Formal Dispute Resolution and the Food and Drug Administration

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ABSTRACT

Although appeals of federal administrative agency action receive considerable attention, appeals within administrative agencies are seldom discussed. This Article focuses on FDA's internal processes for appeals of drug and biologic application decisions, as well as appeals of medical device application determinations. The piece examines FDA's formal dispute resolution process, emphasizing its pragmatic dimensions, and assesses FDA's procedural regime and its conceptual core in light of past agency practice and current experience. The role of FDA's formal dispute resolution process is positioned within the larger regulatory and legal framework of America's human drug and medical device approval systems.

INTRODUCTION

Within the modern administrative state, agency staff wield enormous authority. With that great power comes the responsibility to act in accordance with law, regulation, and agency policy. Checks on this discretionary authority are implicit in the organizational structure of each federal agency; an administrative agency often contains multiple supervisory layers. Though agencies enjoy immense discretion, many federal agencies also afford some sort of internal process to aggrieved parties. At the Food and Drug Administration (FDA), the principal internal agency review system is known as "formal dispute resolution."

This paper in Part I describes the procedure that FDA has implemented to process claims filed pursuant to the agency's formal dispute resolution mechanism. Part II analyzes the major components of the formal dispute resolution apparatus as it relates to human drug and biologic applications, including data from FDA's review of claims. Part III does the same in the context of medical device applications. Part IV explores lessons that emerge from these insights and considers what they convey about FDA's institutional tendencies. The formal dispute resolution process comprises an important part of the agency record in potential judicial review, particularly with regard to exhaustion, ripeness, and standards of agency deference, and also reflects a broad agency interest in ensuring multiple stages of scientific review.

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I. FORMAL DISPUTE RESOLUTION: AGENCY GUIDANCE

Over the past thirty years, congressional action bearing on FDA's regulatory portfolio has ushered in an era where "user fees" collected from drug and device manufacturers are an increasingly important funding source for some of the agency's most time-intensive work.[1] Recognizing that user fees generated from regulated parties would fund some portion of the agency's review process, FDA has agreed to specific performance goals. For example, under the Prescription Drug User Fee Act of 1992 (PDUFA), the Biosimilar User Fee Act of 2012 (BsUFA), and the Generic Drug User Fee Amendments of 2012 (GDUFA), FDA committed to certain parameters in its internal appeals framework for human drug applications.[2] The agency has made similar commitments for medical device applications.[3]

When Congress enacted the FDA Modernization Act of 1997, it amended the Federal Food, Drug, and Cosmetic Act (FD&C Act) to implement adequate dispute resolution mechanisms.[4] Formal dispute resolution for drugs and biologics proceeds under one framework, operated by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER).[5] A separate FDA guidance statement, issued by the Center for Devices and Radiological Health (CDRH), governs formal dispute resolution processes for medical devices.[6] FDA moved to codify the CDRH dispute resolution framework and its standards as a federal regulation and promulgated the review process as a final rule in July 2019.[7] Though FDA's drug and device dispute resolution processes share key themes, the frameworks also diverge in meaningful respects.[8]

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[1] *See, e.g.*, Prescription Drug User Fee Act of 1992, 21 U.S.C. § 379(g)–(h) (2019) (PDUFA VI, as amended) [hereinafter PDUFA]; Medical Device User Fee and Modernization Act of 2002 (MDUFMA), 21 U.S.C. § 379(i)–(j) (2019) (MDUFMA IV, as amended).

[2] *See* Khushboo Sharma et al., *An FDA Analysis of Formal Dispute Resolution in the Center for Drug Evaluation and Research: 2003 Through 2014*, 50(6) THERAPEUTIC INNOVATION & REG. SCI. 697, 698 (2016) [hereinafter Sharma et al.].

[3] *See* Erin D. Williams, CONG. RES. SERV., RL34571, Medical Device User Fees and User Fee Acts, ii (2010) ("The authority was granted to help reduce the time required for the agency to review and make decisions about marketing applications. Lengthy review times harmed establishments, which waited to market devices, and patients, who waited to use them. User fee law provides a revenue stream for the agency, and also requires it to set performance goals for rapid application review.").

[4] 21 U.S.C. § 360bbb-1 (2019).

[5] U.S. DEP'T OF HEALTH AND HUMAN SERVS., FOOD & DRUG ADMIN., CTR. FOR DRUG EVALUATION AND RES. AND CTR. FOR BIOLOGICS EVALUATION AND RES. (CBER), FORMAL DISPUTE RESOLUTION: SPONSOR APPEALS ABOVE THE DIVISION LEVEL GUIDANCE FOR INDUSTRY AND REVIEW STAFF: GOOD REVIEW PRACTICE (2017) [hereinafter CDER & CBER FORMAL DISPUTE RESOLUTION GUIDANCE].

[6] U.S. DEP'T OF HEALTH AND HUMAN SERVS., FOOD & DRUG ADMIN., CTR. FOR DEVICES AND RADIOLOGICAL HEALTH (CDRH), CENTER FOR DEVICES AND RADIOLOGICAL HEALTH APPEALS PROCESSES: GUIDANCE FOR INDUSTRY AND FOOD AND DRUG ADMINISTRATION STAFF (2019) [hereinafter CDRH APPEALS PROCESSES GUIDANCE].

[7] Internal Agency Review of Decisions; Requests for Supervisory Review of Certain Decisions Made by the Center for Devices and Radiological Health, 83 Fed. Reg. 2,388 (proposed Jan. 17, 2018); Internal Agency Review of Decisions; Requests for Supervisory Review of Certain Decisions Made by the Center for Devices and Radiological Health, 84 Fed. Reg. 31,471 (July 2, 2019) (to be codified at 21 C.F.R. pts. 10 and 800).

[8] The largely interchangeable terminology for these processes varies somewhat across FDA centers, offices and divisions within centers, and agency guidance documents. "Dispute resolution," "supervisory

A. Drugs and Biologics

Multiple types of applications submitted to CDER or CBER may wind their way to formal dispute resolution review. An application that is later subject to formal dispute resolution processes may have begun as an investigational new drug application (IND), a new drug application (NDA), a biologics license application (BLA), or an abbreviated new drug application (ANDA). FDA operates its current dispute framework pursuant to a November 2017 guidance document, which "represents the current thinking of the Food and Drug Administration," but "does not establish any rights for any person and is not binding on FDA or the public."[9] This guidance, as opposed to a provision of the FD&C Act or other federal statute or regulation, supplies the most substantial basis for agency decision making. Far from an anomaly, this scheme is dictated by FDA guidance and follows longstanding agency practice.[10] FDA staff conducting review within the dispute resolution framework may only depart from the agency's guidance, which channels staff discretion, with "appropriate justification" and consent from a supervisor.[11]

As enacted, section 562 of the FD&C Act requires FDA to maintain a system through which drug sponsors are able to challenge scientific determinations by agency staff. In implementing section 562, FDA updated its general appeal regulation to include the possibility of independent review by an advisory committee.[12] An appeal brought under this regulation, sometimes referred to as a "10.75 appeal,"[13] is now considered part of the informal dispute resolution process; the agency no longer uses formalistic distinctions between these general appeals and CBER and CDER's individual regulatory appeal pathways.[14]

> [R]egardless of the regulatory mechanism cited by a sponsor, if a sponsor challenges specific administrative and/or procedural decisions that arise during the course of an FDR, CDER and CBER intend to review these interim decisions as part of the review of the pending substantive scientific and/or medical dispute, and not as a separate review.[15]

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review," and "appeal" each make appearances in FDA lexicon. Though they have distinct meanings that this paper explores, the terms are sometimes used interchangeably in agency and sponsor documents.

[9] CDER & CBER FORMAL DISPUTE RESOLUTION GUIDANCE, *supra* note 5, at 1.

[10] *See* PETER BARTON HUTT, RICHARD A. MERRILL & LEWIS A. GROSSMAN, FOOD AND DRUG LAW: CASES AND MATERIALS 56 (4th ed. 2014) (citing statistics illustrating the decline of rulemaking at FDA) ("These statistics do not demonstrate that FDA is less inclined than it once was to articulate and publicize its policies in written form, but only that notice-and-comment rulemaking is no longer the agency's preferred mechanism for doing so. Instead, it has turned to the issuance of guidance documents.") [hereinafter HUTT ET AL.]. Over the last several decades, FDA has increasingly shifted away from notice-and-comment (informal) rulemaking and toward guidance documents. *Id. See also* Todd D. Rakoff, *The Choice Between Formal and Informal Modes of Administrative Regulation*, 52 ADMIN. L. REV. 159, 168 (2000) ("[T]here has been a striking increase in the number of FDA-issued documents intended to give guidance to the regulated industry . . . .").

