Generally Accepted Scientific Knowledge in Applications for Drug and Biological Products: Nonclinical Information

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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Pharmacology/Toxicology

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Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
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Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
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Generally Accepted Scientific Knowledge in Applications for Drug and Biological Products: Nonclinical Information Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

FDA has received an increasing number of questions regarding the extent to which generally accepted scientific knowledge (GASK) may be relied on for drug or biological product approval.[2] This guidance describes instances in which it may be appropriate to rely on GASK to meet certain nonclinical safety requirements for new drug applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(b)) and biologics license applications (BLAs) under section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262(a)). The information that supports the nonclinical safety of a drug and that must be submitted in the application can include references to GASK, when appropriate, instead of or in addition to, specific studies conducted with respect to the drug. In such cases, therefore, it might be unnecessary to conduct certain nonclinical studies.[3]

This guidance focuses on two examples of GASK that could be appropriate to fulfill certain legal and regulatory requirements applicable to the drug or biological product in question. The examples discussed in this guidance reflect areas where we have previously determined that it was appropriate to rely on GASK to meet certain requirements for approval. Notably, while the examples provided here are for illustrative purposes, determinations regarding the appropriateness of data submitted for any application, including GASK, are fact-specific, and the question of whether certain information can be considered GASK and the purpose such information would serve in an application will be considered in the context of a particular application.

[1] This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration (FDA).

[2] For brevity for purposes of this guidance, the term *drug*, unless stated otherwise, is intended to refer to both drugs under the Federal Food, Drug, and Cosmetic Act and biological products under the Public Health Service Act; and the term *approval* is intended to refer to approval and licensure of drug and biological product applications under the respective authorities.

[3] This guidance does not address the use of GASK in other contexts (e.g., clinical studies).

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

A. Nonclinical Studies and Their Role in Drug Development

Applicants are required to submit, among other things, nonclinical information to support approval of an NDA or BLA (see, for example, parts 314 and 601 (21 CFR parts 314 and 601)). For example, the NDA regulations provide that NDAs include data about the drug's pharmacology and disposition (pharmacological effects, including mechanism(s) of action;[4] absorption, distribution, metabolism, excretion[5]) and toxicology (acute, subacute, and chronic toxicity;[6] developmental and reproductive toxicity;[7] carcinogenicity;[8] and *special* toxicology, as appropriate[9]). The NDA regulations note that these data can come from studies conducted in animals or in vitro.[10]

The nonclinical information described above addresses critical issues that allow the Agency to, for example:

- Identify the pharmacological effects, including mechanism(s) of action of the drug in vitro and/or in vivo
- Identify the absorption, distribution, metabolism, and excretion of the drug in vitro and/or in animals
- Identify possible consequences of exposure duration (e.g., chronic)
- Identify risks for special populations (e.g., pediatrics)

[4] § 314.50(d)(2)(i) ("Studies of the pharmacological actions of the drug in relation to its proposed therapeutic indication and studies that otherwise define the pharmacologic properties of the drug or are pertinent to possible adverse effects.")

[5] § 314.50(d)(2)(iv) ("Any studies of the absorption, distribution, metabolism, and excretion of the drug in animals.")

[6] § 314.50(d)(2)(ii) ("Studies of the toxicological effects of the drug as they relate to the drug's intended clinical uses, including, as appropriate, studies assessing the drug's acute, subacute, and chronic toxicity . . ..")

[7] § 314.50(d)(2)(iii) ("Studies, as appropriate, of the effects of the drug on reproduction and on the developing fetus.")

[8] § 314.50(d)(2)(ii) ("Studies of the toxicological effects of the drug as they relate to the drug's intended clinical uses, including, as appropriate, . . . carcinogenicity . . . .")

[9] § 314.50(d)(2)(ii) ("Studies of the toxicological effects of the drug as they relate to the drug's intended clinical uses, including, as appropriate, … studies of toxicities related to the drug's particular mode of administration or conditions of use.")

[10] See, for example, § 314.50(d)(2). See also the BLA regulations at 21 CFR part 601, which are silent with respect to the source of nonclinical data.

- Identify specific parameters to inform safety in humans

- Identify the mechanistic understanding of an adverse biological change observed in animals or humans

Relevant regulations do not specify the exact study types and designs needed to examine particular issues or determine particular outcomes.[11] The studies recommended to address these issues are a matter of scientific and regulatory judgment, and are often described in FDA guidances and International Council for Harmonisation guidelines. The guidances that discuss which studies may be appropriate in a given situation also provide flexibility, and alternative approaches to those recommended can be used if they satisfy the applicable statutes and regulations.

B. Legal and Regulatory Considerations

Standalone marketing applications submitted under section 505(b)(1) of the FD&C Act or section 351(a) of the PHS Act must contain data sufficient to demonstrate the safety and effectiveness of the drug, or the safety, purity, and potency of the biological product, respectively. As a general matter, applicants for standalone marketing applications rely on either their own data or data to which they have a right of reference. A standalone application's nonclinical data (which, as discussed above, may be derived from in vitro or in vivo studies, as appropriate) thus generally come from two potential sources: studies conducted by the sponsor and studies not conducted by or for the sponsor but to which the sponsor has a right of reference. In some instances, such as in those circumstances described in this guidance with regard to nonclinical data, it may also be appropriate in a standalone marketing application to rely on information that is considered GASK to support approval without affecting the regulatory status of standalone marketing applications submitted under section 505(b)(1) of the FD&C Act or section 351(a) of the PHS Act. Similarly, marketing applications submitted under section 505(b)(2) of the FD&C Act or section 351(k) of the PHS Act may rely on information that is considered GASK to support approval.

