UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MARYLAND
GREENBELT DIVISION

MALLINCKRODT INC., Plaintiff, vs. UNITED STATES FOOD AND DRUG ADMINISTRATION et al., Defendants.	)	C.A. No. _____

PLAINTIFF'S MEMORANDUM IN SUPPORT OF MOTION FOR TEMPORARY RESTRAINING ORDER

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INTRODUCTION

Plaintiff Mallinckrodt Inc. respectfully requests the Court to enter a temporary restraining order reversing an arbitrary and capricious action by the United States Food and Drug Administration that effectively takes an approved drug (manufactured by Mallinckrodt) off the market. This is not a case involving agency action based on a public safety issue. To the contrary, FDA admits that it "has not identified any serious safety concerns" and has told patients who still take the drug that they "should not make changes to their treatment except in consultation with their health care professional." Although there is no pressing public interest underlying its action, FDA surprised Mallinckrodt by implementing the action last Thursday with only 24 hours' prior notice, refusing to give the company any opportunity to delay the action or contest its deeply flawed premises. FDA's abrupt action already has caused Mallinckrodt irreparable harm by immediately triggering legal prohibitions, in 31 states and the District of Columbia, that prevent pharmacists from substituting Mallinckrodt's generic drug for the corresponding name-brand product. The irreparable harm to Mallinckrodt will rapidly escalate unless this Court intervenes immediately, because the drug is Mallinckrodt's most profitable product and number one generic drug.

The drug at issue is a generic form of methylphenidate hydrochloride extended release ("methylphenidate ER"), which is an FDA-approved treatment for attention-deficit hyperactivity disorder. FDA approved Mallinckrodt's product in December 2012, and the product marketed today is identical. Eighteen months ago (in May 2013), FDA

received a patient report suggesting that Mallinckrodt's generic methylphenidate ER may be less effective than the corresponding name-brand product. While there have been some additional similar reports since then, FDA admits that the number "is very small compared to the overall usage of the products."

On November 6, 2014, FDA unexpectedly announced a new standard for assessing methylphenidate hydrochloride that neither FDA nor anyone else had ever used before. FDA also applied an untested method — which is contrary to the available published scientific literature — to Mallinckrodt's drug in an analysis that used additional flawed assumptions, relied on erroneous factual premises, and ignored data that supported efficacy. Based on this new method, FDA reclassified Mallinckrodt's drug to a category in which (depending on the state jurisdiction) it is either unlawful or unacceptably risky for pharmacists to fill a prescription by substituting Mallinckrodt's generic for its brand-name counterpart. Unless the Court intervenes, the drug will be effectively taken off the market. If that occurs, patients will suffer too, because there already is a shortage of methylphenidate ER.

Mallinckrodt is likely to succeed on the merits of this case, because FDA's reclassification decision is arbitrary and capricious and also violates Mallinckrodt's statutory and constitutional rights to a hearing before FDA can take away, or impair, the company's rights in its drug approval. FDA's reclassification decision also is unlawful, because the agency issued the new November 6 approval standard without following

required notice and comment rulemaking procedures. This is an unusual case in which likelihood of success on the merits coalesces with massive irreparable harm to the plaintiff, the balance of equities tips toward the plaintiff, and the public interest also supports an injunction. The Court should enter a temporary restraining order restoring the *status quo ante* by directing FDA to reverse its reclassification decision on a temporary basis, until the Court can fully consider the merits of this case.

STATUTORY AND REGULATORY BACKGROUND

The regulatory regime governing FDA's authority for premarket approval of drugs is set forth in the Federal Food, Drug, and Cosmetic Act ("FFDCA"), 21 U.S.C. § 301 *et seq*. The FFDCA applies separate requirements for the approval of new brand-name drugs (also known as innovator drugs) and generic drugs. Although the process of approving brand-name drugs is typically more burdensome and time-consuming, prior to approval of both types of drugs, FDA must conduct an extensive review to determine that the drug is safe and effective. Based on this review, as described below, FDA approved Mallinckrodt's methylphenidate ER as a safe and effective substitute for the brand-name drug Concerta®.