[11] CDER & CBER FORMAL DISPUTE RESOLUTION GUIDANCE, *supra* note 5, at 2.

[12] Internal Agency Review of Decisions, 21 C.F.R. § 10.75(b)(2) (2019).

[13] CDRH APPEALS PROCESSES GUIDANCE, *supra* note 6, at 2.

[14] *See* Investigational New Drug Applications, 21 C.F.R. § 312.48(c) (2019); Applications for FDA Approval to Market a New Drug, 21 C.F.R. § 314.103(c) (2019).

[15] CDER & CBER FORMAL DISPUTE RESOLUTION GUIDANCE, *supra* note 5, at 3.

The modern formal dispute resolution paradigm for drugs and biologics, therefore, generally treats all formal sponsor requests for internal agency review similarly.[16] The agency has also delegated the authority to implement the new requirements articulated in section 562 to its individual centers (like CBER and CDER).[17]

B. Medical Devices

On the medical device side, several modes of internal review are available. First, "10.75 appeals" play a central role in internal device appeals. The 10.75 appeal constitutes the most elemental form of review at CDRH; it asks an immediate supervisor to review an agency official's initial decision.[18] When Congress enacted the FDA Safety and Innovation Act of 2012, it amended the FD&C Act to include new requirements for the 10.75 appeal process for medical devices.[19] As enacted, section 517A of the FD&C Act[20] amended the process and timeline of appeals of "significant decisions"[21] concerning 510(k) premarket notifications, applications for premarket approvals (PMAs), and applications for investigational device exemptions (IDEs).[22] Second, the Medical Devices Dispute Resolution Panel considers disputes between device sponsors and the agency.[23] Section 515(g)(2)(B) of the FD&C Act requires that an advisory committee (not a panel within the meaning of section 513) review premarket approvals and denials.[24] Separately, the aforementioned section 562 of the FD&C Act requires there be a process for review of scientific controversies related to a device product for which no other section of the FD&C Act "provides a right of review of the matter in controversy . . . ."[25] The Medical Devices Dispute Resolution Panel satisfies both of these statutory commands. Finally, there are also petition

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[16] FDA guidance states that the agency will ordinarily not act on a *non-sponsor's* appeal of a scientific or medical issue connected to an application under agency review. Only in "unusual circumstances" would a non-sponsor's appeal go forward as would a sponsor's application, not least because "it is highly unlikely that an individual or entity other than the sponsor would have access to the information necessary to support a request for internal Agency review of these types of decisions." *Id.* at 3 n.7.

[17] *Id.* at 2.

[18] 21 C.F.R. § 10.75.

[19] Dispute Resolution, 21 U.S.C. § 360bbb-1 (2019). Section 603 of the FDA Safety and Innovation Act added the current section 517A to the FD&C Act. Section 517A was later amended by sections 3051 and 3058 of the 21st Century Cures Act of 2016. *See* U.S. DEP'T OF HEALTH AND HUMAN SERVS., FOOD & DRUG ADMIN., CTR. FOR DEVICES AND RADIOLOGICAL HEALTH, CENTER FOR DEVICES AND RADIOLOGICAL HEALTH (CDRH) APPEALS PROCESSES: QUESTIONS AND ANSWERS ABOUT 517A: GUIDANCE FOR INDUSTRY AND FOOD AND DRUG ADMINISTRATION STAFF 1, n.1 (Mar. 27, 2020).

[20] 21 U.S.C. § 360g–1 (2019) (codifying § 517A of the FD&C Act).

[21] FDA issued a revised guidance document in 2020 explaining the meaning of "significant decisions" within section 517A. *See* U.S. DEP'T OF HEALTH AND HUMAN SERVS., FOOD & DRUG ADMIN., CTR. FOR DEVICES AND RADIOLOGICAL HEALTH, CENTER FOR DEVICES AND RADIOLOGICAL HEALTH (CDRH) APPEALS PROCESSES: QUESTIONS AND ANSWERS ABOUT 517A: GUIDANCE FOR INDUSTRY AND FOOD AND DRUG ADMINISTRATION STAFF 1, 3–4 (Mar. 27, 2020).

[22] CDRH APPEALS PROCESSES GUIDANCE, *supra* note 6, at 2–3.

[23] *Id.* at 9.

[24] *See* HUTT ET AL., *supra* note 10 at 1489–90 (citing Food and Drug Administration Advisory Committees, National Research Council of Medicine of the National Academies (1992) ("The use of advisory committees by [CDRH] differs from that of CDER and CBER in one critical aspect: it is required by statute . . . . In 1990, the CDRH recharged its advisory committees into a single Medical Device Advisory Committee with a number of panels.")).

[25] CDRH APPEALS PROCESSES GUIDANCE, *supra* note 6, at 9.

processes available. These include the citizen petition,[26] the request for an administrative reconsideration,[27] and the petition for an administrative stay of action.[28]

Though they may seem like relics of a bygone era, FDA retains procedures for holding formal evidentiary public hearings.[29] These procedures may or may not end in a determination rendered by an administrative law judge (ALJ), but all provide for a right of appeal and "final decision" by the FDA Commissioner.[30] These hearings infamously lasted for months or even years and formed voluminous records.[31] FDA also reserves the right to initiate an alternative process, based on scientific peer review, in convening a Public Board of Inquiry.[32] The agency has utilized this option only twice in its history, however.[33] FDA appears unlikely to resurrect the Public Board of Inquiry in the foreseeable future.

II. FDA FORMAL DISPUTE RESOLUTION IN PRACTICE: DRUGS AND BIOLOGICS

A. Placing the Request

Regardless of whether the formal dispute resolution request is placed with CDER or CBER, the request should relate to an active submission. The request should be submitted as an amendment to the active product application.[34] Agency guidance suggests, but does not require, that a sponsor planning to bring a formal dispute resolution request notify the appropriate division before doing so "to ensure prompt handling of the appeal."[35] In certain cases, a formal dispute resolution request may not even be necessary; in these instances, discussions with the review division or office

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[26] Citizen Petition, 21 C.F.R. § 10.30 (2019).

[27] Administrative Reconsideration of Action, 21 C.F.R. § 10.33 (2019).

[28] 21 C.F.R. § 10.35 (2018). There is also a request for consideration of adverse decisions on mammography facility accreditation/certification. Mammography: Quality Standards and Certifications, Appeals of Adverse Accreditation or Reaccreditation Decisions That Preclude Certification or Recertification, 21 C.F.R. § 900.15 (2019).

[29] *See* HUTT ET AL., *supra* note 10, at 52 (citing 21 C.F.R. pt. 12).

[30] *See id.* (citing 21 C.F.R. pt. 12, Subpart G).

[31] Todd R. Smyth, *The FDA's Public Board of Inquiry and the Aspartame Decision*, 58 IND. L.J. 627 (1983) (recounting an "eight-year approval process" and recognizing that these "[h]earings were perceived to be burdensome").

[32] *See* HUTT ET AL., *supra* note 10, at 53 (citing 21 C.F.R. pts. 12.32 and 13) (describing the "Public Hearing before Public Board of Inquiry").

[33] *See id.* at 54. The two instances were for aspartame, *see* Aspartame; Ruling on Objections and Notice of Hearing Before a Public Board of Inquiry, 44 Fed. Reg. 31,716 (June 1, 1979), and Depo-Provera, *see* Depo-Provera; Hearing on Proposal to Refuse Approval of Supplemental New Drug Application, 44 Fed. Reg. 44,274 (July 27, 1979).

[34] If the appeal is brought with CDER, the sponsor should also submit a copy of the formal dispute resolution request to the CDER Formal Dispute Resolution Project Manager. If the appeal is brought with CBER, the sponsor should also submit a copy of the formal dispute resolution request to the CBER Ombudsman. CDER & CBER FORMAL DISPUTE RESOLUTION GUIDANCE, *supra* note 5, at 7.

