding assays and includes the discussion for the analysis of endogenous compounds, biomarker analysis, and for the application of diagnostic kits and new technologies.

This NMPA guidance is the earliest PK guidance to discuss PK study details. It covers studies of healthy volunteers, patients, special populations, and pediatrics. Later on, the NMPA published more population-specific guidances, that will be discussed later. The FDA and the EMA do not have a single equivalent guidance to cover all of the above topics, but have population-specific and subject-specific PK guidances, including hepatic and renal impairment PK studies, drug interaction, pediatric PK, and population PK. These were referenced by the NMPA when publishing this guidance.

Technical Guideline on Pharmacokinetics and Pharmacodynamics Study in the Development of Antibacterial Drugs[10] was published by the NMPA in 2015. The objective of this guidance is to provide technical standards for PK and PD studies for the development of antibacterial agents. It focuses on the use of PK/PD analyses to identify potentially efficacious dose regimens. Even though this guidance was for antibacterial drugs, this guidance can also be referenced when developing antifungal agents. The main reference guidance is EMA guidance (2016): Guideline on The Use of Pharmacokinetics and Pharmacodynamics in The Development of Antibacterial Medicinal Products.[11] The contents of this NMPA guidance are concordant with the EMA guidance but with different structure. In addition, the NMPA guidance provides more discussion on certain topics (e.g., post antibiotic effects, animal PK/PD studies, traditional PK study, population PK study, metabolites PK/PD study, point estimate method, and Monte Carlo Simulation in the development of antibacterial agents.

Technical Guideline of Pharmacokinetics in Patients with Impaired Hepatic Function[12] was published by the NMPA in 2012. It references FDA guidance (2003): Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.[13] The NMPA guidance was basically translated from the FDA guidance with identical content and structure. The purpose of this guidance is to aid sponsors and applicants in determining whether an adjustment of the dosage would be indicated in patients with hepatic impairment. It covers full and reduced PK study designs, data analysis, and recommendation of labeling statements.

The Technical Guideline of Pharmacokinetics in Patients with Impaired Renal Function[14] was published by the NMPA in 2012. It references FDA guidance (2010): Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling. The NMPA guidance was basically translated from FDA 2010 guidance, with similar contents and structure. It covers study design (full or reduced PK study), data analysis, and label language instruction. The FDA guidance was updated in 2020.[15] The NMPA guidance is not updated accordingly, but presenting data from a global renal impairment study following updated FDA guidance is expected to be acceptable by the NMPA.

Technical Guideline of Drug Interaction Studies (draft)[16] was published by the NMPA in September 2020. It covers in vitro DDI studies, clinical DDI studies, and recommendation for labeling language. It also includes decision trees for in vitro DDI studies, model based DDI prediction and determination, in vitro test systems and details, and probe drugs commonly used in DDI studies.

The FDA published two final DDI guidances in January 2020, one covering in vitro DDI studies and one covering clinical DDI studies as follows:

- In Vitro Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions. 2020[17]
- Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions 2020[18]

The NMPA DDI guidance was compared with the FDA DDI guidances. For in vitro DDI studies, the NMPA guidance is very similar to the FDA guidance in contents and structure, including aspects related to model-based DDI prediction and in vitro test systems. For clinical DDI studies, the NMPA guidance is similar to the FDA guidance but structured slightly different. In general, the FDA guidances provide more background and explanations. The NMPA guidance includes in vitro DDI study decision trees and list of probe drugs recommended to use in in vitro and clinical DDI studies in the appendices, but FDA guidances do not include them. In August 2020, the FDA published a draft guidance: Drug-Drug Interaction Assessment for Therapeutic Proteins.[19] The content of this FDA guidance is not covered in the NMPA DDI guidance.

Technical Guideline of Safety Testing of Drug Metabolites[20] was published by the NMPA in 2012. It references FDA guidance (2008): Safety Testing of Drug Metabolites. The FDA guidance was finalized in 2016.[21] The contents are almost identical between the NMPA and the FDA guidances (2008). Both guidances indicate human metabolites can raise a safety concern for those formed at greater than 10% of total drug-related systemic exposure at steady-state. The systemic exposure to metabolite is generally quantitated using area under the curve (AUC), but sometimes it may be more appropriate to use maximum plasma concentration (C_{max}).

