United States Court of Appeals

FOR THE DISTRICT OF COLUMBIA CIRCUIT

Argued January 15, 2025 Decided August 15, 2025

No. 24-1049

VANDA PHARMACEUTICALS, INC.,
PETITIONER

v.

UNITED STATES FOOD AND DRUG ADMINISTRATION, ET AL.,
RESPONDENTS

On Petition for Review of an Order
of the Food & Drug Administration

Paul W. Hughes argued the cause for petitioner. With him on the briefs were *Sarah P. Hogarth*, *Charles Seidell*, and *Nicole Wittstein*.

Lewis Yelin, Attorney, U.S. Department of Justice, argued the cause for respondents. With him on the brief were *Brian M. Boynton*, Principal Deputy Assistant Attorney General, at the time the brief was filed, *Daniel Tenny*, Attorney, *Samuel R. Bagenstos*, General Counsel, U.S. Department of Health & Human Services, at the time the brief was filed, and *Kwabena Akowuah*, Associate Chief Counsel, U.S. Food & Drug Administration.

Before: PAN and GARCIA, *Circuit Judges*, and EDWARDS, *Senior Circuit Judge*.

Opinion for the Court filed by *Circuit Judge* GARCIA.

GARCIA, *Circuit Judge*: Vanda Pharmaceuticals, Inc. applied for Food and Drug Administration approval to market the drug tasimelteon as a treatment for jet lag. FDA denied Vanda's application without first holding a hearing. Vanda petitioned our court for review. Vanda argues that FDA was required by statute to hold a hearing before denying Vanda's application. Alternatively, Vanda argues that the record here presented material factual disputes requiring a hearing, and that the agency's reasons for denying the application were arbitrary and capricious. We agree with Vanda in part. FDA can deny a new drug approval application without holding a hearing if no material facts are genuinely disputed. On this record, however, FDA's refusal to hold an evidentiary hearing must be set aside.

I

A

The Food, Drug, and Cosmetic Act (FDCA) requires that drug manufacturers apply to FDA for approval before marketing a new drug (or an existing drug for a new purpose). *See* 21 U.S.C. § 355(a). FDA may approve the application only if, among other things, the manufacturer offers "substantial evidence" that the drug is safe and effective for its proposed use. *Id.* § 355(d). The Act defines "substantial evidence" as "adequate and well-controlled investigations, including clinical investigations, by experts" from which "it could fairly

and responsibly be concluded by such experts that the drug will have the effect it . . . is represented to have." *Id.*

After reviewing an application, FDA "shall either . . . approve the application," or if it cannot do so, "give the applicant notice of an opportunity for a hearing . . . on the question whether such application is approvable." *Id.* § 355(c)(1). Per agency regulations, if FDA does not approve an application on first pass, it will notify the applicant of its determination by issuing a "complete response letter" explaining the application's defects and suggesting steps to remedy those defects. 21 C.F.R. § 314.110(a); *see also id.* § 314.125(a). The applicant may then withdraw or resubmit its application, or may request "an opportunity for a hearing." *Id.* § 314.110(b)(3).

If the applicant requests an opportunity for a hearing, FDA can "either approve the application . . . or refuse to approve the application" and issue "the applicant written notice of an opportunity for a hearing" (known as an NOOH). *Id.*; *see also id.* § 314.200(a). Upon receiving an NOOH, an applicant may request a hearing and submit additional materials to support that request. *See id.* § 314.200(c)(1). FDA will hold a hearing, however, only "if the material submitted shows" that there "is a genuine and substantial issue of fact for resolution." *Id.* § 12.24(b)(1). If it instead "conclusively appears from the face of the" record that there is no such issue for resolution, FDA will "enter summary judgment" denying the application. *Id.* § 314.200(g)(1).

B

In 2018, Vanda applied to FDA for approval to market tasimelteon—a drug previously approved as a treatment for a rare sleep disorder—as a treatment for jet lag. As part of its submission to FDA, Vanda offered the results from five clinical trials, three of which form the core of its application.

Vanda's three trials sought to assess tasimelteon's effect on jet lag and its symptoms. The trials measured both "[p]rimary endpoints" (measurements "typically selected to address the main clinical question") and "secondary endpoints" (which may "be used to support the claim of efficacy," including "by demonstrating additional effects"). J.A. 246 ¶ 29 (citation modified). The trials' "primary endpoints" related to the ease with which subjects fell asleep and stayed asleep. These primary endpoints were evaluated objectively, using measures of subjects' brain activity. The "secondary endpoints" related to patients' perceived alertness, and were assessed using subjective tools including the Karolinska Sleepiness Scale (KSS) and the Visual Analog Scale (VAS).

In 2019, FDA's Center for Drug Evaluation and Research (CDER) issued a complete response letter, signaling its intent to deny Vanda's application. CDER refused approval in part because it was unpersuaded that Vanda's trials satisfied the "substantial evidence" burden. CDER explained that it was "not clear how [the] primary endpoints assess the fundamental sleep disturbances associated with jet lag disorder." J.A. 35. The letter described that "[o]ther important aspects of the disorder," beyond sleepiness, were not measured. *Id.* And it concluded that at least one of the subjective tools used to measure the secondary endpoints, the KSS, was "not fit-for-purpose." *Id.*

After receiving CDER's response letter, Vanda repeatedly met with FDA and submitted two formal dispute-resolution requests. Vanda argued that tasimelteon should be approved for the use (or "indication") that Vanda had initially requested: treatment of jet lag as a whole. In the alternative, Vanda argued that, even accepting CDER's critiques, tasimelteon could at least be approved for a narrower indication: treatment of the insomnia symptoms associated with jet lag.