[35] *Id.*

may be the wiser path.[36] FDA also discourages undertaking parallel processes within FDA on the same matter at the same time.[37] This general concern for efficiency extends to pursuing simultaneous legal or regulatory remedies outside the agency.[38]

To maximize the likelihood of a swift and favorable response from FDA division staff, the request should be organized so that the reviewing CBER or CDER official is able to easily identify what must be done to resolve the matter expeditiously. Agency guidance outlines the details each formal dispute resolution request should contain.[39] Particularly important for review is a brief but comprehensive description of each issue the sponsor seeks to resolve. Included within this requirement is a description of the relevant scientific or medical dispute; an account of what has already been done in efforts to resolve the dispute, "including a summary of relevant regulatory history" as well as any previous formal dispute resolution requests; and an articulation of the sponsor's envisioned solutions or outcomes.[40] The agency also asks that the sponsor clarify whether they are requesting a meeting with the deciding official[41] (and if so, which type of meeting they seek), and whether the sponsor is requesting advisory committee review.

B. Appeal-Appropriate Conflicts

CDER and CBER have characterized a matter that may be fit for formal dispute resolution as an FDA regulatory action relating to a sponsor's application for a user fee product that also has scientific and/or medical significance that may be

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[36] "CDER and CBER recommend that before submitting an FDRR, the sponsor should ask the review division or the office that made the decision to reconsider the FDR-related issue(s)." CDER & CBER FORMAL DISPUTE RESOLUTION GUIDANCE, *supra* note 5, at 5.

[37] "Moreover, to further ensure efficient use of Agency resources, the sponsor submitting an FDRR should not actively engage with other entities within the FDA or pursue other regulatory or legal pathways on the same matter at the same time." *Id.*

[38] FDA strictly enforces the proscription against entertaining formal dispute resolution requests where the sponsor has commenced legal action concerning the same issue. *See* Amgen Inc. v. Hargan, 285 F. Supp. 3d 397, 400 (D.D.C. 2017) ("The FDA declined to accept Amgen's request for formal dispute resolution while the company was actively pursuing litigation on the same matter.").

[39] Other requirements are: 1) "[i]dentification of the sponsor's submission as FORMAL DISPUTE RESOLUTION REQUEST in bold, uppercase letters"; 2) "[t]he application number for the IND, NDA, BLA, or ANDA, if applicable"; 3) "[t]he proprietary and/or generic name and established name for drug products; the proprietary and/or proper name for biological products"; 4) "[t]he division or office where the application is filed"; 5) "[t]he proposed indication(s), if applicable"; 6) "[a] statement identifying the division and/or office that issued the decision on the matter being disputed and, if applicable, the deciding official on any prior FDRRs related to the same scientific and/or medical dispute"; 7) "[a] list of documents previously submitted to the sponsor's application that are deemed necessary for resolution of the matter, with reference to submission dates so the documents can be readily located"; 8) "[a] statement that no new information has been submitted in support of the FDRR and, if applicable, that the last deciding official received and had the opportunity to review all of the material now being relied upon for the sponsor's FDRR"; and 9) "[t]he name, title, and contact information (i.e., mailing address, email address, telephone number, fax number) for the sponsor's contact for the appeal." CDER & CBER FORMAL DISPUTE RESOLUTION GUIDANCE, *supra* note 5, at 8–9.

[40] *Id.* at 8.

[41] A deciding official "is the person assigned to make the decision on the appeal and is usually the Director or Deputy Director of the Office, Super Office, or Center. These officials evaluate whether the appeal satisfies the procedural criteria and whether the appeal will be accepted for review." Sharma et al., *supra* note 2, at 698.

appropriately handled through formal dispute resolution.[42] This somewhat circular definition is supplemented by specific examples FDA guidance has offered. Matters well suited for potential determination through formal dispute resolution include those that have received a regulatory action of Complete Response (CR), an IND clinical hold (partial or full), a denial of a request for breakthrough therapy designation, a denial of a request for proprietary name review, and a refusal to receive for an ANDA.[43]

The CBER and CDER formal dispute resolution process disfavors other types of conflicts. Generally speaking, agency communications or statements that are not FDA regulatory actions do not supply a basis for initiating a formal dispute resolution request. FDA does not treat information contained in meeting minutes or general advice letters, for example, as regulatory action that would support a formal dispute resolution request.[44] The agency's rationale for this distinction is two-fold. First, sponsors are not bound by these more informal recommendations; they are free to adhere to the advice or pursue equally or more effective alternative approaches. Second, CBER and CDER see a formal dispute resolution request as an unnecessary elevation of the sponsor's remedy in response to advice conveyed in meeting minutes or other correspondence. Rather than beginning a formal dispute resolution request, a sponsor may simply request that the review division or the supervising management level engage in further informal discussions.[45] FDA's view is not self-evident, though. The statutory provision speaks in terms of a "scientific controversy" but does not say that definitive agency statements can never be found in less-formal meeting minutes or advice letters.[46]

Procedural considerations, rooted in interests in conserving agency resources and promoting finality, also weigh on whether a formal dispute resolution request is appropriate. Agency guidance reveals that CBER and CDER will rarely process a formal dispute resolution request that seeks an appeal where an initial review determination has not yet been rendered[47] or where there is a simultaneous regulatory

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[42] CDER & CBER FORMAL DISPUTE RESOLUTION GUIDANCE, *supra* note 5, at 4.

[43] *Id.* at 5.

[44] *Id.*

[45] Agency guidance provides a few examples on these follow-up actions, each of which remain available outside of the formal dispute resolution process. "[S]ponsors may request a Type C guidance meeting under PDUFA, a biosimilar biological product development (BPD) Type 2 meeting under BsUFA, or a meeting under GDUFA with the review division, and request the next highest management level be present at the meeting (typically in a nondecisional capacity)." *Id.*

[46] If "there is a scientific controversy between the Secretary and a person who is a sponsor, applicant, or manufacturer and no specific provision of the Act involved, including a regulation promulgated under such Act, provides a right of review of the matter in controversy, the Secretary shall, by regulation, establish a procedure under which such sponsor, applicant, or manufacturer may request a review of such controversy." 21 U.S.C. § 360bbb-1 (2019).

[47] This presumption against appeals of ongoing matters extends to several scenarios where a formal dispute resolution request would be improper or premature: first, where an IND has been placed on clinical hold but the sponsor has not sought reconsideration of this hold; second, where a post-action meeting has been scheduled following sponsor receipt of a Complete Response (CR) letter but the meeting has not yet occurred; third, where a sponsor anticipates receiving a CR action but has not yet received a CR action; fourth, where a sponsor simultaneously seeks an end-of-review meeting after receiving a CR action *and* submits a formal dispute resolution request to the net management level; fifth, where a formal dispute resolution request seeks an appeal of an interim response to an earlier formal dispute resolution request. CDER & CBER FORMAL DISPUTE RESOLUTION GUIDANCE, *supra* note 5, at 4–6.

action wending its way through another of FDA's processes.[48] Even though regulations[49] authorize a sponsor to contact a center's ombudsman about procedural or administrative matters concerning a product at any time, FDA guidance states that "they should not engage the ombudsman in this manner and, at the same time, pursue FDR."[50] Any formal dispute resolution request "must be based on the same information as was relied on to make the original decision."[51] New information is not appropriate for a formal dispute resolution request. Even new sponsor analysis of previously submitted data is considered new information.[52] Though this approach arguably creates inefficiencies, CDER and CBER embrace this view because the original deciding FDA official might have reached a different conclusion had he or she reviewed the new sponsor analysis.

C. Timeliness of Agency Resolution

The Prescription Drug User Fee Act of 1992 (PDUFA), as amended, outlines certain performance goals for CDER and CBER's review of human drug applications.[53] For disputes involving human drug applications covered by PDUFA, the statutorily defined goal is for the relevant center to respond to a dispute resolution request within thirty calendar days of receiving the initial appeal. This response time standard is known as the "30-day goal."[54] The 30-day goal also relates to biosimilar biologic applications under the Biosimilar User Fee Act of 2012 (BsUFA)[55] and to generic drugs under the reauthorization of the Generic Drug User Fee Amendments of 2012 (GDUFA).[56] For all applications not falling within the statutory boundaries of PDUFA, BsUFA, and GDUFA, FDA grants that "the procedures described in this

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[48] On this score, agency guidance offers the following example: "A sponsor submits a Petition for Stay of Action under 21 CFR 10.35(b) and, for the same matter, several days later submits an FDRR. CDER and CBER do not intend to accept the FDRR because the sponsor is already engaged in another regulatory/legal proceeding within the Agency regarding the scientific and/or medical matter in dispute." CDER & CBER FORMAL DISPUTE RESOLUTION GUIDANCE, *supra* note 5, at 6.