Technical Guideline of Bioavailability and Bioequivalence Studies[22] was published by the NMPA in 2005. It summarized the concept of BA and BE and its application scope, and clarified the requirements for BA and BE studies in ordinary and specific formulations. It references FDA guidance (2003): Bioavailability and Bioequivalence Studies for Orally Administered Drug Products-General Considerations. Later on, the FDA updated the BA and BE guidance in 2014: Bioavailability and Bioequivalence Studies Submitted in New Drug Applications or Investigational New Drugs — General Considerations.[23] In 2019, the FDA issued a draft guidance, Bioavailability Studies Submitted in New Drug Applications or Investigational New Drugs — General Considerations.[24] After finalization, the 2019 guidance will replace the 2014 guidance. Recently, the NMPA was asking sponsors from other regions to conduct BA or BE studies in China to demonstrate BA or BE in the Chinese population, in addition to the BA or BE data generated from other regions. Therefore, in addition to referencing the NMPA guidance, it

is reasonable for the sponsor to reference the latest version of BA or BE guidance from the FDA.

Technical Guideline for Human Bioequivalence Studies with Pharmacokinetic Endpoints for Chemical Drug Generics[25] was published by the NMPA in 2015. It references FDA guidance (2013): Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application.[26] The NMPA guidance covers topics about overall designs, population, PK parameters for evaluating BE, recommendations for different dosage forms, special considerations, general principles for study design, and data treatment in BE studies. The contents of the NMPA guidance, in principle, are similar to that in the FDA guidance, but structured slightly different. The FDA guidance provides more explanation and examples in certain sections. In addition, the FDA guidance discusses "Sprinkle Bioequivalence Studies," "Bioequivalence Studies of Products Administered in Specific Beverages," and "Drug Products with Complex Mixtures as the Active Ingredients," but these topics are omitted from the NMPA guidance.

Guideline of Waiver of In Vivo Bioequivalence Studies[27] was published by the NMPA in 2016. It references FDA draft guidance (2015): Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System. This FDA guidance was finalized in 2017.[28] In general, the NMPA guidance is very similar to the FDA guidance. EMA guidance (2010): Guideline on the Investigation of Bioequivalence,[29] has a short appendix "BCS-based biowaiver." The contents in this appendix are covered by the NMPA guidance.

In the NMPA and the FDA guidances, both class 1 (high solubility and high permeability) and class 3 (high solubility and low permeability) can apply biowaiver, but class 3 has tighter requirements. For fixed dose combination (FDC), if both drugs are class 1 drugs, the FDA can consider a biowaiver if there are DDIs between the two drugs, but the NMPA will not consider a biowaiver. If both drugs belong to Biopharmaceutics Classification System (BCS) class 3 or a combination of class 1 and 3, and there is a DDI between the two drugs, the FDA can consider BCS-based biowaiver for immediate release FDC if excipients fulfill the considerations outlined in the guidance, however, the NMPA will not consider a biowaiver in this situation. As the NMPA is asking sponsors to conduct BE studies in the Chinese population now even with BE data available from other regions, the sponsor should share the China BE study design and engage biowaiver strategy discussion with NMPA as early as possible.

Guideline of Statistical Approaches to Establishing Bioequivalence[30] was published by the NMPA in 2016 first, then updated in 2018. It references FDA guidance (2001): Statistical Approaches to Establishing Bioequivalence.[31] The EMA does not have an equivalent guidance. The FDA guidance is very comprehensive, covers multiple statistical models (average BE, population BE, individual BE, etc.), study design, statistical analysis, and miscellaneous issues. The NMPA guidance is more focused on study design, statistical model based on average BE, and relevant data analysis, which are similar in contents to corresponding sections in the FDA guidance.

In the NMPA guidance, it defines that "BE set" includes subjects with at least one evaluable PK parameter in at least one period, which means that a subject who has only one PK parameter from one period (test or reference) will be included for BE calculation. That is different from common practice that only subjects who have at least one evaluable PK parameter from both periods (test and reference) will be included in BE calculation, as stated in EMA guidance 2010: Guideline on The Investigation of Bioequivalence,[29] "Ideally, all treated subjects should be included in the statistical analysis. However, subjects in a crossover trial who do not provide evaluable data for both of the test and reference products (or who fail to provide evaluable data for the single period in a parallel group trial) should not be included." The differences in the "BE set" definition may mean larger sample size in the China BE study. With regard to sample size, both the NMPA and the FDA guidances recommend that sample size should be estimated appropriately for study design if average BE approach is the selection. The FDA guidance further recommends that a minimum number of 12 evaluable subjects should be included in any BE study.

Technical Guideline of Bioequivalence of Highly Variable Drugs[32] published by the NMPA in 2018 comprehensively discussed BE study design, statistical analysis, and data analysis for highly variable drugs (HVDs). In comparison, both the FDA and the EMA only provided a short discussion as part of their BE guidances (FDA 2014: Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs — General Considerations[23]; EMA 2010: Guideline on the Investigation of Bioequivalence[29]).