New Drug Approvals

In order to market and sell a brand-name drug, a company must submit a New Drug Application ("NDA"). As set forth in 21 U.S.C. § 355, an NDA must outline and explain the drug's ingredients, the results of clinical tests, the results of animal studies, how the drug behaves in the body, and how the drug is manufactured, processed, and

packaged. Before approving an NDA, FDA must evaluate numerous statutorily-defined criteria, including whether the drug is safe and effective in its proposed use. *See* 21 U.S.C. § 355 *et seq*.

In order to market and sell a generic drug, a company must submit an Abbreviated New Drug Application ("ANDA"). As set forth in 21 U.S.C. § 355(j), an ANDA applicant may obtain FDA approval of a drug that is the "same" as a previously approved brand-name drug without conducting the full battery of clinical and non-clinical studies that are required for an NDA. *See generally* 21 U.S.C. § 355(j). An ANDA applicant is allowed to rely upon a prior FDA finding of safety and efficacy for the approved brand-name drug that is referenced by the ANDA applicant, provided that the proposed generic drug is the "same" as the approved brand-name drug with regard to active ingredients, dosage form, route of administration, strength, and labeling. *Id*. § 355(j)(2)(A)(i), (ii), (iii), and (v). In addition, before approving an ANDA, FDA is required to determine that the proposed generic drug is "bioequivalent" to the referenced brand-name drug. *See* 21 U.S.C. § 355(j)(4)(F); 21 C.F.R. § 314.127(a)(6)(i). In general, a generic drug is "bioequivalent" to the corresponding brand-name drug if, in single-dose or multiple dose clinical studies, the "rate and extent of absorption" of the two drugs are not significantly different. *See* 21 U.S.C. § 355(j)(8)(B).

The Orange Book

The FFDCA mandates that FDA publish a list all drugs that have been approved, *see* 21 U.S.C. § 355(j)(7)(A)(i)(I)-(III), and FDA has elected to fulfill this statutory duty

by publishing the *Approved Drug Products with Therapeutic Equivalence Evaluations*, commonly known as the "Orange Book."

Among other things, the Orange Book contains FDA's evaluations of "therapeutic equivalence." In sum and substance, FDA defines therapeutic equivalence as a combination of two elements: (i) "pharmaceutical equivalence" (*e.g.*, having the same active ingredient, dosage form, route of administration); and (ii) "bioequivalence" (defined *supra*). Ex. 1 at vi-viii.

FDA lists its therapeutic equivalence ratings in the Orange Book in the form of two-letter codes — *e.g.*, AA, AB, BP, BX. According to FDA, these therapeutic evaluations "have been prepared to serve as public information and advice to state health agencies, prescribers, and pharmacists to promote public education in the area of drug product selection and to foster containment of health care costs." *Id*. at iv. The Orange Book provides an explanation of the specific therapeutic equivalence codes. Relevant here, FDA uses various "A codes" and "B codes" to designate whether the drug product is considered by FDA to be therapeutically equivalent to another listed drug. Those drugs considered by FDA to be therapeutically equivalent are listed with a two-letter code beginning with "A." Those drugs not considered by FDA to be therapeutically equivalent are listed with a two-letter code beginning with "B."

The Orange Book therapeutic equivalence ratings are commonly used by pharmacists to determine whether a generic drug may be dispensed to a patient who has

been prescribed the brand-name version of the same drug. FDA states in the Orange Book that therapeutically equivalent drugs "can be substituted with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product." Ex. 1 at vii. As a result, FDA's therapeutic equivalence ratings have become the recognized authoritative standard for determining whether a pharmacist may substitute one drug for another, and pharmacists typically use generic drugs to fill prescriptions for brand-name drugs (such as Concerta®) only if the generic version is classified in the Orange Book as automatically substitutable for the brand drug.

Withdrawal of Drugs From the Market

Once an ANDA is approved, FDA is authorized to take a drug off the market through a statutorily-mandated process, as defined in 21 U.S.C. § 355(e). Section 355(e) requires "due notice and opportunity for hearing to the applicant."

There is no statutory or regulatory mechanism by which FDA can take a generic drug off the market without providing the applicant notice and an opportunity for a hearing. In fact, FDA is required by law to provide the applicant notice and an opportunity for a hearing even in those instances in which FDA believes there is an imminent health risk. The statute requires FDA to allow the applicant an opportunity for an "expedited hearing" in the event the Secretary finds there is "an imminent hazard to the public health." 21 U.S.C. § 355(e). FDA has expressly acknowledged that no such safety risk is at issue here. Decl. of Mario Saltarelli ("Saltarelli Decl.") (filed under seal), Ex. B.