[49] Investigational New Drug Application, 21 C.F.R. § 312.48(b) (2019); Applications for FDA Approval to Market a New Drug, 21 C.F.R. § 314.103(b) (2019).

[50] CDER & CBER FORMAL DISPUTE RESOLUTION GUIDANCE, *supra* note 5, at 3 n.8.

[51] *Id.* at 6.

[52] The agency allows for amendments to earlier applications in a variety of contexts, but requires that any such new information or analysis be submitted for review before CBER or CDER accept a formal dispute resolution request. "If the sponsor wants to have CDER or CBER consider new information that may affect the original decision on a matter, it should submit the new information to the sponsor's application (i.e., IND, NDA, BLA, or ANDA) for review by the division and the original deciding official." *Id.*

[53] PDUFA, *supra* note 1.

[54] Sharma et al., *supra* note 2, at 698.

[55] Pub. L. 115–52, § 904(d), 131 Stat. 1087 (2017) (codified at 21 U.S.C. § 379j–53(a); *Biosimilar Biological Product Reauthorization Performance Goals and Procedures Fiscal Years 2018 Through 2022*, FOOD & DRUG ADMIN. 17–18 (2017), https://www.fda.gov/media/100573/download [https://perma.cc/6VUD-2THM].

[56] Pub. L. 115–52, § 904(d), 131 Stat. 1086 (2017) (codified at 21 U.S.C. § 379j–43(a)); *GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018–2022*, FOOD & DRUG ADMIN. 13 (2017), https://www.fda.gov/media/101052/download [https://perma.cc/G8FA-XCKZ].

guidance generally will be applied and the time frames will be met as resources permit."[57]

When it comes to agency response time, the total lifespan of the appeal appears to make some difference. CDER logs a median response time of thirty days for formal dispute resolution requests that are appealed to only one management level.[58] For requests that seek review at two management levels, the median response time increases to 211 days.[59] And for requests that seek the determination of three management levels, CDER's median response time is 256 days.[60] Mean, as opposed to median, response time is longer for formal dispute resolution requests reviewed at one management level (57 days), at two management levels (249 days), and at three levels of review (265 days).[61] There is reason, though, to believe that average response time may be misleading: outliers like nonuser fee applications and appeals that the sponsor subsequently withdrew may "skew the time data."[62]

Where a sponsor requests a meeting in conjunction with its formal dispute resolution request, the meeting date may alter the response timeline. Meetings requested as part of a formal dispute resolution request are treated as Type A meetings under PDUFA, Biosimilar Biological Product Development Type 1 Meetings under BsUFA, or meetings under GDUFA.[63] If the meeting request is honored, the 30-day response goal timeline will apply prospectively from the date of the meeting.[64] At least when requested in conjunction with a formal dispute resolution request, a meeting is usually granted. For example, CDER granted ninety-six percent of all Type A meeting requests sought between 2003 and 2014.[65]

Sometimes, a deciding official at CBER or CDER may provide an interim response within the 30-day period in lieu of a definitive answer to the dispute resolution request.[66] An interim response might request clarifying information or a meeting with the sponsor.[67] Alternatively, an interim response might communicate to the sponsor the deciding official's intention to confer with experts, advisory committee members, or a fully convened advisory committee before the deciding official issues a final decision.[68] Data from the agency shows that a sponsor received an interim response in

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[57] CDER & CBER FORMAL DISPUTE RESOLUTION GUIDANCE, *supra* note 5, at 4.

[58] Sharma et al., *supra* note 2, at 702.

[59] *Id.*

[60] *Id.*

[61] *Id.*

[62] *Id.*

[63] CDER & CBER FORMAL DISPUTE RESOLUTION GUIDANCE, *supra* note 5, at 10.

[64] *Id.*

[65] Sharma et al., *supra* note 2, at 702. This figure represents forty-four of forty-six Type A meetings requested. Exactly half of these requests for meetings (twenty-three) were appended to the sponsor's formal dispute resolution request at the Office level, while the other half (twenty-three) accompanied formal dispute resolution requests submitted to CDER levels above the Office level. CDER "received no appeal requests for BsUFA products" and no requests for BPD Type 1 meetings during this timeframe. *Id.*

[66] CDER & CBER FORMAL DISPUTE RESOLUTION GUIDANCE, *supra* note 5, at 10.

[67] *Id.*

[68] Sharma et al., *supra* note 2, at 698.

twenty-nine percent of appeal submissions that CDER accepted for review.[69] Of these interim responses, almost half (forty-nine percent) featured a CDER-generated request for a meeting, thirty-nine percent sought more information from the sponsor, seven percent indicated that the deciding official planned to confer with other experts, and five percent notified that the deciding official planned to obtain review from an advisory committee.[70]

D. Agency Responses to Appeals

Empirical evidence suggests that at least at CDER, the majority of appeals submitted for formal dispute resolution are accepted—at least for initial review.[71] Between 2003 and 2014, CDER accepted eighty-one percent of all unique appeals.[72] Recent data suggests this figure may represent a high-water mark, as "CDER has seen a steep rise in the number of unique appeals declined for review" since 2012.[73] Even so, CDER "still accept[s] the majority of appeals submitted" for formal dispute resolution.[74]

The most common scenario in which CDER does not accept formal dispute resolution requests for review is where the sponsor provides new information that was not included in the initial application. Data shows that forty-four percent of all refusals to review result from this request defect.[75] The second most common reason for refusals to review are cases where the sponsor has failed to seek "reconsideration of the decision at the division level," which accounts for twenty-eight percent of formal dispute resolution request denials.[76] The remaining scenarios for CDER refusals to accept formal dispute resolution requests include matters where the decision the sponsor is appealing originated from another center of FDA (sixteen percent); matters where another FDA entity or other regulatory or legal body is conducting a parallel proceeding on the same appeal issue (eight percent); and matters where a decision in a lower-level appeal of the same issue has not yet been finalized (four percent).[77]

At CDER, the vast majority of appeals that are initially accepted for review (and therefore at least considered) through the formal dispute resolution process are ultimately denied. Data from 2003 to 2014 indicates that eighty-four percent of appeals were denied, while just sixteen percent were granted.[78] These above-the-fold figures, however, may obscure important nuance in sponsors' outcomes. Some in the industry have noted as much. "In our experience, 'Denials' often conceal important 'Wins' in the sense of establishing a more favorable path to approval than originally presented

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[69] *Id.* at 702. CDER issued an interim response in "41 of the 140 (29%) appeal submissions accepted for review." *Id.*

[70] *Id.*

[71] *Id.* at 697.

[72] *Id.* For purposes of this discussion, a "unique appeal" is any request a sponsor submits to FDA in seeking the agency to modify or overturn a previous decision in a scientific matter. *Id.* at 699. It may include multiple appeals within the same appeal issue. *See id.*

[73] *Id.* at 699.

[74] *Id.*

[75] *Id.* at 700.

[76] *Id.*

[77] *Id.*

[78] *Id.* at 697.

by the review division."[79] Because FDA does not subdivide what a sponsor may consider to be a partial approval or a partial denial, the binary "win" or "loss" taxonomy may obscure the reality of sponsors' experiences.

Before providing a Complete Response to a formal dispute resolution request, the deciding official may ask the sponsor to provide clarifying information.[80] In these instances, the 30-day response goal will begin to run after the deciding official receives clarifying information from the sponsor.[81] A deciding official may also request a meeting with a sponsor, which agency guidance stipulates should be arranged at the earliest mutually convenient date.[82] After the meeting has concluded, the 30-day response time window will reset.[83] During the course of its review of a formal dispute resolution request, CBER or CDER may consult with an internal expert, external expert, a member of an advisory committee, or a full advisory committee.[84] In these cases, CBER or CDER will notify a sponsor that the center is conducting such consultation and will be subject to the 30-day response goal upon conclusion of the relevant discussions with the expert party or parties.[85] Agency guidance stipulates that a deciding official's telephone response must be followed by a written confirmation within fourteen days of the initial verbal communication to the sponsor.[86]

A sponsor retains a right of appeal to a higher supervisory level within CDER if it finds the outcome for the formal dispute resolution request to be unsatisfactory. A right of appeal exists all the way up to the Office of the Commissioner at FDA.[87] Repeat appeals, however, are rare and rarely successful. Over a twelve-year period, only sixteen percent of all "appeal families"—consisting of all "unique appeals related to the same appeal issue"[88]—proceeded to two levels of review. A mere five percent of all requests involved three levels of review.[89] All told, seventy-nine percent of formal dispute resolution requests were considered by only one management level.[90] Of those twenty-nine appeals that sought some sort of upper-level review of a formal dispute resolution disposition, CDER overturned the lower-level decision in its entirety only

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79 Josephine M. Torrente & Gugan Kaur, *Formal Dispute Resolution: A Different Perspective on Wins and Losses*, FOOD & DRUG ADMIN. BLOG (Oct. 9, 2018), http://www.fdalawblog.net/2018/10/formal-dispute-resolution-a-different-perspective-on-wins-and-losses-2/ [https://perma.cc/W2ED-PSHC].