HVD is defined as one or more major PK parameter's coefficient of variation percentage (CV%) is greater than or equal to 30%. The NMPA guidance states that wider BE criteria can be considered under the condition of good tolerability and large safety margin. However, it does not further discuss how wide the criteria can be. The EMA guidance (2010)[29] specified that the BE criteria window is based on the variability of the drug, for example, if CV% is greater than or equal to 50%, the BE range can be widened to 69.84% to 143.19%. The possibility to widen the acceptance of BE criteria does not apply to AUC where the acceptance range should remain at 80.00% to 125.00%, regardless of variability.

NMPA Guidance Flexibilities: Guidance, in general, provides recommendations from regulators. For example, the FDA states in the first page of guidance "Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions[18] that "This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page." Similar language is included in all FDA guidances. The EMA is in the similar position to the FDA. For example, the EMA states in "Guideline on The Use of Pharmacokinetics and Pharmacodynamics in The Development of Antibacterial Medicinal Products"[11] that "This Guideline has been developed to outline the regulatory expectations for application dossiers and reflects both the scientific advances and the regulatory experience" and "it is recognised that sponsors may propose alternative strategies to those outlined in this Guideline, in which case discussion with EU Competent Authorities would be appropriate." Similar flexibility was not stated in NMPA guidances included in this analysis that were published in 2018 and before. However, in "Technical Guideline of Drug Interaction Studies (draft)"[16] that was published in 2020, it is stated that "This guideline only represents the current views and understandings of NMPA, it serves as a references only for sponsors and is not legal binding. As scientific research progresses, the relevant content in this guideline will be continuously improved and updated" and "If needed, methods other than those described in this guideline can also be used." By searching the NMPA guidance website (http://www.cde.org.cn), it was noted that a similar flexibility statement is included in most of guidances published in 2020, indicating that the NMPA is adapting flexibility into their newly published guidances, which gives the sponsor more flexibility to apply new methods that were not included in the guidance to achieve the objective of the guidance.

Overall, by reviewing these clinical pharmacology related NMPA guidances, it is clear that the NMPA guidances are very similar to the FDA, the EMA, or ICH guidances. There is no difference in major principles, but some differences in structure, contents, and focus were found. NMPA referenced guidances from the FDA, the EMA, or the ICH when preparing their guidances even before China joined the ICH in 2017. The harmonization of guidance does not only help sponsors from overseas to bring their drugs to Chinese patients faster, but also helps China's domestic companies to bring their drugs to international markets. When referencing old NMPA guidances that were published early or referenced old version of FDA, EMA, or ICH guidances, it is reasonable to reference the latest version of FDA, EMA, or ICH guidances and engage early conversation with the NMPA as they are open for scientific discussions.

ETHNIC SENSITIVITY ANALYSIS

The ICH published "E5: Ethnic Factors in the Acceptability of Foreign Clinical Data"[33] in 1998. It describes factors to consider when extrapolating and facilitating acceptance of foreign clinical data in a new region, and describes development strategies for ethnic sensitivity analysis. Ethnic sensitivity factors defined in ICH E5 include not only internal factors, such as genetics and physiology, but also social culture, living environment and other external factors (Table 2). Based on these factors, drug ethnic sensitivity can be defined (see Table 2). In 2017, the ICH published another guidance, "E17: General Principles for Planning and Design of Multi-Regional Clinical Trials,"[34] where ethnic sensitivity was further discussed.

Using clinical data generated from overseas and bringing innovative drugs from other countries to China, one of the key factors to consider is ethnic sensitivity. In July 2018, the NMPA published "Technical Guidelines for Accepting Data from Overseas Clinical Trials of Drugs."[35] For clinical trials conducted in overseas, when applying for registration in China, the sponsor needs to fully analyze the ethnic sensitivity of the Chinese population versus the non-Chinese population to support the bridging of overseas clinical data to the Chinese population (Table 3).

TABLE 2 Drug sensitivity to ethnic factors[a]

	Less sensitive	More sensitive
PKs	Linear	Nonlinear
PD curve for efficacy and safety	Flat	Steep
Therapeutic dose range	Wide	Narrow
Metabolism	Minimum or multiple pathways	Highly or single pathway; genetic polymorphism
Bioavailability	High	Low
PK intersubject variability	Low	High
Protein binding	Low	High
DDI, food effect, and drug-diseases interaction	Low	High
Mechanism of action	Non-systemic	Systemic
Abuse potential	Low	High

Abbreviations: DDI, drug-drug interaction; PD, pharmacodynamic; PK, pharmacokinetic.

[a]Summarized based on International Conference on Harmonization E5, Ethnic factors in the acceptability of foreign clinical data,[33] Appendix D.