Both of Vanda's dispute requests were denied. The reviewing officers agreed with the initial conclusion that Vanda had not sufficiently demonstrated that tasimelteon could treat the distinct symptoms of jet lag. And they concluded that a request for a narrower indication was outside the scope of the dispute-resolution request, as Vanda had not asked for a narrower indication before CDER issued the complete response letter.

In June 2022, Vanda requested an opportunity for hearing. Two months later, FDA issued an NOOH, repeating its skepticism that Vanda's studies measured the relevant symptoms of jet lag. FDA explained that demonstrating a drug's efficacy in treating jet lag required showing improvement on two categories of symptoms: (1) "insomnia or excessive daytime sleepiness, accompanied by a reduction of total sleep time, associated with transmeridian jet travel across at least two time zones" and (2) the "associated impairment of daytime function, general malaise, or somatic symptoms within one to two days after travel." J.A. 134. FDA concluded that Vanda's studies did not provide substantial evidence that tasimelteon improved either symptom—much less that tasimelteon improved both symptoms, as would be required for approval. FDA found that Vanda's primary endpoints at best measured only sleepiness symptoms. It further found that the tools Vanda used to evaluate its secondary endpoints did not measure next-day impairment, were internally flawed, and suffered from statistical error.

In November 2022, Vanda requested a hearing, arguing in part that the FDCA mandated one. To support its request, Vanda would eventually submit five expert declarations. The declarations responded to each of FDA's objections, explained the experts' views that Vanda's three clinical studies constituted substantial evidence of tasimelteon's efficacy for

treating jet lag, and argued that a hearing was required to resolve factual disputes over the adequacy of the clinical trials.

On February 29, 2024, FDA issued a final decision denying Vanda's application and its hearing request. The agency's Principal Deputy Commissioner found there was "no genuine and substantial issue of fact justifying a hearing." J.A. 1987. She again defined jet lag as encompassing both insomnia symptoms and next-day impairment. J.A. 1988–89. And she reiterated that Vanda's studies were statistically flawed and, even if sound, failed to demonstrate that tasimelteon impacted next-day impairment. *See* J.A. 2026–30.

Vanda petitioned our court for review of FDA's final decision and hearing denial. We have jurisdiction under 21 U.S.C. § 355(h).

II

Vanda lodges three primary challenges to FDA's order. First, Vanda argues that FDA unlawfully denied its request for a hearing—either because the FDCA requires FDA to conduct a hearing whenever an applicant requests one, or because Vanda raised a material factual dispute precluding summary judgment. Next, Vanda contends that FDA acted inconsistently, and therefore arbitrarily and capriciously, both by refusing to grant Vanda a narrower indication and by demanding that Vanda offer evidence of jet lag's second symptom. Finally, Vanda claims that the Principal Deputy Commissioner's issuance of FDA's final decision violated the Appointments Clause.

We disagree with each of Vanda's arguments, save one: Though the FDCA does not mandate that FDA must hold a hearing before denying any new drug application, in this case, FDA's decision denying Vanda a hearing was arbitrary and

capricious. We therefore remand to FDA for further proceedings.

A

Vanda's primary challenge is to FDA's denial of its hearing request. As noted, it argues both that FDA was statutorily required to hold a hearing, and that summary judgment was inappropriate here regardless. We consider each argument in turn.

1

The FDCA does not require FDA to hold a hearing before denying any new drug approval application that it receives.

Sections 355(c) and (d) of Title 21 outline hearing procedures for new drug applications. Section 355(d) specifies that an application will be approved if "the Secretary finds, after due notice to the applicant . . . and giving him an opportunity for a hearing," that certain criteria are met, including that the applicant provided substantial evidence of the drug's efficacy. 21 U.S.C. § 355(d). Section 355(c) commands that the HHS Secretary has 180 days to "(A) approve [an] application" or "(B) give the applicant notice of an opportunity for a hearing . . . on the question whether such application is approvable." *Id.* § 355(c)(1). It then describes the timeline on which a "hearing shall commence." *Id.*

For decades, FDA regulations implementing those provisions have subjected new drug applications to summary judgment procedures. *See* Hearing Regulations and Regulations Describing Scientific Content of Adequate and Well-Controlled Clinical Investigations, 35 Fed. Reg. 7250, 7252 (May 8, 1970). Pursuant to those procedures, FDA can, in specified circumstances, deny an application on its merits without holding a hearing. Vanda argues that those regulations are invalid because Section 355(c) requires FDA to hold a

hearing for every application it intends to deny, regardless of the application's merit. We have never directly considered that issue. *Cf. Pharm. Mfg. Rsch. Servs., Inc. v. FDA*, 957 F.3d 254, 266 (D.C. Cir. 2020) (applying FDA's summary judgment procedures without explicitly considering their conformity with the statute). But we do not write on a blank slate.