STATEMENT OF FACTS

This lawsuit arises out of an abrupt action taken by FDA last week that threatens to cause immediate and devastating harm to Mallinckrodt. At the center of the dispute is an important drug product, methylphenidate ER, a generic drug marketed and sold by Mallinckrodt as an alternative to the brand drug Concerta®. Mallinckrodt's product is used to treat patients suffering from attention-deficit hyperactivity disorder ("ADHD"). *See* Saltarelli Decl. ¶ 6.

FDA's Approval and Determination of Therapeutic Equivalence

FDA approved Mallinckrodt's methylphenidate ER on December 28, 2012. Saltarelli Decl. ¶ 11. Based on scientific studies and data reviewed and analyzed by FDA at the time, none of which have changed, FDA concluded the product was "therapeutically equivalent" to Concerta®. *Id*. As a result, FDA listed the methylphenidate ER tablets as "AB" rated in the Orange Book, signifying FDA's considered conclusion that Mallinckrodt's "application contains scientific evidence establishing through *in vivo* and/or *in vitro* studies the bioequivalence of the product to a selected reference product." *See* Ex. 1 at xiv.

Mallinckrodt's Successful Marketing and Sale of Methylphenidate ER

Since being approved, Mallinckrodt's product has proven to be an important, cost-effective alternative to the brand drug, as well as a successful and safe product. More than 88 million doses of the drug have been prescribed, and it has been dispensed in tens of thousands of pharmacies. Saltarelli Decl. ¶¶ 13-16. Mallinckrodt has successfully

marketed methylphenidate ER in 27 mg, 36 mg, and 54 mg tablets. Until now, all three dosage strengths have had a therapeutic equivalence rating of AB in the Orange Book, making them automatically substitutable for the same dosage strengths of Concerta® at the pharmacy level. Decl. of Walt Kaczmarek ("Kaczmarek Decl.") ¶¶ 5, 20-21, 25 (filed under seal); Saltarelli Decl. ¶ 18.

Methylphenidate ER was Mallinckrodt's most profitable product in fiscal year 2014 — not only for generic drugs but for all products and across all business units of the company. *Id*. ¶ 26. For the fiscal year ended September 30, 2014, Mallinckrodt generated more than $209 million in sales of methylphenidate ER tablets. *Id*. ¶ 27. In terms of sales and profitability, methylphenidate ER is critical to Mallinckrodt's business.

Methylphenidate ER is also critical to the patient community. In particular, Mallinckrodt's product is currently filling a serious need, as there is a supply shortage in the methylphenidate ER market. FDA's Drug Shortage Program website lists Methylphenidate Hydrochloride ER Capsules/Tablets as "Currently in Shortage." *Id*. ¶ 52, Ex. B.

FDA's Abrupt Reversal and Reclassification Action

Last week (on November 12), after Mallinckrodt's product had been successfully on the market for almost two years, and without any warning, FDA informed Mallinckrodt during a teleconference that the agency planned to take an immediate action reclassifying Mallinckrodt's methylphenidate ER tablets from an AB rating to a BX rating in the Orange Book, denoting the agency's apparent conclusion that the drug is not

automatically substitutable for the brand-name drug. Saltarelli Decl. ¶ 18; Kaczmarek Decl. ¶ 20. An FDA official expressly confirmed that the reclassification was a "final agency action." Saltarelli Decl. ¶ 20.

During the November 12, 2014 teleconference, FDA officials told Mallinckrodt that the agency's reclassification action was based on the application of a new "draft guidance" document regarding bioequivalence for methylphenidate hydrochloride products. Saltarelli Decl. ¶ 19. FDA took the position that the "draft guidance" applied even though FDA had published the "draft guidance" less than one week earlier, on November 6, 2014, and even though the "draft guidance" remains open for comment through January 5, 2015. *Id*.

In response to Mallinckrodt's queries, an FDA official stated that the agency would provide Mallinckrodt with "compelling" supporting data, including case report forms, and specifically referred to a detailed report of over 100 pages supporting FDA's decision. Even though Mallinckrodt has made additional requests for this alleged data, the only written rationale that the agency has provided for its action is a 15-page summary memorandum. Saltarelli Decl. ¶¶ 21, 25, 26. That memorandum contains numerous factual inaccuracies, faulty assumptions, and otherwise flawed analyses. *Id*. ¶¶ 28-50.