TABLE 3 Acceptability of overseas clinical trials data in China[a]

Acceptability	Data reliable	Efficacy and safety supported by foreign data	Ethnic sensitivity
Acceptable	Yes	Yes	No
Partially acceptable[b]	Yes	Yes	Yes
Not acceptable	No	No	

[a]Summarized based on the National Medical Products Administration guidance 2018: Technical Guidelines for Accepting Data from Overseas Clinical Trials of Drugs.[35]

[b]For rare disease, pediatric drug, or severe diseases, it can be considered as "conditional acceptable" with a commitment to conduct postmarketing studies.

In 2020, the NMPA published "Clinical Requirement for Drugs Approved on Overseas but not in China",[36] highlights the importance of ethnic sensitivity analysis on approvability of innovative drugs or generic drugs that are approved overseas (Table 4).

The NMPA clinical pharmacology reviewers summarized their views about conducting PK ethnic differences analyses in China in a Chinese language publication.[37] To address PK ethnic differences, traditional PK comparison with intensive PK samples and/or population PK (PopPK) analysis can be used. The results of the PK ethnic difference analysis will not only impact the decision of acceptability or approvability, but also the usage and dosage adjustment based on ethnicity. It is recommended to use the above two methods to evaluate ethnic differences separately, and to combine the evaluation results of the two methods to comprehensively evaluate the drug PK ethnic differences. Under special circumstances, if it is not possible to collect intensive PK samples from the Chinese population, then only the PopPK method can be considered for the evaluation of PK ethnic differences. If the PK ethnic comparison analysis shows a certain PK difference, the clinical impact of the PK ethnic differences on safety and effectiveness will have to be evaluated. If the PK ethnic differences are considered as clinically meaningful, more studies or data analysis, including dose adjustment, will have to be considered. Chinese people and Asian people, such as Japanese, Koreans, Indians, and Southeast Asians, have large differences in living environment and eating habits, sometimes in terms of background treatment, medical practice, and availability. Therefore, the ethnic sensitivity analysis generally needs to be done by comparing Chinese versus non-Chinese populations. The non-Chinese can be other Asians, Whites, and Blacks. The necessary clinical studies in the Chinese population are the basis for the evaluation of PK ethnic differences. For drugs that have not been studied clinically in the Chinese population, in view of the unknown ethnic sensitivity issues that may exist, based on risk considerations, it is generally recommended that the sponsors first evaluate their tolerability and safety in the Chinese population and PK ethnic differences. After ensuring that the drug is tolerated in the Chinese population and PK ethnic differences are assessed, follow-up clinical studies can be conducted accordingly.

In summary, for the sponsors from overseas seeking to conduct clinical studies or bring their drugs to China market, ethnic sensitivity analysis has to be implemented in the drug development plan early. The NMPA encourages the sponsors to conduct early clinical trials in China or include China in multiregional clinical trials early, to obtain safety, efficacy, and PK data for ethnic sensitivity analysis. Depending on the stage of the development, ethnic sensitivity analysis can be conducted based on in vitro or literature data, based on Asian clinical data, or based on Chinese data. As there are many questions that are not addressed in the NMPA guidances, for example, for an ethnic insensitive drug (such as monoclonal antibody), is a PK study sufficient to support China joining global phase III? What is the likelihood of waiving a phase I study in China

TABLE 4 Approvability of overseas innovative drugs or generic drugs in China[a]

Approvability	The overall benefits outweigh the risks	The benefits in Chinese outweigh the risks	Insensitive to ethnic factors	Unmet medical needs
Directly approved	Yes	Yes	Yes	
Approved with post marketing commitment[b]	Yes	No	Yes	Yes
Conducting bridging studies	Yes	No	Yes	No
Conducting bridging studies	Yes		No	
Systemic development or not approved	No			

[a]Summarized based on National Medical Products Administration guidance 2020: Clinical Requirement for Drugs Approved on Overseas but not in China.[36]

[b]It can be approved under the premise of strict risk control and postmarketing clinical trials on effectiveness and safety to support whole life cycle benefit/risk assessment of the drug.

if joining phase II and generate PopPK data? If we have sufficient data to support ethnic justification in adults, can we extrapolate it to the pediatric population? What is the minimum number of Chinese subjects for PK ethnic difference analysis? Can we use Chinese data collected from Chinese subjects living overseas? An early consultation with the NMPA will help to plan studies and strategies of drug development in China.

CONCLUSION

Fifteen clinical pharmacology-related NMPA guidances have been reviewed and compared with reference guidances from the FDA, the EMA, or the ICH. There is no difference in the major principles, but some difference in structure, content, and focus were found between the NMPA guidance and reference guidances. Ethnic sensitivity analysis in Chinese populations has to be implemented in drug development plans early.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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