In *Weinberger v. Hyson, Westcott & Dunning, Inc.*, 412 U.S. 609 (1973), the Supreme Court interpreted the very similar text of Section 355(e) of the FDCA—which governs FDA's withdrawal of prior drug approvals—to permit FDA's use of summary judgment procedures. *Id.* at 620–23. The *Weinberger* Court reached that holding even though the "Act require[d] FDA to give 'due notice and opportunity for hearing to the applicant' before [withdrawing] its approval." *Id.* at 620 (quoting 21 U.S.C. § 355(e)). The Court explained that the provision's text did not "preclude" an agency "from particularizing statutory standards through the rulemaking process and barring at the threshold those who [do not] measure up to them." *Id.* (quotation omitted). The Court added that it could not "impute to Congress the design of requiring, nor [did] due process demand, a hearing when it appears conclusively from the applicant's 'pleadings' that the application cannot succeed." *Id.* at 621.

Weinberger's interpretation of Section 355(e) guides our interpretation of Sections 355(c) and (d). Most centrally, *Weinberger* informs our reading of the plain text. It holds that FDA may use summary judgment procedures to deny a hearing when no material facts are genuinely disputed, despite Section 355(e)'s requirement that the Secretary provide "notice and opportunity for hearing." Like Section 355(e), Section 355(d) states that the Secretary "shall issue an order refusing to approve the application" after "due notice to the applicant . . . and giving him an opportunity for a hearing." 21 U.S.C. § 355(d). And Section 355(c) similarly requires the Secretary

to "give the applicant notice of an opportunity for a hearing." *Id.* § 355(c)(1)(B). Given the comparable phrasing across these provisions, it stands to reason that if Section 355(e) does not preclude summary judgment procedures, then Sections 355(c) and (d) do not either. After all, we generally "give . . . consistent meaning" to the same or similar terms when they are used "throughout [an] Act." *Gustafson v. Alloyd Co*., 513 U.S. 561, 568 (1995). That interpretive principle applies with even greater force where, as here, the provisions are next to one another, within the same section of a statute, and pertain to parallel processes. *See Nat'l Credit Union Admin. v. First Nat'l Bank & Tr. Co.*, 522 U.S. 479, 501 (1998) (describing "the established canon of construction that similar language contained within the same section of a statute must be accorded a consistent meaning").

Weinberger also rests on a practical rationale that applies to new drug approvals as much as to withdrawals. *Weinberger* reasoned that requiring FDA "automatically to hold a hearing for each product whose efficacy was questioned . . . even though many hearings would be an exercise in futility" would preclude FDA from "fulfill[ing] its statutory mandate to remove from the market all those drugs which do not meet the effectiveness requirements of the Act." 412 U.S. at 621. So too if FDA were required to hold a hearing for every new drug approval application it planned to deny. After all, addressing applications for new drug approval is also a "massive regulatory task." *SmithKline Corp. v. FDA*, 587 F.2d 1107, 1116 (D.C. Cir. 1978). In the approval context, then, we also "cannot impute to Congress" a meaning that strains logic, imposing a requirement that FDA expend resources even "when it appears conclusively from the applicant's 'pleadings' that the application cannot succeed." *Weinberger*, 412 U.S. at 621.

Vanda would have us distinguish *Weinberger* by fixating on one phrase that appears in Section 355(c) but not in Section 355(e). Subsection (c) states that, absent agreement between FDA and the applicant, a hearing "*shall commence*" within 120 days of an NOOH's issuance "[i]f the applicant elects to accept the opportunity for hearing." 21 U.S.C. § 355(c) (emphasis added). Vanda contends that this language is "unambiguous" and "command[s]" that FDA conduct every hearing that a party requests. Petitioner's Brief 18.

That language, however, must be read in context. Subsection (c) is, at least primarily, a timing provision. It is entitled "Period for approval of application; period for, notice, and expedition of hearing; period for issuance of order." 21 U.S.C. § 355(c). And it describes the pace at which various actions take place: Subsection (c)(1) specifies that the Secretary must either approve an application or issue an NOOH within 180 days of receiving an application. *Id.* at § 355 (c)(1). Subsection (c)(2) describes the time by which "the holder of [an] approved application" must "file with the Secretary" relevant patent information. *Id.* § 355(c)(2). And subsection (c)(3) establishes a timetable for when applications including certain certifications become effective. *Id.* § 355(c)(3).

Moreover, it is Section 355(d)—and not Section 355(c)—that governs the substantive contours of the hearing process. Subsection (d) is entitled "Grounds for refusing application; approval of application; 'substantial evidence' defined." *Id.* § 355(d). And it recounts the substantive considerations that FDA must weigh, including the requirement that the applicant offer substantial evidence. *See id.* Even the text of subsection (c) itself suggests that subsection (d) governs substance; subsection (c) says that "the Secretary shall . . . give the applicant notice of an opportunity for a hearing before the Secretary *under subsection (d)* on the question whether such application is approvable." *Id.* § 355(c)(1)(B) (emphasis

added). No similar mandate that a hearing "shall commence" appears in the substantive instructions that Section 355(d) outlines.

Read against that statutory context, subsection (c)'s "shall commence" language does not create an unconditional right to a hearing. Instead, it fits within the following statutory scheme: FDA can, consistent with *Weinberger*, establish by regulation that an "opportunity for a hearing" exists only if there is a material factual dispute. If a material factual dispute exists and an opportunity for a hearing arises, FDA must "give the applicant notice" of that opportunity and the applicant may "elect[] to accept the opportunity." *Id.* And if the applicant does so, "such hearing shall commence" within 120 days of such notice. *Id.* In short, the "shall commence" language—like the balance of subsection (c)—simply sets a timing requirement, providing that any hearings that do occur "shall commence *not more than ninety days after the expiration of . . . thirty days*" from when notice is given. *Id.* (emphasis added).