80 CDER & CBER FORMAL DISPUTE RESOLUTION GUIDANCE, *supra* note 5, at 10 n.17. Agency guidance establishes that "clarifying information does not include new information or reanalysis of data that has not been reviewed by the division." *Id.* FDA treats such information as new information that should be offered as an amendment to the sponsor's initial application; it will not be considered for the first time in a request for formal dispute resolution. *Id.*

81 *Id.* at 10.

82 *Id.* ("CDER or CBER should schedule any meetings as quickly as the sponsor and the FDA are able to agree on a mutually acceptable date and time.").

83 *Id.*

84 *Id.* at 10–11.

85 *Id.*

86 *Id.* at 11.

87 Sharma et al., *supra* note 2, at 698. Unlike other levels of review, which are governed by the 30-day goal, "[a]ppeals submitted to the Commissioner do not have timelines in the user fee program performance goals." *Id.*

88 *Id.* at 699.

89 *Id.* at 702.

90 *Id.* at 700.

once.[91] The probability of a sponsor's formal dispute resolution request moving through multiple CDER review levels before finding eventual success, then, is statistically improbable.

III. FDA FORMAL DISPUTE RESOLUTION IN PRACTICE: MEDICAL DEVICES

A. Placing the Request

At CDRH, a 10.75 supervisory appeal is distinct from a formal dispute resolution request. If a formal dispute resolution request is denied, "then the section 10.75 review process will go forward" at the relevant level within CDRH, but it will be "without the involvement of the [dispute resolution panel]."[92] A formal dispute resolution request may also be included in a petition for administrative reconsideration of action.[93]

In 2019, FDA promulgated a final rule that clarified the CDRH supervisory review process.[94] The 2019 regulation also applied "the procedures and timeframes in section 517A of the FD&C Act to an initial or sequential request for" CDRH supervisory review of "significant decisions."[95] The rule further clarified that requests for internal CDRH review must comply with the new section 800.75, explaining that "[t]he amendments to § 10.75(e) are not limited to significant decisions under section 517A of the FD&C Act."[96]

The submission requirements for a supervisory appeal and a formal dispute resolution request mirror one another. Section 517A of the FD&C Act requires a sponsor to submit a request for supervisory review or a formal dispute resolution request no later than thirty days after receiving the decision that forms the basis for an appeal.[97] The request must be clearly marked "APPEAL" and should reference any related document necessary to resolution of the request, such as a 510(k) application submission number.[98] Section 517A authorizes a sponsor seeking supervisory review to request an in-person meeting or telephone conference in conjunction with the appeal.[99] Any such meeting will occur within thirty days of the request.[100]

When a request for internal agency review under section 10.75 concerns a non-517A decision, the CDRH supervisory review process operates on a different timeline. The 2019 rule that codified the CDRH appeals framework allows non-517A appeals

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[91] *Id.*

[92] CDRH APPEALS PROCESSES GUIDANCE, *supra* note 6, at 11.

[93] *Id.* at 10 n.10. This internal review mechanism is governed by 21 C.F.R. § 10.33. *Id.*

[94] Internal Agency Review of Decisions; Requests for Supervisory Review of Certain Decisions Made by the Center for Devices and Radiological Health, 84 Fed. Reg. 31,471 (July 2, 2019) (to be codified at 21 C.F.R. pts. 10 and 800).

[95] *Id.* at 31,473.

[96] *Id.* The rule adopts a more expansive Rule 10.75(e): "[Section] 10.75(e) also encompasses supervisory review within CDRH of decisions other than 517A decisions made by CDRH." *Id.*

[97] 21 U.S.C. § 360g–1(b)(2) (2019).

[98] CDRH APPEALS PROCESSES GUIDANCE, *supra* note 6, at 6–7.

[99] 21 U.S.C. § 360g–1(b)(2) (2019).

[100] CDRH APPEALS PROCESSES GUIDANCE, *supra* note 6, at 7.

to be filed up to sixty days after the decision was rendered.[101] Under this rule, requests received after sixty days "will be denied as untimely" unless CDRH finds a good-cause exception.[102] The regulation carefully circumscribes those possible exceptions, limiting them to "circumstances beyond the control of the submitter."[103] FDA's examples carry a certain force majeure quality: good cause may only be shown in situations such as a "snow emergency, Federal Government shutdown, or other unforeseen emergency event."[104]

Compared to the regimented submission requirements for formal dispute resolution requests in drug and biologic applications, the standards for supervisory appeals and formal dispute resolution requests of medical device applications are somewhat more relaxed. In guidance, CDRH notes that section 10.75 does not require a specific format. Instead, "submitters may employ whatever format best meets their needs."[105] The center offers sponsors "a general-purpose format that has tended to be an effective means for conveying a review request," but also notes that "[f]ailure to follow these guidelines does not disqualify the request from review."[106]

Generally, sponsors will submit a "four to six page executive summary in narrative form as a cover letter,"[107] as well as copies of any "relevant documents cited in the executive summary as references or appendices."[108] This executive summary should "conclude with an explicit statement of the relief or action" that the sponsor seeks from CDRH.[109] Compromise solutions are valued; in guidance, CDRH says that if a sponsor envisions "an acceptable alternative to a complete reversal of the decision being challenged, such as deletion of certain deficiencies and referral of the matter back to the review team for reconsideration under specific conditions, that alternative should be stated in the conclusion."[110]

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[101] "A request for supervisory review of a CDRH decision other than a 517A decision is to be received no later than 60 days after the date of the decision that is subject to review." Internal Agency Review of Decisions, 84 Fed. Reg. at 31,473–74. The agency has said the "primary purpose" of this longer deadline is to "provide predictability, and to ensure that such requests are filed in a timely manner." *Id.* at 31,475.

[102] *Id.* at 31,474. In its final rule announcing the timeframe, FDA noted that this period is "twice as long as that for submission of a request for supervisory review of a 517A decision." *Id.* at 31,475.

[103] *Id.*

[104] *Id.*

[105] CDRH APPEALS PROCESSES GUIDANCE, *supra* note 6, at 8.

[106] *Id.* These standards apply to either a supervisory appeal or a formal dispute resolution request. *Id.* at 10.

[107] *Id.* at 8. CDRH guidance provides "guidelines intended to facilitate the Center's timely processing of requests for review." *Id.* These guidelines describe an executive summary that might include: (1) "[a] statement that a review is being requested and the requested level of review (i.e., the next supervisory level or higher above the individual who made the decision) and the matter of the decision under 21 CFR 10.75"; "[a] request for either an in-person meeting or a teleconference to provide the submitter an opportunity to make the case directly to the review authority, or a request for review without a meeting or teleconference"; (3) "[i]f desired, a request for the review authority to convene a meeting of the relevant Advisory Panel, or a request for referral of the review to outside expertise in the form of a 'homework assignment' along with a justification for either such request"; and (4) "[a] clear statement of the issue in dispute and a discussion of why the relief sought by the submitter should be granted." *Id.*

[108] *Id.*

[109] *Id.* at 9. Possible examples include overturning a 510(k) NSE determination or a PMA Not-Approvable letter. *Id.*

[110] *Id.*

B. Appeal-Appropriate Conflicts

A request to convene a formal dispute resolution panel must follow exhaustion of other internal review options at CDRH. A sponsor generally must first initiate a section 10.75 supervisory appeal, for example.[111] The request should be principally concerned with a scientific controversy. CDRH in guidance has said that it "interpret[s] this concept broadly so as to allow the [Dispute Resolution Panel] to consider a range of issues that may be associated with a scientific dispute."[112]

CDRH clarifies that certain topic areas are not proper subjects for a dispute resolution request. Requests for formal dispute resolution should not concern "a regulatory, legal, or statutory authority dispute"; any "actual or alleged criminal activity"; a question of "regulatory jurisdiction, such as Designation of Lead Center for a combination product"; any matter that falls outside the purview of CDRH, such as "a dispute already referred to the Commissioner's Office"; or "allegations of bias or retaliation by FDA employees."[113]