III. DISCUSSION

As discussed above, in most cases, nonclinical studies provide necessary information relevant to the determination of the safety and effectiveness of a drug, or the safety, purity, and potency of a biological product, to support approval of a marketing application.[12] In some cases, however, what is already known, for example, about a drug, the patient's condition, or a relevant biological process (i.e., the biological context in which a drug is expected to act) in a given patient population is sufficient to confidently predict the outcome of a given nonclinical study. If there is GASK relevant to the application, it may be unnecessary for a sponsor to conduct certain nonclinical studies. This may result in streamlined product development that avoids unnecessary animal testing, decreases a drug's development costs, and quickens the drug's time to approval and marketing — and thus, its availability to patients.

[11] See, for example, § 314.50.

[12] See generally, 21 CFR part 312; and 21 CFR parts 314 and 601.

A. GASK: A General Description

For the purposes discussed in this guidance, the term *GASK* is used to refer to medical or scientific information that is generally accepted by experts qualified by scientific training and experience in the relevant field, including FDA experts. Generally, GASK is based on widely accepted scientific principles that are typically long-standing. In addition, it may also be possible for GASK to be based on a sufficiently large volume of scientific studies/information that would be applicable beyond the specific instances in which that information was developed.

For example, information derived from the study of anatomy and physiology, of the type traditionally learned as part of an advanced science or medical degree, might be considered GASK, in which case it could be relied upon to fulfill certain regulatory requirements that otherwise would be fulfilled through nonclinical studies. In addition, many studies or multiple streams of information collectively may also provide a body of information sufficient to support GASK. For example, GASK could be evidenced by submitting textbook excerpts that include basic scientific principles for which specific products are not cited as the source of the information. If you have questions about the applicability of GASK to a particular application, contact the appropriate review division.

B. Two Examples of GASK

This guidance describes two circumstances in which sponsors have relied on GASK in their product development programs to meet relevant approval requirements: (1) where a product contains a substance (either naturally derived or synthesized) that occurs naturally in the body, and sponsors have relied on GASK regarding that substance and its known effect on biological processes instead of conducting certain nonclinical studies; and (2) where a sponsor has demonstrated a drug's impact on a particular biological pathway, and then relies on GASK regarding that impact to conclude that certain nonclinical studies are not necessary to support approval and labeling of the drug.

1. Substances Typically Present in a Healthy Human Body

a. Endogenous substances

Some drugs have as their active ingredient a substance that is naturally present in the human body — for example, in situations where the drug replaces a substance that should naturally be present but, for pathological reasons, a patient may lack sufficient amounts of the substance to enable proper functioning. In those cases, where the drug is an unmodified[13] endogenous substance and a patient's exposure to the drug reflects the same level of exposure and distribution of the endogenous substance seen in a healthy individual, GASK regarding the safety of such a drug may be used to obviate the need for certain nonclinical data.

[13] For substances that have been modified, contact the appropriate review division to discuss appropriate study or studies to support approval.

We note that, for some endogenous substances, natural exposure to the substance may be cyclical, or may vary depending on biofeedback mechanisms. When administration of a drug could result in a different pattern or amount of exposure than the endogenous pattern or amount (e.g., hormones), human pharmacokinetic studies would likely be recommended and certain toxicology studies may be warranted to support these differences.

b. Exogenous substances present in the diet

For substances exogenous to the body that are nevertheless a part of a typical diet, exclusive of dietary supplements, it may be appropriate in some circumstances to rely on GASK to meet certain requirements for approval of applications. In such cases, certain nonclinical studies may be unnecessary. For such exogenous substances, when a patient's clinical exposure to an unmodified[14] food substance does not exceed typical levels of dietary exposure and the drug has an oral route of administration, GASK regarding safety of the unmodified substance as part of the diet may suffice to fulfill certain requirements for approval instead of nonclinical studies, as appropriate. When a patient's clinical exposure to the unmodified substance does not exceed typical levels of dietary exposure but the drug has a non-oral route of administration, route-specific nonclinical studies may still be needed. When drug exposure is in excess of typical dietary exposure, a full battery of nonclinical studies would likely be needed.

2. GASK Regarding an Altered Biological Mechanism or Pathway

Some drugs have very distinct effects on well-known biological pathways, such that certain outcomes can be predicted once a sponsor has demonstrated the drug's effect on the biological pathway. In some cases, a drug has either on- or off-target impacts on a biological pathway or molecular mechanism of action that is known to result in adverse effects at clinically relevant exposures based on the operation of the biological pathway. Thus, it may be appropriate to rely on GASK regarding the impact of the pathway rather than to conduct specific pharmacology and/or toxicology studies intended to measure the impact of the pathway.

For example, if a sponsor demonstrates clearly that a drug inhibits angiogenesis, which is necessary for fetal development, FDA may accept a rationale that includes the use of GASK to fulfill certain requirements instead of requiring the sponsor to conduct certain reproductive toxicology studies. In such cases, a drug's demonstrated (i.e., via appropriate studies) effect on angiogenesis, plus GASK regarding the need for angiogenesis in maintaining a pregnancy, may suffice to label the drug with a statement warning of adverse effects on embryofetal development for women who are or may become pregnant while taking the drug. GASK in the nonclinical context has generally been used in circumstances in which the drug-related alteration in a pathway results in adverse effects.

C. Submission of GASK in Product Applications

If a sponsor believes that certain information is GASK, the sponsor should submit their rationale to the review division as early as possible in product development to obtain feedback with

[14] For substances that have been modified, contact the appropriate review division to discuss appropriate study or studies to support approval.

respect to the proposed regulatory strategy for approval. The submission should include relevant evidence supporting GASK, including textbook excerpts and/or non-product-specific published literature.