In sum, Vanda's argument assigns too much weight to Section 355(c)'s "shall commence" language. The Supreme Court has authoritatively construed Section 355(e) to permit summary judgment procedures despite similar language requiring "notice and opportunity for a hearing." The same reasoning applies here. We therefore find that FDA's summary judgment procedures comport with the statute.

2

Vanda next argues that, even if the FDCA does not always mandate a hearing, Vanda was entitled to one here. Vanda submits that FDA's contrary decision was "arbitrary, capricious, . . . or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A). "[O]ur review focuses on whether the agency's decision was reasonable and reasonably explained." *Pharm. Mfg.*, 957 F.3d at 262 (citation modified). We agree

with Vanda that FDA's order must be set aside under that standard.

FDA may deny a request for a hearing unless "the applicant . . . identif[ies] a material issue of fact." *Am. Cyanamid Co. v. FDA*, 606 F.2d 1307, 1314 (D.C. Cir. 1979); *see also* 21 C.F.R. § 12.24(b). To survive summary judgment, then, an applicant must raise a dispute that concerns factual issues, rather than "issues of policy and law," *Pharm. Mfg.*, 957 F.3d at 266 (quoting 21 C.F.R. § 12.24(b)(1)), and that is material because it "might affect the outcome . . . under the governing law," *John D. Copanos & Sons, Inc. v. FDA*, 854 F.2d 510, 523 (D.C. Cir. 1988) (quoting *Anderson v. Liberty Lobby*, *Inc.*, 477 U.S. 242, 248 (1986)).

When FDA denies an applicant a hearing, we review that denial to determine "whether the agency has given adequate consideration to all relevant evidence in the record." *Pharm. Mfg.*, 957 F.3d at 266 (citation modified). In so doing, "we give a high level of deference to the agency's scientific analysis of the evidence before it." *Id.* at 262 (citation modified). Our review is particularly deferential where FDA identifies a "precise" regulatory standard that forms the basis for its denial. *See SmithKline*, 587 F.2d at 1117–18; *Copanos*, 854 F.2d at 522. Our review becomes somewhat more searching, however, where the agency's denial is premised solely on a more general standard that provides less precise guidance. *See SmithKline*, 587 F.2d at 1117–18; *Copanos*, 854 F.2d at 522; *see also Am. Cyanamid*, 606 F.2d at 1312–13. In that case, we consider whether the applicant "manifest[ly]" failed to comply with the "general statutory or regulatory provisions." *Copanos*, 854 F.2d at 522 (citation modified). Put otherwise, we ask if FDA has demonstrated that the applicant's evidence was "conclusively deficient." *Am. Cyanamid*, 606 F.2d at 1319.

Here, FDA denied Vanda a hearing on the ground that no factual dispute existed that, if resolved in Vanda's favor, could establish "substantial evidence" supporting its application. *See* 21 U.S.C. § 355(d)(5). Recall that the statute defines "substantial evidence" in relevant part as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved." *Id.* § 355(d). Under our precedents, that is ordinarily a more "general," rather than "specific," standard (as no party squarely disputes). *See SmithKline Corp*, 587 F.2d at 1117–18; *Am. Cyanamid*, 606 F.2d at 1312–13. We therefore review FDA's denial to determine whether FDA has shown that Vanda's experts' studies and testimony are "conclusively deficient." *Am. Cyanamid*, 606 F.2d at 1319.

FDA's primary argument is that it properly denied Vanda a hearing "in light of the company's complete failure to establish that tasimelteon improved impairment in next-day functioning," the second symptom of jet lag. Respondents' Brief 41. On FDA's view, Vanda's clinical studies could never demonstrate that tasimelteon effectively treated next-day impairment because they did not measure that symptom. At most, FDA found, the studies evaluated only subjective impressions of sleepiness and alertness—primarily using the KSS and VAS tools—and those tools are not proven to measure the distinct symptom of next-day impairment. The "link" between next-day impairment and the sleepiness measured by the KSS and VAS tools, FDA said, "cannot be assumed." J.A. 2028.

That rationale could carry the day if it were a reasonable description of the record evidence, as FDA would then have "identified at least one conclusive deficiency in" Vanda's evidence. *Am. Cyanamid*, 606 F.2d at 1314. But it is not an accurate description of the evidence submitted here. Vanda did

not merely assume that these tools measured next-day impairment. Nor did it enlist experts who merely submitted "general and unsupported" assertions to that effect. *Copanos*, 854 F.2d at 526. Vanda instead offered pages of expert testimony describing that improvement on the KSS and VAS corresponded to improvement in next-day functioning. And here, FDA primarily dismissed Vanda's arguments as assumptions without adequately explaining any flaws in Vanda's evidence. As a result, on this record, FDA has not shown that the testimony is "conclusively deficient," and so a material factual dispute remains. *Am. Cyanamid*, 606 F.2d at 1319.