Both during and after the phone call with FDA, Mallinckrodt representatives objected — orally and in writing — to FDA's surprise reclassification action as not

supported by appropriate evidence and not consistent with patients' best interests. Mallinckrodt also requested an opportunity to address any concerns identified by FDA, and to engage in a dialogue with FDA. FDA, however, has not provided any opportunity for Mallinckrodt to be heard since announcing FDA's reclassification action. Saltarelli Decl. ¶¶ 21-22.

On November 13, 2014, one day after first announcing its surprise action, FDA formally reclassified Mallinckrodt's methylphenidate ER tablets to a BX rating in the Orange Book. Ex. 2; Saltarelli Decl. ¶ 23. The same day, FDA issued a press release and a separate public document containing "Questions and Answers" about the product and action. Saltarelli Decl. ¶ 24. In these public pronouncements, FDA stated that it had "concerns about whether or not" Mallinckrodt's product is "therapeutically equivalent to the brand name drug" for "some patients." *Id.*, Ex. B. The agency emphasized that "FDA has not identified any serious safety concerns" with the product. *Id.* FDA claimed that it had based its decision on some number of "adverse event reports," but FDA acknowledged that "the total number of lack of effect reports" was "very small compared to overall usage of the product." *Id.*, Ex. C.

The reclassification action triggered immediate harmful effects described below. This action followed.

ARGUMENT

Mallinckrodt respectfully requests the Court to issue a temporary restraining order directing FDA to reinstate the Orange Book AB rating for the company's methylphenidate ER drug on a temporary basis, until the Court can fully consider the merits of this case. The requested temporary restraining order is a prohibitory injunction, because it "'aim[s] to maintain the status quo and prevent irreparable harm while a lawsuit remains pending.'" *League of Women Voters of N.C. v. N.C.*, 769 F.3d 224, 236 (4th Cir. 2014) (quoting *Pashby v. Delia*, 709 F.3d 307, 319 (4th Cir. 2013)). Here the "status quo" means an Orange Book AB rating for the drug, because that is "'the *last uncontested status* between the parties which *preceded* the controversy.'" *League of Women Voters*, 769 F.3d at 236 (citation omitted) (emphasis added). Although the temporary restraining order would "'require a party who has recently disturbed the status quo'" — namely FDA — to "'reverse its actions, . . . [s]uch an injunction restores, rather than disturbs, the status quo ante.'" *Id*. (quoting *Aggarao v. MOL Ship Mgmt. Co.*, 675 F.3d 355, 378 (4th Cir. 2012)).

The Court may grant the requested temporary restraining order if Mallinckrodt establishes the following: (1) that it is likely to succeed on the merits; (2) that it is likely to suffer irreparable harm in the absence of preliminary relief; (3) that the balance of equities tips in its favor; and (4) that the injunction is in the public interest. *Real Truth About Obama, Inc. v. FEC*, 575 F.3d 342, 346 (4th Cir. 2009) (citing *Winter v. NRDC*, 555 U.S. 7, 20 (2008)), *vacated on other grounds*, 559 U.S. 1089 (2010). This case

involves a strong justification under all four factors. The Court therefore should issue the temporary restraining order.

I. MALLINCKRODT IS LIKELY TO SUCCEED ON THE MERITS OF ITS CLAIMS

Mallinckrodt is likely to succeed on the merits of its claims that in effectuating the reclassification action, FDA exceeded its statutory and constitutional authority, violated notice and comment rulemaking requirements, and acted arbitrarily and capriciously.

A. Mallinckrodt is Likely to Succeed on the Merits of its Claims That FDA Acted Unlawfully By Effectively Taking the Drug Off the Market Without Providing Mallinckrodt With a Hearing Where it Could Defend the Product

Mallinckrodt is likely to succeed on the merits of its claims that FDA acted unlawfully by effectively taking the drug off the market without providing Mallinckrodt with a hearing where it could defend the product. Mallinckrodt's statutory and constitutional rights to a hearing are discussed in sections A.2 and A.3 below.

