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Client Alert

FDA and Life Sciences

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FDA Issues Draft Guidance on Use of "Generally Accepted Scientific Knowledge" to Support Drug and Biologic Applications

Could Help to Streamline Development and Approval

On May 25, 2023, the Food and Drug Administration ("FDA" or the "Agency") announced the availability of a new Draft Guidance for Industry, *Generally Accepted Scientific Knowledge in Applications for Drug and Biological Products: Nonclinical Information* (May 2023) ("Draft GASK Guidance"),[1] which explains the Agency's thinking on the thorny regulatory question of when an applicant may rely on generally accepted scientific knowledge ("GASK") in a marketing application. FDA has positioned the Draft GASK Guidance as highlighting increased flexibility in drug and biologic applications. And indeed, relying on GASK to meet certain nonclinical safety requirements in applications can be quite helpful. From our vantage, though, the Draft GASK Guidance also highlights the frustrating ambiguity around when an application can rely on GASK for other kinds of regulatory decision making.

BACKGROUND

FDA reviews new drug applications ("NDAs") under section 505 of the Federal Food, Drug, and Cosmetic Act ("FD&C Act"), and biologics license applications ("BLAs")[2] under section 351 of the Public Health Service Act ("PHS Act"). Although all NDAs must independently demonstrate that the drug is safe and effective,[3] and include "full reports of investigations which have been made to show whether such drug is safe for use and whether such drug is effective in use,"[4] some NDAs (those submitted under section 505(b)(2) of the FD&C Act) can satisfy this requirement by relying on data or information that the NDA sponsor does not own or have a right to reference (*e.g.*, FDA's finding of safety and effectiveness of another drug).[5] FDA has long taken the position that "standalone applications," by which we mean NDAs submitted under section 505(b)(1) of the FD&C Act, as well as BLAs (other than biosimilar BLAs), must include all of the data and information necessary to demonstrate that the product is safe and effective.[6] In other words, FDA

has required that a 505(b)(1) NDA or a BLA contain *only* data and information owned by the applicant (or to which the applicant has a right of reference)—with only narrow, application-specific exceptions.

Conspicuously, there is no equivalent to the 505(b)(2) NDA pathway for a BLA applicant to use, for example, FDA's finding of safety and effectiveness of another drug or biologic—or even published literature. If a prospective NDA applicant seeks to leverage GASK, if FDA ultimately disagrees, the applicant generally can still rely on that information in a 505(b)(2) NDA. A prospective BLA applicant, on the other hand, has no choice but to invest the time and resources into generating all of the information necessary to support approval (or obtaining all relevant rights of reference).

The Draft GASK Guidance describes FDA's thinking regarding the exception for GASK to this policy.[7] In doing so, it shines light on the rigidity of the overall policy—and perhaps also illuminates a path to a less strict application of this policy.

THE DRAFT GASK GUIDANCE

As described in the new draft guidance, GASK is "medical or scientific information that is generally accepted by experts qualified by scientific training and experience in the relevant field, including FDA experts"—*i.e.*, long-standing, widely accepted scientific principles.[8] The draft guidance explains that GASK also can be based on a "sufficiently large" volume of scientific studies or information that can be considered "applicable beyond the specific instances in which that information was developed."[9] The draft guidance does not, however, define "sufficiently large"; FDA might mean a handful or dozens (or even hundreds) of studies. Similarly, GASK might derive from "textbook excerpts that include basic scientific principles" as long as "specific products are not cited as the source of the information."[10]

Accordingly, the Draft GASK Guidance purposefully does not clarify the critical line between published literature (which is *not* permissible in a standalone application) and GASK (which *is* permissible in a standalone application). Instead, the Draft GASK Guidance describes two instances in which it may be appropriate to rely on GASK to satisfy certain nonclinical safety requirements. First, GASK may be used in lieu of conducting certain nonclinical safety studies with respect to substances typically present in a healthy human body, including both endogenous substances and exogenous substances present in the diet (other than dietary supplements), under the following conditions:

1. the drug is an unmodified substance;
2. if an exogenous substance, the drug is administered by an oral route of administration; and
3. the level of exposure is the same as the endogenous substance or, for an exogenous substance, the level of exposure does not exceed typical levels of dietary exposure.[11]

Second, GASK may be used to explain the impact of an "altered biological mechanism or pathway," instead of conducting "specific pharmacology and/or toxicology studies intended to measure the impact of the pathway."[12] Because FDA reserves the use of GASK for products that have "very distinct effects on well-known biological pathways" and typically only for circumstances in which the "drug-related alteration in a pathway results in adverse effects,"[13] this example may be of limited utility.

BROADER POLICY IMPLICATIONS

Neither of the Draft GASK Guidance examples provides a robust blueprint for using GASK beyond the limited circumstances identified in the draft guidance. On its face, the Draft GASK Guidance reinforces FDA's inflexible approach to the data and information that can be included in a standalone application. Beneath the surface,

however, FDA's affirmation that reliance on GASK will be permitted in these narrow circumstances should herald an opening for reliance on scientifically justified information in innovative standalone applications more generally.

Although the Draft GASK Guidance contains a footnote disclaiming its applicability to other contexts (*e.g.*, clinical studies),[14] the draft guidance generally recognizes that relying on data and information in lieu of conducting studies can streamline development, decrease development costs, and "quicken[] the drug's time to approval and marketing"—and, correspondingly, its availability to patients.[15] And, it generally recognizes that reliance on data and information outside a standalone application can be appropriate—without even a passing attempt at articulating a legal or policy rationale for limiting the draft guidance's applicability to nonclinical data.

The Draft GASK Guidance directs sponsors seeking to rely on GASK to submit their rationale to the relevant review division as early as possible in product development to obtain feedback with respect to the proposed regulatory strategy for approval.[16] A standalone applicant may now have a small opening to argue that it should be able to rely on not only the small sliver of available scientific information that qualifies as GASK but also non-product-specific literature more broadly. With the lines already blurred between GASK and non-product-specific literature, this approach naturally extends the logic underlying the Draft GASK Guidance.

CONCLUSION

We will be watching FDA's movement in this space very closely, given the potential for large ripple effects from any changes in data reliance policies.

FDA is seeking comments by July 24, 2023 to ensure that it can consider those comments before it begins working on the final version.

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King & Spalding LLP regularly counsels sponsors on issues related to data reliance for drugs and biological products. Please let us know if you have any questions regarding the Draft GASK Guidance or are interested in submitting a comment.

ABOUT KING & SPALDING

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[1] Notice of Availability, *Generally Accepted Scientific Knowledge in Applications for Drug and Biological Products: Nonclinical Information; Draft Guidance for Industry; Availability*, 88 Fed. Reg. 33,887 (May 25, 2023).
[2] The definition of "drug" in section 201(g)(1) of the FD&C Act (21 U.S.C. § 321(g)(1)) includes biologics. For simplicity, we use "drug" to refer to non-biologic drugs, unless otherwise noted.
[3] Section 505(d) of the FD&C Act (21 U.S.C. § 355(d)).
[4] Section 505(b)(1)(A)(i) of the FD&C Act (21 U.S.C. § 355(b)(1)(A)(i)).
[5] Section 505(b)(2) of the FD&C Act (21 U.S.C. § 355(b)(2)).
[6] Under section 351(a)(2)(C) of the PHS Act (42 U.S.C. § 262(a)(2)(C)), a biological product must be safe, pure, and potent. FDA has long interpreted "potency" to include effectiveness.
[7] The Draft GASK Guidance explicitly reaffirms that inclusion of GASK in a standalone marketing application will not affect its regulatory status. *See* Draft GASK Guidance at 3.
[8] *Id*. at 4.
[9] *Id*.
[10] *Id*.
[11] *See id*. at 4-5.
[12] *Id*. at 5.
[13] *Id*.
[14] *See id*. at 1 n.3.
[15] *See id*. at 3.
[16] *See id*. at 5-6.