Examples of Vanda's testimony and FDA's responses demonstrate the point. To start, Vanda submitted expert testimony from Dr. Daniel Combs concluding that both the KSS and VAS could measure the next-day impairment relevant to jet lag. J.A. 490–93 ¶¶ 207–19. Dr. Combs supported that conclusion with reasoning and with citations to relevant literature. He first explained that "next-day alertness was measured by VAS" in one of Vanda's trials; that in that trial "it was shown that patients treated with tasimelteon had reduced next-day symptoms as evidenced by significantly higher alertness compared to the placebo"; and thus that those findings "show[ed] that next-day daytime functioning impairment is lessened with tasimelteon use because higher alertness and less exhaustion results in better daytime functioning." J.A. 490 ¶ 207. Dr. Combs then described that Vanda's studies demonstrated similar results on the KSS. J.A. 491 ¶ 208. And Dr. Combs noted that "[t]he KSS has been demonstrated to correlate closely with measures of cognitive function," citing a study to support that claim. J.A. 491 ¶ 209. He directly disputed CDER's conclusion that the KSS was not "fit-for-purpose." J.A. 491 ¶ 211 (citation modified); J.A. 492 ¶ 214; J.A. 493 ¶ 219.

Dr. Combs also explained that, contrary to FDA's claims, "[t]he KSS is a validated instrument for measuring sleepiness and has been found to highly correlate to behavioral variables and brain functioning." J.A. 491–92 ¶ 213. He added that "the validity of the KSS as a measure of sleepiness and indicator of impaired waking function has been recognized by the scientific community," citing multiple studies. *Id.* And sleep, he explained, "is essential for cognitive performance, as reported next-day sleepiness and low alertness directly affect next-day functioning when travelers are engaging in tasks such as driving or working." J.A. 492–93 ¶ 217 (footnote omitted). Dr. Combs then cited studies in which sleep deprivation has been linked to dangerous errors that stem from functional impairment. J.A. 492–93 ¶ 217 & n.8.

Vanda provided further testimony from Dr. Thomas Roth, who similarly concluded that each subjective tool Vanda used could measure the next-day impairment relevant to jet lag. *See* J.A. 1506–13 ¶¶ 89–105. Dr. Roth described that "KSS scores and VAS scores all correlate strongly with daytime function." J.A. 292 ¶ 175. He also cited three studies for the proposition that it "is common within the sleep research community to use [the] VAS to measure aspects of sleep and daytime functioning and the effects of therapeutic interventions on them." J.A. 249 ¶ 41 (quotation omitted). To rebut FDA's claims that the KSS does not measure the impairment that accompanies jet lag, he explained that the KSS has previously been used in studies measuring jet lag disorder, citing five examples. J.A. 321–22 ¶ 266. He also explained *why* the KSS would adequately measure the next-day impairment associated with jet lag: "[D]aytime sleepiness is an aspect of daytime function" and so "relates to impaired next-day function," as illustrated by a cited study linking sleepiness to impairment of functioning. J.A. 1513–14 ¶ 107.

FDA did not (and likely could not) dispute either of these experts' credentials. Instead, FDA principally argued that the experts' claims were merely conclusory—that "Vanda ha[d] not specifically identified reliable evidence to support [its] assertions," J.A. 2068, and had simply "assumed" a link between what the KSS and VAS measured and impaired daytime function, J.A. 2028. Those statements, though, mischaracterize the evidence before FDA. As the above excerpts show, these experts fully explained their reasons for concluding that the KSS and VAS could measure next-day impairment, then cited studies from their field to support that position. The experts' views were thus specific, reasoned, and rooted in evidence. Their declarations are unlike the "general and unsupported" attestations that we have found insufficient to create a genuine dispute of material fact. *Copanos*, 854 F.2d at 526.

In the alternative, FDA disputes these experts' claims by questioning the validity and applicability of the particular studies on which they rely. *See* J.A. 2030–35. That iteration of FDA's argument, though, only helps to prove Vanda's point: Vanda provided evidence that created a genuine dispute over the strength of the scientific evidence supporting the link between the KSS and VAS tools and next-day impairment. Had FDA pointed to some "conclusive" flaw in the experts' rationale or the studies they rely on—the sort of flaw, for instance, that renders those studies facially irrelevant—then FDA might nonetheless have demonstrated that no dispute existed, despite the evidence Vanda provided. *See Am. Cyanamid*, 606 F.2d at 1314. But FDA has not made any such showing here. Instead, its treatment of Vanda's evidence is cursory (and was barely mentioned in FDA's brief, *see* Respondents' Brief 38–39).

Insofar as FDA addresses Vanda's evidence at all, the agency mostly dwells on minor and seemingly irrelevant

disagreements with the cited studies' analysis. For example, FDA claimed that two studies Vanda identified as using the KSS to assess jet-lag-related topics were irrelevant because they studied Swedish or Chinese volunteers, and not U.S. populations. *See* J.A. 2031–33. Similarly, FDA noted that a third study did not label the response options in its version of the KSS in precisely the same way as Vanda's studies did. J.A. 2032. Dr. Roth responded that those distinctions were immaterial to whether the KSS is a viable measure of next-day functioning for purposes of jet lag disorder, which was what Vanda had relied on the KSS studies to show. J.A. 1515 ¶ 111. Even according deference to FDA's scientific judgments, the issues FDA identified do not establish a conclusive deficiency in Vanda's evidence. *See Am. Cyanamid*, 606 F.2d at 1314–16 (finding applicant raised material issue of fact where parties' experts disagreed over scientific meaning of clinical trials' results); *see also SmithKline*, 587 F.2d at 1119.