1. FDA's Classification Action Effectively Takes the Drug Off the Market

As an initial matter, the Court should conclude that FDA's action reclassifying Mallinckrodt's methylphenidate ER tablets to a BX rating effectively takes the drug off the market. The "B" part of the rating signifies a drug that "FDA, at this time, considers not to be therapeutically equivalent to other pharmaceutically equivalent products." Ex. 1 at xvii (emphasis in original). That determination by FDA means that (depending on the

jurisdiction) it is either unlawful or unacceptably risky for pharmacists to fill a prescription by substituting Mallinckrodt's generic for the brand-name drug Concerta®.

In 31 states (including Maryland) and the District of Columbia, it is *unlawful* for a pharmacist to fill a prescription with a generic drug (by substituting it for the corresponding brand-name drug) if the generic is rated "B" (*i.e.*, not therapeutically equivalent) in the Orange Book. *See, e.g.*, Md. Code Ann., Health Occ. § 12-504 (generic substitution is only permissible if "the substitution is recognized in the United States Food and Drug Administration's current list of approved drug or device products with therapeutic equivalence evaluations."); *see also* Ex. 3 (chart setting forth the generic substitution laws for all fifty states and the District of Columbia). Accordingly, on November 13 — the date FDA amended the Orange Book to reflect the BX classification — it immediately became *per se* unlawful for pharmacists to substitute Mallinckrodt's generic when filling prescriptions for Concerta® in those 31 states and the District of Columbia.

In another fourteen states, the statutes and regulations governing generic substitutions do not expressly refer to the Orange Book but nonetheless use the Orange Book's terms of art (including the terms "therapeutic equivalence" and "pharmaceutical equivalence") when addressing generic substitution. *See* Ex. 3.[1] In these states, the legal

[1] FDA refers to these terms as its "terms of art" and has taken the position in prior litigation that it has "an interest in insuring that only one definition of FDA terms of art,

(Footnote cont'd on next page)

duty guiding pharmacists' generic substitutions is the duty to abide by applicable professional standards. *See, e.g.*, Ga. Code. Ann. § 26-4-81 ("Substitutions . . . are authorized for the express purpose of making available to the consumer the lowest retail priced drug product which is in stock and which is, in the pharmacist's reasonable professional opinion, both therapeutically equivalent and pharmaceutically equivalent."). The Orange Book is — and is intended by FDA to be — the most authoritative standard that pharmacists rely on to guide their professional judgment regarding generic substitution.[2]

In these fourteen states (as well in as the remaining five states that have statutory terminology less specifically tied to the Orange Book terms of art), pharmacists' duty to abide by professional standards is enforced through state regulations and tort law. These state laws compel pharmacists to follow the Orange Book classification, because it is the

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such as 'therapeutically equivalent' and 'generic,' is used in the context of drug approval, acceptance and use." *Healthpoint, Ltd. v. Ethex Corp.*, 273 F. Supp. 2d 817, 866 (W.D. Tex. 2001).

[2] The Orange Book is only the most recent effort by the FDA to provide uniform therapeutic equivalence standards for the states. FDA has been providing uniform standards for over thirty years. *See, e.g.*, 45 Fed. Reg. 72,582, 72,582 (Oct. 31, 1980) (stating that the list of therapeutically equivalent drugs "was prepared in response to requests from State health agencies for assistance in administering their drug product selection laws"). On September 24, 1984, the President signed into law the Drug Price Competition and Patent Term Restoration Act, which requires the FDA to make publicly available a list of approved drug products with monthly supplements. The Orange Book is published to satisfy this requirement. Ex. 1 at v.

authoritative professional standard. The regulatory effect of the Orange Book classification is the same whether the pharmacist's professional duty arises under state statute or regulation, state tort law, or both. *See, e.g.*, *Riegel v. Medtronic, Inc.*, 552 U.S. 312, 324-25 (2008) (equating regulatory effect of state regulatory law and state tort duties because both change private parties' conduct). Regardless of the details of these states' regulatory regimes, pharmacists will seek to avoid liability by refusing to substitute Mallinckrodt's "BX" generic when filling prescriptions written for Concerta®.

The effect of FDA's reclassification action cannot be overstated — it will lead to the removal of Mallinckrodt's generic methylphenidate ER product from the U.S. market. Prohibiting generic substitutions effectively takes the drug off the market, because pharmacists will not substitute the drug in filling brand-name prescriptions, and Mallinckrodt's distributor customers will not buy it. *See* Kaczmarek Decl.

