Guidance on Communications of Using Real-World Evidence to Support Registration Applications for Drug and Biological Products

(Final)

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1. Introduction

According to the *Guidance on Using Real-World Evidence to Support Drug Development and Regulatory Evaluation (Final)*, the use of real-world evidence to support drug registration requires sufficient communication with regulatory agency to ensure a consensus on the use of real-world evidence and the conduct of real-world studies.

Based on the *Provisions for Drug Registration* and the *Administrative Regulation on the Communication for Drug R & D Activities and Technical Review,* this guidance has identified the core questions to be discussed in communication and meeting information package when using real world evidence to support registration application, and provided suggestions for sponsors to carry out communication at key time points to improve the efficiency of drug clinical development.

This guidance is applicable to supporting the communication with regulatory agency during drug registration application by taking real-world evidence as the key evidence of efficacy and/or safety evaluation, and the specific process is managed and implemented in accordance with the *Administrative Regulation on the Communication for Drug R & D Activities and Technical Review*.

2. Key issues discussed at the communication meeting

2.1 Necessity and feasibility of real-world studies

Before any communication with regulatory agency, the sponsor should specify the overall clinical development strategy of the investigational drug

and the necessity to implement real-world studies. The sponsor should first identify the clinical questions, and secondly consider whether the real-world evidence can be used to answer the clinical questions, which should be evaluated in terms of science, regulation, ethics, and operability. Based on the purpose and position of the real-world study to be conducted, the sponsor should state the background information (such as disease background, clinical needs, etc.) and the necessity of conducting the real-world study when communicating with regulatory agency. The specific circumstances in which real world evidence is used to support drug regulatory decisions are detailed in the *Guidance on Using Real-World Evidence to Support Drug Development and Regulatory Evaluation (Final)*.

The sponsor should also discuss the rationality and feasibility of conducting real-world studies, including assessing the representativeness of the target population, important factors involved in the efficacy evaluation, data acquisition and its governance/management, ethics, compliance, etc., to determine whether it satisfies the study objectives and supports regulatory decision-making.

2.2 Key elements of the study protocol

For the real-world study to be conducted, the specific study purpose, type of design, population selection and sample size estimation should be clearly stated in the study protocol in advance. In addition, a description of real-world data sources should be included. Prior to the conduct of the study, the sponsor should provide at least protocol synopsis, including but not limited to the following key elements: target population and inclusion/exclusion criteria, definitions of efficacy and safety endpoints, set up of control group, sample size determination, potential biases and measurements to control them, primary statistical analysis methods, sensitivity analyses, and transparency in the process of generating evidence.

If communication is proposed for specific issues in key elements of the protocol, the sponsor's comments and corresponding rationale should be provided, to improve the communication efficiency. Specific requirements for protocol should be referred to the *Guidance on the Design and Protocol Development of Real-World Studies for Drug and Biological Products (Final)*.

2.3 Fitness of real-world data

The sponsor should describe the real-world data sources and quality, and describe the preliminary fitness evaluation of the source data or the curated data, based on the study objectives and the type of design selected. The sponsor should develop and submit a real-world data curation plan. For specific technical requirements, please refer to the *Guidance on Using Real-World Data to Generate Real-World Evidence (Final)*.

2.4 Transparency of real-world studies

Sponsors should describe their consideration of transparency in real-world studies, including how the whole process of real-world data collection and curation/management ensures transparency, clarity, and traceability, especially that exposure/treatments, key covariates, and outcome variables should be traceable back to the source data. The data curation plan and master analysis plan should be revised in parallel with the study protocol.

Such ways as timely communication between the sponsor and regulatory agency, disclosure of key information in the study protocol and so on can help to increase the transparency of the study.

3. Requirements for communication materials

3.1 Prior to the study initiation

According to the clinical development strategy, if it is planned to take real-

world study as the key evidence to support drug registration, the sponsor should proactively communicate with regulators on the study plan and protocol. The sponsor may propose technical issues for discussion in which case the sponsor needs to prepare materials including at least the overall clinical development pathway, study background, necessity of the study, feasibility assessment, study protocol synopsis, preliminary assessment of data fitness, etc.

After the communication with regulatory agency, the sponsor should submit the revised protocol, real-world data curation/management plan and the primary analysis plan based on the communication results. The primary analysis plan may be described in detail in the protocol or in an addendum to the protocol.

3.2 During the study

During the study, in case of substantial changes in key elements of the protocol, including the resulting changes in the data curation plan and/or statistical analysis plan, the sponsor should timely submit a request for communication. When requesting for communication on the technical issues to be discussed, the preparation materials should at least include study protocol, study status, issues to be discussed, and the sponsor's comments and corresponding rationale on the issues. For substantial changes that may significantly increase the safety risks of subjects, a supplementary application shall be submitted in accordance with the *Provisions for Drug Registration* and other relevant regulatory requirements.

3.3 Prior to the marketing application

Before submitting a marketing application after the study is completed, the sponsor should communicate with regulators on the real-world study

results. The materials to be prepared should at least include study overview, the final protocol and a description of all the revisions, data curation/management plan, data fitness assessment, previous communication, preliminary study results, issues to be discussed, and sponsor's comments and corresponding rationale on the issues.

4. Post-meeting requirements

Afterwards, meeting minutes should be formed with CDE based on the discussion in accordance with the *Administrative Regulation on the Communication for Drug R & D Activities and Technical Review*.

The sponsor should submit the meeting materials prior to the marketing application, such as meeting minutes, together with the application dossiers.

References

1 NMPA. Provisions for Drug Registration. Center for Drug Evaluation, National Medical Product Administration, China, 2020.

2 NMPA. Administrative Regulation on the Communication for Drug R & D Activities and Technical Review. Center for Drug Evaluation, National Medical Product Administration, China, 2020.

3 NMPA. Guidance on Using Real-World Evidence to Support Drug Development and Regulatory Evaluation (Final). Center for Drug Evaluation, National Medical Product Administration, China, 2020.

4 NMPA. Guideline on Using Real-World Data to Generate Real-World Evidence (Final). Center for Drug Evaluation, National Medical Product Administration, China, 2021.

5 NMPA. Guidance on the Design and Protocol Development of Real-World Studies for Drug and Biological Products (Final). Center for Drug Evaluation, National Medical Product Administration, China, 2022.