3

In addition to its core claim that Vanda did not offer evidence measuring next-day impairment, FDA also notes an array of other problems with Vanda's evidence that might foreclose taismelteon's approval and make a hearing unnecessary. But none of FDA's other arguments show that Vanda "manifest[ly]" failed to carry its substantial evidence burden. *Copanos*, 854 F.2d at 522 (quotation omitted).

To start, FDA argues that the KSS and VAS tools are improperly designed, and so cannot accurately evaluate even the subjective "sleepiness" and "alertness" they were created to measure. FDA offers little scientific substantiation for its arguments, and some of its claims appear facially implausible. (FDA claims without support, for example, that trial subjects would be unable to understand that "rather alert" indicates a degree of alertness lower than "alert," even when the terms are

ordered and labeled on a numeric scale. J.A. 2027.) Moreover, Vanda's experts explained why those concerns with the KSS and VAS tools were not merited, pointing to numerous other sleep studies where the KSS and VAS tools were deployed. *See, e.g.*, J.A. 321–22 ¶¶ 264–68; J.A. 491–92 ¶¶ 212–15; J.A. 1504–06 ¶¶ 83–88; J.A. 2235–37 ¶¶ 83–88; J.A. 1511–13 ¶¶ 102–05; J.A. 2247–48 ¶¶ 102–05. At the very least, that evidence created a genuine factual dispute over the validity of these tools.

FDA next argues that, in their measurement of secondary endpoints, Vanda's studies failed to control for the risk of "Type I error"—or false indications that the treatment has a statistically significant affect. "The overarching statistical defect," FDA explains, was that "Vanda failed to prespecify the statistical analysis to be conducted after collecting data concerning certain secondary study outcomes." Respondents' Brief 33 (citation modified). And without such prespecification, "the likelihood of false positive outcomes increases." *Id.*

The presence of Type I error, if fully explained by FDA and left meaningfully unanswered by Vanda, might also be the sort of flaw that establishes a conclusive deficiency in a party's evidence. Here, however, a nonconclusory declaration from Dr. Platt described why Vanda's trial design would not result in Type I error in this instance, even if prespecification is ordinarily a best practice. *See* J.A. 1563 ¶¶ 29–30; J.A. 1567 ¶ 47. Dr. Platt's declaration included a meta-analysis of the three clinical studies Vanda submitted. And it articulated, based on that analysis, why the risk of Type I error was negligible here. *Id.*

In turn, neither FDA's final decision nor its brief on appeal directly acknowledges Dr. Platt's analysis. FDA responded to a related argument in Dr. Roth's declaration, *see* J.A. 2039–40

& n.187, but did not directly respond to Dr. Platt's more-developed assessment. It would thus be quite difficult for us to conclude, on this record, that FDA reasonably explained why Dr. Platt's analysis did not raise a material dispute of fact as to the reliability of Vanda's studies. Ultimately, although "[m]any of FDA's reservations about [the statistical rigor of Vanda's] stud[ies] may be valid," our court's "function is not to choose among expert opinions but to determine whether FDA's evaluation of the study conclusively establishes" its invalidity. *Am. Cyanamid*, 606 F.2d at 1315. Given Dr. Platt's thorough declaration, we cannot agree that FDA has made that showing.[1]

Finally, FDA contested Vanda's ability to demonstrate taismelteon's efficacy in treating the first symptom of jet lag, sleep disturbance. Vanda, however, clearly offered meaningful evidence of tasimelteon's efficacy in improving sleep disturbance. Its three clinical trials were each designed to primarily measure improvement on one of two sleep-focused metrics. And each trial showed statistically significant improvement on the primary endpoint measured. *See* J.A. 721; J.A. 843; J.A. 266–67 ¶ 96.

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[1] FDA's decision below (though, again, not its brief to us) does refer in a footnote to a portion of a CDER submission that engages with Dr. Platt's analysis. *See* J.A. 2040 & n.189. Even if FDA is fairly treated as adopting CDER's response as part of its final decision, on our review, CDER's explanation does not describe any conclusive deficiency in Dr. Platt's analysis; CDER instead disagrees with Dr. Platt over a specific scientific question that he addresses at length. *See* J.A. 2449–53. Ultimately, at this stage, the dispute remains a battle of experts who offer conflicting and nonconclusory views—and that is exactly the type of dispute our precedent says is inappropriate for resolution without a hearing. *See Am. Cyanamid*, 606 F.2d at 1315–16.

FDA challenged Vanda's reliance on those three trials by questioning the relevance of the two primary endpoints Vanda selected—endpoints that respectively focused on how quickly subjects achieved persistent sleep and how well they slept during the first two-thirds of the night.[2] *See* Respondents' Brief 15. But Vanda provided a reasonable answer to FDA's concerns. Vanda offered experts who attested that those measurements were relevant to jet-lag-related sleep disturbance. And these experts again provided sufficiently detailed support for their view to raise a factual dispute. For example, Dr. Roth and Dr. Combs identified other sleep-drug studies and jet lag studies that similarly relied on measures of patients' time to fall asleep. *See* J.A. 300–02 ¶¶ 198, 204; J.A. 486 ¶ 186. They named multiple other sleep drugs that FDA has approved based on studies measuring that endpoint. *See* J.A. 486 ¶ 187; *see also* J.A. 300 ¶¶ 198–99. And while insomnia studies typically measure *total* sleep time, Dr. Roth explained (with cited support) that "jet lag disorder is most likely to have a sleep-disturbing effect during the first two thirds of a person's total sleep time" and that it therefore