2. FDA Exceeded its Statutory Authority By Effectively Taking the Drug Off the Market Without Providing Mallinckrodt With a Hearing

FDA exceeded its statutory authority by effectively taking the drug off the market without providing Mallinckrodt with a hearing. The FFDCA provides only ***one*** mechanism for taking a generic drug off the market: withdrawing (or suspending) ANDA approval under 21 U.S.C. § 355(e). *See supra* at 6. Section 355(e) requires that the drug's sponsor is entitled to "due notice and opportunity for hearing" *before* FDA can withdraw the ANDA approval. 21 U.S.C. § 355(e). FDA's regulations provide the

specific procedures for the statutorily-required hearing. *See* 21 C.F.R. § 314.150; 21 C.F.R. pt. 12.[3]

FDA has no statutory authority to take a drug off the market through other actions not specified in section 355(e). *See Cal. Canners & Growers Ass'n v. United States*, 7 Cl. Ct. 69, 88 (1984) (FDA had no statutory authority to remove drugs from the market through an immediately-effective regulation and was required to follow the hearing process specified in 21 U.S.C. § 355(e)). That conclusion flows directly from a recent D.C. Circuit decision construing the parallel statutory requirements governing FDA's authority to remove a medical device from the market (following an earlier FDA decision that authorized marketing the device). In *Ivy Sports Medicine, LLC v. Burwell*, 767 F.3d 81 (D.C. Cir 2014), *pet. for reh'g en banc* filed Nov. 11, 2014, the D.C. Circuit held that to remove the medical device at issue from the market, FDA must follow a statutorily-prescribed notice and comment procedure and could not "achieve the same result" through a different reconsideration process not mentioned in the statute. *Id*. at 87. The reason is that when Congress expressly provides a mechanism for FDA to reconsider and

[3] There is a narrow exception to the advance hearing requirement under circumstances in which — unlike this case — there is "an imminent hazard to the public health." 21 U.S.C. § 355(e). Under those unusual circumstances, the Secretary of the Department of Health and Human Services (in an action that "shall not be delegated" to any subordinate official) can immediately suspend the approval of an ANDA without first holding a hearing — but the sponsor is *still* entitled to "prompt notice" and the "opportunity for an expedited hearing" shortly after the suspension occurs. *Id.*

reverse an earlier premarket clearance decision, Congress "displace[s]" FDA's authority to reconsider and reverse such a decision through actions not specified in the statute. *Id.* at 86; *see also id.* ("any inherent reconsideration authority does not apply in cases where Congress has spoken").

FDA has exceeded its statutory authority by effectively taking Mallinckrodt's methylphenidate ER off the market through other actions not specified in section 355(e). On information and belief, FDA has reclassified the drug with a "BX" code for the express purpose of removing it from the market. The effect is the same as withdrawing the drug's ANDA approval. *See supra* at 6. As in *Ivy Sports Medicine*, FDA had no statutory authority to "short-circuit [the] statutory process" for removing Mallinckrodt's drug from the market by taking a different type of action to "achieve that same result." 767 F.3d at 87.

In addition, as in *Ivy Sports Medicine*, the fact that the statutory process is slower and more deliberative than an extra-statutory process is a virtue, not a vice. In *Ivy Sports Medicine*, the D.C. Circuit addressed FDA's view that notice and comment (regarding removing a medical device from the market) was unnecessary — a view the court called "a not-uncommon sentiment among agencies that want to take action more promptly." 767 F.3d at 87. The court explained that "notice and comment helps to prevent mistakes, because agencies receive more input and information before they make a final decision." *Id.* The court further explained that "notice and comment also helps ensure that regulated

parties receive fair treatment, a value basic to American administrative law." *Id.* at 87-88. These concepts apply with equal force in this case. The section 355(e) hearing procedures help prevent FDA mistakes and also ensure that parties such as Mallinckrodt receive the fair treatment that Congress intended them to have when FDA considers removing their drugs from the market.

3. FDA Violated Mallinckrodt's Fifth Amendment Due Process Rights By Impairing the Company's Property Right in its Drug Approval Without Providing Mallinckrodt With a Hearing

The statutory hearing rights described above derive from an underlying constitutional right to notice and a hearing guaranteed by the Fifth Amendment's Due Process Clause. Mallinckrodt is likely to prevail on the merits of its claims that FDA violated the company's due process rights by effectively taking its generic methylphenidate ER off the market without providing Mallinckrodt with a hearing.