Though the subject of a request for supervisory review need not be a "significant decision" within the meaning of section 517A of the FD&C Act, agency determinations that so qualify proceed under a modified appeal framework. The statute does not define what amounts to a "significant decision," but CDRH has issued a regulation (and previously, guidance) that gives context to the term.[114] A significant decision (alternatively described as a 517A decision)[115] includes a determination that a 510(k) device is or is not "substantially equivalent" to a previously approved device; a designation of not approvable, approvable, or an approval or denial for a premarket approval (PMA) or humanitarian device exemption (HDE); a grant or denial of a breakthrough device application; an investigational device (IDE) approval or disapproval; "[f]ailure to [r]each [a]greement on a [p]rotocol under section 520(g)(7) of the FD&C Act"; and a clinical hold determination under section 520(g)(8) of the FD&C Act.[116] CDRH is obligated to provide a "substantive summary" of a significant

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[111] *Id.* at 11. There are exceptions to this general rule, however. Agency guidance provides that "[u]nder special circumstances, a review under 21 CFR 10.75 may warrant a direct referral to the Center level, including a request to convene the [Dispute Resolution Panel], before the review options at the Division and Office levels have been exhausted. These situations may include, for example, an issue that is of significant interest or impact to the public health, such as an innovative device intended to treat critically ill members of a vulnerable patient population for whom no other viable treatment alternative exists." *Id.* In any of these cases, "[i]f a stakeholder believes that such special circumstances exist, the matter should be discussed expeditiously with the Ombudsman." *Id.*

[112] *Id.* at 11 n.11. By way of example, CDRH guidance mentions that "a scientific dispute regarding clinical evidence may also involve questions regarding the need for a training program," which might warrant the convening of a formal dispute resolution panel. *Id.*

[113] *Id.* at 11.

[114] Internal Agency Review of Decisions, 84 Fed. Reg. at 31,473.

[115] FDA has elected to use "517A decision'' instead of ''significant decision'' because "we do not want to imply that any other decisions of CDRH that do not fall within section 517A of the FD&C Act are not significant." *Id.*

[116] CDRH APPEALS PROCESSES GUIDANCE, *supra* note 6, at 3. CDRH guidance states that there are other regulatory actions that, while they do not qualify as "significant decisions" under section 517A, are still reviewable through the 10.75 supervisory appeal process. Examples of these actions include "510(k) Requests for Additional Information"; "PMA Major Deficiency Letter"; "510(k) and PMA Refuse to Accept Letters"; "Postmarket Surveillance Orders under section 522 of the FD&C Act"; "CLIA Waiver Decisions"; "Warning Letters"; and "Response Letter to a Request for Information under section 513(g) of the FD&C Act." *See* CDRH APPEALS QUESTIONS AND ANSWERS, *supra* note 21, at 4.

decision upon request from the sponsor. FDA regulation has detailed what this standard entails.[117]

C. Timeliness of Agency Response

A 10.75 appeal is subject to the standard 30-day goal. For 517A "significant decisions," the 30-day standard will govern each request for CDRH supervisory review.[118] "For example, if a company that requests supervisory review of a 517A decision at the Office level further appeals the Office decision to the Center level, FDA would apply the procedures and timeframes specified in section 517A of the FD&C Act to both of these appeals.[119]

If a 10.75 appeal seeks resolution by a formal dispute resolution panel, the Deputy Center Director at CDRH will consult with the center's ombudsman and will attempt to respond to the sponsor within fifteen days of receiving the request.[120] If a formal dispute resolution panel is convened, CDRH will initiate the process the center uses for Medical Devices Advisory Committee panels. Though the process used for Medical Devices Advisory Committee panels largely governs formal dispute resolution panels for medical devices, the sequence of the panel's action may vary on a case-by-case basis.[121] As opposed to the collaborative advisory panel, the dispute resolution panel sits in an adjudicative capacity and assesses the positions of the sponsor and center—parties that are opposite one another in the formal process.[122]

D. Agency Responses to Appeals

The CDRH will respond to a 10.75 supervisory appeal, acknowledging receipt and designating the official to consider the dispute request. If the request is rejected on procedural grounds, CDRH will disclose its rationale (e.g., the request was untimely) and will then close the matter.[123] The supervisory appeal process ends when the reviewer issues a decision letter. The letter describes the basis for the request for review, conveys the decision of the review authority, and explains the basis for the decision.[124]

In cases where CDRH convenes a formal dispute resolution panel, the chair of the panel will compose a report detailing the panel's findings and its recommendation.

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[117] The substantive summary must contain a "brief statement of how the least burdensome requirements were considered and applied consistent with sections 513(i)(1)(D), 513(a)(3)(D), and 515(c)(5) of the FD&C Act (21 U.S.C. 360c(i)(1)(D), 360c(a)(3)(D), and 360e(c)(5)), as applicable." 84 Fed. Reg. 31,473.

[118] CDRH APPEALS QUESTIONS AND ANSWERS, *supra* note 21, at 2.

[119] *Id.* at 3.

[120] CDRH APPEALS PROCESSES GUIDANCE, *supra* note 6, at 11.

[121] *Id.* at 12.

[122] *Id.* at 12. CDRH describes the process for questioning at the dispute resolution panel sitting itself as follows: "[M]embers of the Panel may question the parties directly; however, no questioning by or debate between the parties should be permitted. Once deliberations have been completed, the Chair will determine whether consensus exists among the panel members and, if not, will call for a vote." *Id.*

[123] *Id.* at 7.

[124] *Id.* at 9. Usually, these letters will offer recommendations to the sponsor with additional steps that might settle the matter. *Id.* Decision letters might also include instructions about possibilities of further appeal, including the formal dispute resolution panel process, in the event the sponsor wishes to pursue additional action in the matter. *Id.*

Dissenting or minority views will also be recorded.[125] Within fifteen days of the panel meeting, documents related to the disposition of the matter will be provided to the CDRH Director or the FDA Commissioner, who will then render a final decision.[126]

IV. FDA FORMAL DISPUTE RESOLUTION'S INSIGHTS

A. Implications for Judicial Review

If an application's sponsor hopes to preserve the option for possible judicial review of an adverse decision by FDA, the sponsor typically must avail itself of the agency's internal review procedures. This requirement flows from the administrative law doctrine of exhaustion of agency remedies.[127] This means that "[a] disappointed applicant thus cannot appeal FDA's decision immediately upon denial of the application, but must first attempt to reverse the decision using these agency procedures."[128] The purposes of exhaustion include "giving agencies the opportunity to correct their own errors, affording parties and courts the benefits of agencies' expertise, [and] compiling a record adequate for judicial review[.]"[129] In cases where a plaintiff has failed "to pursue an administrative process that could remedy" his claim, the doctrine of administrative exhaustion "will preclude judicial review of agency action, so long as the purpose of administrative exhaustion supports such bar."[130]

The exhaustion doctrine can in some instances have preclusive effect in the FDA realm, as well. Where a sponsor raises an argument in court that it did not raise in FDA formal dispute resolution or other internal administrative process, the court may refuse to consider the claim and remand the matter to the agency.[131] As the First Circuit has explained:

> The exhaustion requirement, as it applies to administrative agencies, is no mere technical rule to enable courts to avoid difficult decisions. It is grounded in substantial concerns not only of fairness and orderly procedure, but also of competence. Courts are not best equipped to judge the merits of the scientific studies and FDA was created to serve that function.[132]

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[125] *Id.* at 12.

[126] *Id.*

[127] *See, e.g.*, Lannett Co., Inc. v. U.S. Food and Drug Admin., 300 F. Supp. 3d 34, 43 (D.D.C. 2017) ("Another 'long-settled rule of judicial administration' is the principle that a court that has been asked to compel an agency to act 'will stay its hand until the plaintiff has exhausted whatever internal remedies the agency provides[.]") (quoting Mackinac Tribe v. Jewell, 87 F. Supp. 3d 127, 137 (D.D.C. 2015)); Myers v. Bethlehem Shipbuilding Corp., 303 U.S. 41, 50–51 (1938).

[128] HUTT ET AL., *supra* note 10, at 68–69.