[2] In its final decision, FDA also quibbled with broader study design choices, arguing these choices invalidated Vanda's measurements even of its primary endpoints. FDA contended, for instance, that too few participants were used in one study. *See* J.A. 1983–84. And it contested the fact that the two other studies were conducted in a laboratory (and so did not require participants to undergo transmeridian travel) and did not screen subjects for prior symptoms of sleep disturbance. *See* J.A. 2044–45. Those issues are not squarely raised in FDA's brief. *But cf.* Respondents' Brief 8, 11, 15. And even to the extent they were properly presented to our court, they primarily involve a scientific assessment of the adequacy of the evidence, on which Vanda's experts offered thoroughly explained contrary views. *See, e.g.*, J.A. 297–98 ¶¶ 187–89; J.A. 1470–71 ¶ 12; J.A. 1501 ¶¶ 73, 75–76; J.A. 1525 ¶ 14. These concerns, then, also raise factual disputes and so would not foreclose approvability.

"makes sense that jet lag disorder studies focus on [sleep time] during the first two thirds of a night." J.A. 302 ¶ 207. Dr. Combs described why that is true: "By the last third of the night, individuals would have reached their circadian night and would be expected to have better sleep compared to the first two-thirds of the night, when they would be expected to still be in their circadian day." J.A. 485 ¶ 185.

Even affording substantial deference to FDA's expertise, we cannot say on this record that FDA has reasonably articulated any conclusive flaw in Vanda's evidence that forecloses approval without requiring the resolution of material factual disputes. Instead, it again casts Vanda's evidence on this issue as "conclusory" when it plainly was not. J.A. 2006. Thus, FDA could not properly deny Vanda's application on that basis without holding a hearing.

B

Vanda also raises several arbitrary-and-capricious challenges to the reasoning in FDA's denial. We generally decline to reach those challenges, given that FDA will be required to conduct further proceedings on remand. Nonetheless, we address two arguments that relate to the reasoning above and that bear on the proper scope of those further proceedings.

First, Vanda contests its obligation to prove the second symptom of jet lag, next-day impairment. Vanda argues that tasimelteon should be considered an effective treatment for jet lag even if Vanda's evidence shows only that tasimelteon can remedy sleep-disturbance symptoms. FDA reasonably disagreed.

FDA defined jet lag disorder as encompassing both sleep disturbance and next-day impairment. To arrive at that definition, FDA looked to the International Classification of

Sleep Disorders (ICSD-3) published by the American Academy of Sleep Medicine. As Vanda does not dispute, the ICSD-3 is the "internationally recognized standard for diagnosing jet lag disorder." J.A. 1989.

The ICSD-3 describes jet lag as characterized by three diagnostic criteria: "A. There is a complaint of insomnia or excessive daytime sleepiness"; "B. There is associated impairment of daytime function, general malaise, or somatic symptoms"; and "C. The sleep disturbance is not better explained by another current sleep disorder . . . or . . . medication." J.A. 1263. It also explains the "[e]ssential [f]eatures" of the disorder: "Jet lag disorder is characterized by a temporary mismatch between the timing of the [internal] sleep and wake cycle . . . and . . . [the external] sleep and wake pattern required by a change in time zone. Individuals complain of disturbed sleep, sleepiness and fatigue, and impaired daytime function." *Id.* Based on those materials, FDA concluded that jet lag's symptoms consisted—as the ICSD-3 described—of both sleep disturbance and next-day impairment. *See* J.A. 1988–90.

Vanda argues that, when approving other sleep-disorder drugs, FDA has not required manufacturers to prove "Criterion B" symptoms—those symptoms categorized by the letter "B" in the ICSD-3's diagnostic criteria list. On Vanda's view, it is therefore inconsistent to require proof of a Criterion B symptom—next-day impairment—only for jet lag. And FDA, Vanda insists, has not adequately explained its choice to hold Vanda to a new and different standard.

But FDA did explain why it looked at a Criterion B symptom in defining jet lag, even if it has not always done so for other sleep disorders. Here, next-day impairment was not only listed in Criterion B but was also described as one of the "essential features" of jet leg. J.A. 1989–90; J.A. 2013–15.

Other sections of the ICSD-3 also describe how jet lag works in greater detail. And they explain that "[t]he symptoms of jet lag disorder are due to both desynchronization of endogenous circadian rhythms with local time *and* sleep disturbance." J.A. 1265 (emphasis added). Thus, by looking to the whole of the ICSD-3—and particularly the "essential features" portion of the definition—FDA reasonably concluded that "jet lag disorder necessarily encompasses more than sleep disturbance alone." J.A. 1989; *see also* J.A. 2014–15.[3]

Second, Vanda challenges FDA's refusal to consider a "narrower indication" and approve tasimelteon as a treatment only for *insomnia* related to jet lag (rather than as a treatment for jet lag as a whole). Vanda again claims that FDA acted inconsistently. Vanda contends that FDA ordinarily considers narrower indications that companies propose and cites a list of other drugs where narrower indications were approved. *See* Petitioner's Brief 35–37.