Minimum due process requirements include notice and an opportunity for a hearing. *See, e.g., Propert v. D.C.*, 948 F.2d 1327, 1331 (D.C. Cir. 1991) (citing *Logan v. Zimmerman Brush Co.*, 455 U.S. 422, 433 (1982)). Among other things, the due process clause bars the government from modifying, suspending, revoking, or withdrawing a private party's property right without an opportunity to be heard "at a meaningful time and in a meaningful manner." *See, e.g., Mathews v. Eldridge*, 424 U.S. 319, 333 (1976) (citation omitted); *Bell v. Burson*, 402 U.S. 535, 539 (1971). As FDA's own regulations recognize, Mallinckrodt's approved ANDA is such a property right. *See,*

e.g., 21 C.F.R. § 314.72 (describing ANDA as an interest that is "owne[d]" and indicating that "rights to the application" can be "transferred to [a] new owner").

When FDA approves an ANDA, it grants the ANDA sponsor permission to market its drug lawfully in interstate commerce. *See* 21 U.S.C. § 355(a) (marketing in interstate commerce prohibited until approval occurs); 21 C.F.R. § 314.105(d) (same). It is well settled that such a government-issued permit or license is a property interest protected by the Due Process Clause. *See, e.g.*, *Barry v. Barchi*, 443 U.S. 55 (1979); *Richardson v. Town of Eastover*, 922 F.2d 1152, 1156 (4th Cir. 1991) (license issued by the government that can be suspended or revoked only upon a showing of cause creates a property interest protected by constitutional due process); *Scott v. Williams*, 924 F.2d 56, 58 (4th Cir. 1991) (citing *Burson*, 402 U.S. at 539); *Ihnken v. Gardner*, 927 F. Supp. 2d 227, 237 (D. Md. 2013) (citing *Richardson* with approval); *U.S. ex rel. Joslin v. Cmty. Home Health of Md., Inc.*, 984 F. Supp. 374, 379 (D. Md. 1997) ("[C]ourts have uniformly held that the holder of a license has a property right protected by the appropriate Federal Due Process Clause."); *see also* Donald O. Beers & Kurt R. Karst, Generic and Innovator Drugs: a guide to FDA approval requirements § 3.04 (8th ed. 2013) ("It seems clear that the approval of an [ANDA], an approval of considerable financial value in many instances, would be considered a property right in the due process context.").

When it reclassified Mallinckrodt's methylphenidate ER, FDA eviscerated the company's property right in its ANDA by effectively taking the drug of the market. FDA had no constitutional authority to impair Mallinckrodt's property right without giving Mallinckrodt notice and an opportunity to be heard. *See, e.g., Connecticut v. Doehr*, 501 U.S. 1, 12 (1991) (even "temporary or partial impairments to property rights" are sufficient to merit due process protection).

B. Mallinckrodt is Likely to Succeed on the Merits of its Claim That FDA Has Not Satisfied the Statutory Evidentiary Standard Necessary to Take a Drug Off the Market

Mallinckrodt also is likely to succeed on the merits of its claim that FDA has exceeded its statutory authority, because it has taken a drug off the market without satisfying the evidentiary standard of 21 U.S.C. § 355(e). Under section 355(e) — which as explained above establishes the only mechanism for taking a generic drug off the market — there are specific evidentiary standards that FDA must satisfy to justify its action. FDA only has statutory authority to take a drug off the market for lack of effectiveness if "there is a *lack of substantial evidence* that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof." 21 U.S.C. § 355(e)(3) (emphasis added). FDA cannot meet this statutory standard.

The administrative law substantial evidence standard is well established. Courts have defined it to mean "'more than a scintilla, but . . . something less than a preponderance of the evidence.'" *Minisink Residents for Envtl. Pres. & Safety v. FERC*,

762 F.3d 97, 108 (D.C. Cir. 2014) (quoting *FPL Energy Me. Hydro LLC v. FERC*, 287 F.3d 1151, 1160 (D.C. Cir. 2002); *see also SEC v. FLRA*, 568 F.3d 990, 995 (D.C. Cir. 2009) (substantial evidence is "'something less than the weight of the evidence'") (citation omitted). The most that FDA can purport to show here — a mere "'possibility of drawing . . . inconsistent conclusions from the evidence'" — does *not* mean that there is a lack of substantial evidence. *Id.* (quoting *Consolo v. Fed. Maritime Comm'n*, 383 U.S. 607, 620 (1966). For FDA to establish a *lack* of substantial evidence under section 355(e)(3), FDA would need to show that the evidence of effectiveness is *substantially* less than a preponderance of the evidence (and perhaps only a "scintilla"). *See Minisink Residents*, 762 F.3d at 108.