[129] Mackinac Tribe v. Jewell, 87 F. Supp. 3d 127, 137 (D.D.C. 2015) (quoting Avocados Plus Inc. v. Veneman, 370 F.3d 1243, 1247 (D.C. Cir. 2004)).

[130] *Id.*

[131] HUTT ET AL., *supra* note 10, at 69.

[132] Bradley v. Weinberger, 483 F.2d 410, 415 (1st Cir. 1973). This understanding of the exhaustion requirement, as applied to FDA's internal processes, finds broad support. *See, e.g.*, Pub. Citizen Health Research Grp. v. Comm'r, 740 F.2d 21, 35 (D.C. Cir. 1984); Nat'l Nutritional Foods Ass'n v. Califano, 603 F.2d 327 (2d Cir. 1979).

This position reflects an interest in efficiency as well as a comparative institutional competence perspective—that is, a federal court is unlikely to pass on a specific question arising out of a complex and fact-bound scientific dispute without the benefit of reviewing FDA's own determination. Even before the user fee era at FDA ushered in the formal dispute resolution framework as it is currently constituted, "[s]everal decisions of the Supreme Court demonstrate[d] that the traditional exhaustion requirement applies to one seeking judicial review of FDA status determinations."[133] Given these longstanding precedents, it seems unlikely that a federal court is likely to carve out a new exception from the exhaustion doctrine for FDA, its formal dispute resolution process, and its various other internal appeal mechanisms.

Sponsors who prematurely attempt to litigate their claims in federal court may also face ripeness challenges. Under the Supreme Court's test in *Abbott Laboratories v. Gardner*[134] (itself an FDA-originating case), a party must demonstrate the fitness of the issue for adjudication and must affirmatively show hardship that would result from federal court delay. For a litigant who has not pursued internal agency administrative process, this can be a tall order.

B. Internal Deference

At first blush, the entire concept of appeals of FDA decisions that proceed under the aegis of FDA itself may seem unfairly prejudicial. Drawing from the Latinate maxim *nemo judex in causa suas*, Edward Coke observed that "it is also against the law of nature for a man to be judge in his own proper cause."[135] Data suggests that in at least some instances, a formal dispute resolution request may be worthwhile; in other cases, the agency has essentially made up its mind. The opportunity for review in an Article III court remains an option for disaffected parties who feel they have not received a fair shake in the administrative process. Of course, litigants challenging FDA determinations must overcome generous standards of review that afford an agency considerable deference in interpreting a congressional enactment,[136] the text of an administrative regulation,[137] and agency interpretive rules.[138] Given how difficult it can be to clear these hurdles, a sponsor who receives an adverse determination at the agency may find that its energies are better spent in further discussions with FDA, rather than litigating the matter in federal court.

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[133] Biotics Research Corp. v. Heckler, 710 F.2d 1375, 1378 (9th Cir. 1983) (citing Weinberger v. Hynson, Westcott & Dunning, Inc., 412 U.S. 609, 627 (1973); CIBA Corp. v. Weinberger, 412 U.S. 640, 644 (1973); Weinberger v. Bentex Pharmaceuticals, Inc., 412 U.S. 645, 653–54 (1973)).

[134] Abbott Laboratories v. Gardner, 387 U.S. 136, 153 (1967).

[135] R.H. Helmholz, *Bonham's Case, Judicial Review, and the Law of Nature*, 1 J. LEGAL ANALYSIS 325, 335 (2009) (citing Coke's Institutes). *See also* THE FEDERALIST NO. 80, at 477 (Alexander Hamilton) (Clinton Rossiter ed., 1961) ("No man ought certainly to be a judge in his own cause, or in any cause in respect to which he has the least interest or bias.").

[136] *See* Chevron U.S.A., Inc. v. Natural Resources Defense Council, Inc., 467 U.S. 837 (1984).

[137] *See* Auer v. Robbins, 519 U.S. 452 (1997); Bowles v. Seminole Rock & Sand Co., 325 U.S. 410 (1945). The Supreme Court modified this standard in Kisor v. Wilkie, 588 U.S. __ (2019) (limiting the cases in which the *Auer*/*Seminole Rock* doctrine applies but declining to abandon the deference standard entirely).

[138] *See* Skidmore v. Swift & Co., 323 U.S. 134 (1944).

C. Understanding Sponsor Experience

In some cases, a sponsor may not have truly exhausted all possible avenues of relief within the initial review division. Agency guidance statements are replete with reminders that a sponsor may turn to other remedies before escalating a matter to formal dispute resolution. For example, CDRH says that "[t]he most effective means of resolving a dispute between the Center and an external stakeholder is through discussion and agreement."[139] At CDRH, both division officials and the center's ombudsman are "available to assist in clarifying issues, mediating meetings and teleconferences, and conducting discussions with the parties in an effort to resolve disagreements short of a formal review or appeal."[140]

The expressed preference of CDER and CBER is similar: "sponsors may approach the review division and/or the next highest management level to further discuss advice provided in meeting minutes or other correspondences related to their clinical development program outside of an FDRR."[141] Yet data suggests that relatively few sponsors who bring formal dispute resolution requests heed this advice. At CDER, for example, a little less than one-third of all sponsors who brought appeals had some sort of early engagement (through a pre-IND meeting) with FDA.[142] It is, however, ultimately "up to the party seeking review of an adverse decision or resolution of a difference of opinion to determine the appropriate process for a given circumstance or issue."[143]

Even presuming the deck is not stacked against a party seeking internal review of an FDA determination and there are no other available remedies within the review division, a sponsor should consider the costs of formal dispute resolution. These costs might be analyzed in terms of time, expense, and the value of the ongoing relationship with the agency official whose determination a formal appeal seeks to modify or overturn. A formal dispute resolution request may require the hiring of outside counsel, for example. For CDER appeals studied over a twelve-year period, small and mid-sized companies hired outside regulatory counsel for forty percent and thirty percent of their appeals, respectively. Large companies brought on outside counsel for only fourteen percent of their formal dispute resolution requests. Companies whose size is unknown (which suggests they are more comparable to small companies) hired outside regulatory counsel to assist in fifty-eight percent of analyzed matters.[144]

Understanding *why* sponsors seek formal dispute resolution is key to analyzing its place within FDA's regulatory architecture. At CDER, a plurality of decisions appealed by sponsors came in matters where FDA had issued a Complete Response action to an application for an NDA, BLA, or ANDA, which made up thirty-eight percent of all appeal families.[145] The next most common type of decision that sponsors

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[139] CDRH APPEALS PROCESSES GUIDANCE, *supra* note 6, at 1.

[140] *Id.* at 1–2.

[141] CDER & CBER FORMAL DISPUTE RESOLUTION GUIDANCE, *supra* note 5, at 5.

[142] Sharma et al., *supra* note 2, at 701. "Of the 137 appeal families, approximately one-third (44 of 137; 32%) of the sponsors who submitted appeals had early engagement." *Id.*

[143] CDRH APPEALS PROCESSES GUIDANCE, *supra* note 6, at 1.

[144] Sharma et al., *supra* note 2, at 701–02 ("If a company did not make information available that enabled CDER to determine size, then CDR considered it private.").

[145] *Id.* at 700. Note that this figure includes both Complete Response letters and the now-defunct "not approvable" action, which CDER provided in response to some NDA and ANDA applications prior to 2008.

appealed were IND clinical holds or continued clinical hold actions; these decisions represented fifteen percent of all appeal families.[146] The remaining areas of formal dispute resolution requests were varied: they included roughly equal numbers of appeals of "priority review classification, breakthrough therapy designation, inadequate proposed pediatric study request[s], refus[als] to receive for ANDAs, review classification, pediatric written requests, and safety labeling changes order[s]."[147]

Though the formal dispute resolution request process applies equally to all parties without regard to their relative size or regulatory expertise, data suggests that more sophisticated parties may be underrepresented in FDA's formal dispute resolution framework. Parties who are comparatively less familiar with the agency's practices and procedures may be overrepresented. Consider that the division between sponsors who do and do not have prior FDA regulatory experience is almost exactly proportional in the context of CDER appeals: fifty-one percent of formal dispute resolution requests were submitted by sponsors who had successfully received FDA approval in a previous NDA, BLA, or ANDA application; sponsors without equivalent regulatory experience submitted forty-nine percent of requests during the studied period.[148] Yet over the same time span, formal dispute resolution requests submitted by small and medium-sized companies formed a higher proportion of CDER appeal families—sixty-seven percent in all—than did large companies, whose requests accounted for only twenty-three percent of all appeal families.[149] If the assumption that larger companies are more likely to have relevant FDA regulatory experience than other sponsors is granted, it seems probable that larger sponsors are resolving a higher proportion of their contested matters through the alternative informal mechanisms that FDA prescribes, while smaller and less-experienced sponsors are disproportionately represented in formal dispute resolution requests.[150] There are, of course, pragmatic dimensions related to a sponsor's decision to pursue formal dispute resolution.[151]

The final metric that is instructive for contextualizing sponsor experience with the formal dispute resolution request process is its relative rarity as an administrative

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Id. As CDER explains, "[a] Complete Response is a letter from FDA to an applicant explaining why the agency will not approve the application in its present form." *Id.* These letters comprised 52 of 137 appeal families during the twelve-year study period. *Id.*

146 *Id.*

147 *Id.*

148 *Id.* at 701.