FDA does not dispute that it commonly considers requests to narrow proposed indications. *See* Respondents' Brief 49–50; J.A. 2061. Here, however, Vanda requested a narrower

[3] In its reply brief, Vanda suggests that FDA's explanation that next-day impairment is an essential feature is also inconsistent and arbitrary; in other cases, Vanda claims, FDA has not required applicants to prove Criterion B symptoms even when those symptoms are listed as essential features. Reply Brief 11–12. Vanda forfeited that argument, however, by failing to raise it in its opening brief without justification. *See Johnston v. SEC*, 49 F.4th 569, 578 n.3 (D.C. Cir. 2022). The argument also appears meritless. In the examples Vanda points to, the ICSD-3 definitions do not characterize any Criterion B symptom as an "essential feature" of the disorder; to the contrary, the "essential features" section of the ICSD-3 explicitly labels only a Criterion A symptom as the "essential feature" of the disorder and notes that Criterion B symptoms merely "accompan[y]" that single "essential feature." *See* J.A. 2085–87; J.A. 2105–07.

indication only after FDA had issued its complete response letter. FDA explained that it does not consider requests for narrower indications raised after issuance of a complete response letter. J.A. 61; J.A. 2062–63. And Vanda never claims that, in any of the cases it identified, FDA considered narrower indications that, like Vanda's, were proposed at that late stage.[4] Indeed, contrary to Vanda's argument, our court recently found that FDA reasonably refused to consider a narrower indication for another drug for much the same reason. *See Pharm. Mfg.*, 957 F.3d at 263–64, 266.

FDA did not act arbitrarily and capriciously either in defining jet lag to include next-day impairment or in refusing to consider Vanda's narrower proposed indication.

C

Finally, Vanda argues that the Principal Deputy Commissioner's issuance of FDA's final decision violated the Constitution's Appointments Clause. Vanda, however, forfeited its Appointments Clause challenge by failing to raise it before the agency.

The FDCA provides that "[n]o objection to the order of the Secretary shall be considered by the court unless such

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[4] In response, Vanda suggests that it had earlier informally raised the idea of pursuing a narrower indication but was dissuaded from doing so, as FDA represented that the narrower indication likely would not be approved. *See, e.g.*, Petitioner's Brief 34. That answer, though, is nonresponsive. It matters little whether FDA earlier signaled it was unpersuaded that a narrower indication was approvable; Vanda still itself chose not to pursue the narrower indication until after the complete response letter was issued. And Vanda offers no argument as to why FDA acted inconsistently in refusing to consider the narrower indication due to that procedural failing.

objection shall have been urged before" the agency, or "there were reasonable grounds for [the] failure so to do." 21 U.S.C. § 355(h). The statute's text provides no carveout for constitutional arguments. *See id.* And our court has applied similar statutory exhaustion requirements to constitutional claims. *See Fleming v. USDA*, 987 F.3d 1093, 1098 (D.C. Cir. 2021) (finding challenge to for-cause removal protections forfeited where not raised before the agency because that "argument is subject to a mandatory, non-excusable, issue-exhaustion requirement imposed by statute").

Vanda argues that it did raise its Appointments Clause challenge to the FDA by repeatedly requesting a "hearing *before the Commissioner*." Reply Brief 23–24 (emphasis in original). But Vanda identifies no place in its agency filings where it explicitly argued that the Commissioner must personally conduct the hearing. Nor does Vanda claim to have mentioned the Appointments Clause—or even the Constitution—in requesting a hearing before the Commissioner. Because Vanda did not provide FDA a meaningful "opportunity to pass on [the] issue," the argument is forfeited. *Fleming*, 987 F.3d at 1100 (citation modified).

Vanda next claims it had reasonable grounds to excuse its forfeiture. Vanda explains that before FDA issued its final decision, Vanda "had no occasion to suspect that anyone *but* the Commissioner would issue the order," or that any Appointments Clause violation might occur. Reply Brief 24 (emphasis in original). Vanda's claim is unpersuasive. Many final decisions publicly available in the Federal Register are signed by officials other than the Commissioner. *See, e.g.*, Final Decision on the Proposal to Refuse to Approve a New Drug Application for ITCA 650, Docket No. FDA-2021-N-0874 (Aug. 23, 2024) (signed only by the Principal Deputy Commissioner); Final Decision on the Proposal to Withdraw Approval of Pepaxto (melphalan flufenamide) for Injection,

Docket No. FDA-2023-N-3167 (Feb. 23, 2024) (signed by Director of FDA's Center for Biologics Evaluation and Research). Vanda is a sophisticated repeat player before the FDA; we are not persuaded that it could not reasonably have anticipated that someone other than the Commissioner would issue the decision.

Finally, Vanda argues that we retain the discretion to entertain a forfeited Appointments Clause challenge. *Cf., e.g.*, *Freytag v. Comm'r of Internal Revenue*, 501 U.S. 868, 878–79 (1991). Even if we possess such discretion where, as here, the petitioner's claim is subject to a mandatory statutory exhaustion requirement, *cf. Fleming*, 987 F.3d at 1098, we decline to exercise any such discretion in this case. The complexity of the questions Vanda belatedly seeks to raise and the weakness of its explanation for not complying with the statute suggest this is not one of the "rare cases" where we should overlook Vanda's forfeiture. *Freytag*, 501 U.S. at 879.

III

The petition for review is granted in part, and the case is remanded to FDA for future proceedings not inconsistent with this opinion.

So ordered.