149 *Id.* The sixty-seven percent figure for small and medium-sized sponsors breaks down into forty-five percent and twenty-two percent, respectively, with small-sized sponsors responsible for initiating 62 of 137 appeal families and medium-sized sponsors responsible for 30 of 137. *Id.* In addition, "private companies" (those for which data about their comparative size was unavailable) accounted for nine percent (13 of 137) of appeal families. *Id.*

150 If this assumption holds, it carries implications for how best to interpret the data about outcomes of formal dispute resolution requests. Perhaps the number of denials or partial denials of requests for formal dispute resolution is artificially inflated, for example.

151 Large company sponsors typically have a larger number of drugs to investigate. They are often repeat players at FDA and might be less inclined to bring dispute resolution requests given that each individual product represents a smaller proportion of the company's portfolio. Small and medium-sized companies may develop only a handful of products (or even just one). The effect of an unfavorable decision from FDA is felt more acutely by small or medium-sized sponsors, and they may therefore be more inclined to challenge an FDA determination through dispute resolution.

procedure, at least compared with other procedural processes that FDA undertakes on a regular basis. Over a twelve-year period, CDER received an average of fourteen unique appeals and initiated 30-day goals only twenty-two times each year.[152] Though extrapolating from available CDRH data is a bit more complicated, FDA experience with medical devices seems to be largely the same.[153] CDRH received an annual average of twenty[154] or twenty-one[155] internal appeals of medical device decisions over a multi-year period. Compared with the fifty-five PMA applications and the 3,389 510(k) applications that FDA received in 2016, the number of formal internal appeals represents a relatively small proportion of total submissions received from sponsors.[156]

D. Agency Policy and Procedural Choices

FDA internal appeals practices reflect a concern with preserving multiple stages of scientific review. In some respects, the agency's emphasis on ensuring robust intra-agency assessment incorporates the scientific community's general belief in peer review. Here, though, where the stakes of approving or denying a drug or device are arguably higher than the publication of a single academic article, the need to arrive at the "right answer" seems even more acute.

Embedded within FDA's procedural edifice are advisory committees—the quintessential arbiters of substance. "FDA relies heavily on technical advisory committees for advice on such issues as the approval of new drugs and the adequacy of clinical designs."[157] Advisory committees serve an important legitimating function in FDA's internal review processes. Their decisions carry an aura of scientific expertise and lend credence to career officials' determinations (at least when advisory committees ratify those decisions). "Committees have also reviewed proposed approval or denial of new uses of products, or new warnings, or even revocation of prior approvals."[158] In recent years, the constellation of advisory committees that FDA relies on has swelled to at least fifty.[159]

The current formal dispute resolution framework, complete with its reliance on experts and advisory committees, in many respects incorporates distinct elements of FDA's previous dispute resolution regimes. For many years, FDA attempted to strike a balance between a scientific and adversarial process in disputed matters of scientific

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[152] Sharma et al., *supra* note 2, at 699.

[153] Though lacking in complete empirical evidence about medical device appeals, review of CDRH appeals practices offers helpful data spanning from 2005 to 2016. *See* GOVERNMENT ACCOUNTABILITY OFFICE, GAO-18-140, FDA MEDICAL DEVICE REVIEWS: EVALUATION IS NEEDED TO ASSURE REQUESTS FOR ADDITIONAL INFORMATION FOLLOW A LEAST BURDENSOME APPROACH (2017).

[154] Between 2005 and 2012, CDRH received approximately 141 internal appeals of decisions rendered in response to 510(k) and PMA submissions. *Id.* at 18 n.38. FDA did not have a formal mechanism to track internal appeals of these medical device appeals prior to May 2013, but reconstructed CDRH data from this period offers helpful insight. *Id.*

[155] Between 2013 and 2016, CDRH received sixty-three appeals. *Id.* at 17–18.

[156] *Id.* at 16 (Table 1).

[157] HUTT ET AL., *supra* note 10, at 1490 n.1 (citing 21 C.F.R. § 14.160).

[158] *Id.* (citing instances of important advisory committee action announced in the Federal Register).

[159] "[T]o assist in its mission to protect and promote the public health, [FDA] uses 50 committees and panels to obtain independent expert advice on scientific, technical, and policy matters." *Advisory Committee Research, Reports, and Announcements*, FOOD & DRUG ADMIN. (Apr. 13, 2019), https://www.fda.gov/AdvisoryCommittees/AboutAdvisoryCommittees/ucm165313.htm [https://perma.cc/QD6U-9VU6].

judgment. FDA officials determined that evidentiary hearings were ill-suited for the sort of determinations the agency must make on a regular basis.[160] But are formal hearings the only remaining substitute to the current decentralized procedure of internal appeals and review?

FDA's brief foray into convening a "science court" suggests alternative approaches are available. The Public Board of Inquiry (PBOI), first introduced at FDA in 1975, offers one such approach.[161] In a PBOI, an informal public hearing is conducted as a scientific inquiry rather than a trial-like evidentiary hearing. But the science court model can be measured not only against FDA formal evidentiary hearings; it is also worth comparing it to advisory committees. Professor Sidney Shapiro has observed that the "process offers the FDA a unique option with several important advantages over the agency's advisory committee system."[162] The first advantage is the post-approval nature of the PBOI; ex-post review therefore "serve[s] as an independent check on the validity of [the agency's] decision" and supplies a more fully-developed record so that the PBOI may "focus on the key issues in the agency's decision."[163] As opposed to advisory committees, a PBOI places a somewhat greater emphasis on data analysis.[164] This feature of the PBOI has two salutary effects: it "increase[s] the accuracy of the decisionmaking process, even if the panel can offer no particular assistance to the agency on issues of regulatory judgment."[165] According to Shapiro, this independence "enhances the legitimacy of the agency's decisionmaking process."[166]

CONCLUSION

Whether formal dispute resolution at FDA is perceived as accurate or legitimate by those who interact with the system is an issue that lies beyond the scope of this piece. The answer to that open question aside, the scheme offers a revealing window into how the agency approaches challenges to its own decisions. FDA's internal appeals processes are at once collaborative and self-reinforcing. Implicit within the agency's formal dispute resolution framework is a recognition that it is doing far more than the moniker suggests. Resolving disputes is only the beginning of the system's relevance; of far greater import is FDA's interest in approving safe and effective drugs and medical devices that will improve the lives of the American public. Above all else, the

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160 HUTT ET AL., *supra* note 10, at 53 ("The most cogent criticisms of the FDA experience include Ben G. Fisher, *Procedural Techniques in Food and Drug Administration Proceedings*, 17 FOOD DRUG COSM. L.J. 724 (1962); Robert Hamilton, *Rulemaking on a Record by the Food and Drug Administration*, 50 TEX. L. REV. 1132 (1972); Note, *FDA Rulemaking Hearings: A Way Out of the Peanut Butter Quagmire*, 40 GEO. WASH. L. REV. 726 (1972).").

161 *See* Notice of Proposed Rulemaking Administrative Practices and Procedures, 40 Fed. Reg. 40,682 (Sept. 3, 1975).

162 Sidney A. Shapiro, *Scientific Issues and the Function of Hearing Procedures: Evaluating the FDA's Public Board of Inquiry*, 1986 DUKE L.J. 288, 342 (1986).

163 *Id.*

164 *Id.*

165 *Id.* at 323 ("Moreover, this advantage is present even if the FDA ultimately disagrees with the PBOI; to overrule the panel, the commissioner must be able to rebut the board's conclusions. Thus, the PBOI forces the FDA to take a 'hard look' at the validity of the agency's position.").

166 *Id.*

agency's internal appeals framework aims to achieve that vital end.