FDA does not even attempt to assert that it has reclassified Mallinckrodt's methylphenidate ER because of such minimal evidence of effectiveness. As explained in the declaration of Dr. Mario Saltarelli, Mallinckrodt's Chief Science Officer, FDA set forth its rationale for the reclassification decision in a 15-page memorandum provided to Mallinckrodt after FDA advised the company of the reclassification. In that memorandum, FDA concluded merely that it "has *reason to believe* that the Mallinckrodt products *may not* be therapeutically equivalent to Concerta." Saltarelli Decl. ¶ 25, Ex. D at 14 (emphasis added). In a related press release, FDA was even more equivocal, asserting: "FDA has concerns about whether or not" Mallinckrodt's product is therapeutically equivalent. Saltarelli Decl. Ex. B. FDA acknowledged that its "concerns"

relate only to "some patients," and FDA emphasized that "the total number of lack of effect reports . . . is *very small* compared to the overall usage of the products." *Id.*, Ex. C (emphasis added). Therefore FDA advised that patients currently taking Mallinckrodt's product "should not make changes to their treatment." *Id.*, Ex. B.

Of course, the statute does not permit FDA to take a generic drug off the market based on "concerns" about "whether or not" the drug is therapeutically equivalent for "some patients." And even assuming FDA's analysis of adverse event reports were valid, *but see infra*, even FDA acknowledges Mallinckrodt's product has proven to be effective for all but "a very small" number of patients. Thus, by FDA's own admission, there is more than substantial evidence that Mallinckrodt's product is therapeutically equivalent. The agency therefore has not met the evidentiary standard in the statute for removing the product from the market.

C. Mallinckrodt is Likely to Succeed on the Merits of its Claim That FDA's Reclassification Action is Arbitrary and Capricious

1. FDA's Reclassification Action is Arbitrary and Capricious Because FDA Has Not Even Satisfied its Own Standard for Reclassification Set Forth in the Orange Book

Mallinckrodt also is likely to prove that FDA's reclassification action is arbitrary and capricious, because FDA has not even satisfied its own standard for reclassification stated in the Orange Book. The Orange Book includes FDA's internal procedural rules for classifying drugs according to their therapeutic equivalence. Those rules define the different classifications at least in part by reference to the data pertinent to a drug's

therapeutic equivalence. The Orange Book defines the BX classification at issue here as "drug products for which the data that have been reviewed by the Agency are *insufficient to determine therapeutic equivalence* under the policies stated in [the Orange Book]." Ex. 1 at xx (emphasis added). However, in its reclassification decision rationale, FDA does not even attempt to suggest that the data meet this "insufficiency" standard.

Instead, FDA asserts simply that it "has *reason to believe* that the Mallinckrodt products *may not be* therapeutically equivalent to Concerta." Saltarelli Decl. Ex. D at 14 (emphasis added). That equivocal statement falls far short of a determination that therapeutic equivalence data "*are* insufficient" — which is the standard set forth for the classification BX in the Orange Book. Because FDA failed to follow its own definitional standard set forth in the procedural rules of the Orange Book, the agency's reclassification action is arbitrary and capricious. *See, e.g.*, *D&F Afonso Realty Trust v. Garvey*, 216 F.3d 1191, 1196 (D.C. Cir. 2000) (an agency acts arbitrarily and capriciously when it "act[s] contrary to its own procedure"); *see also Town of Barnstable, Mass. v. FAA*, 659 F.3d 28, 36 (D.C. Cir. 2011) (standard of reasoned decisionmaking not satisfied when agency "abandon[ed] its own established procedure").

2. FDA's Reclassification Action is Arbitrary and Capricious Because FDA Has Not Satisfied Applicable Requirements for Reasoned Decisionmaking

Mallinckrodt also is likely to prove that FDA's reclassification action is arbitrary and capricious, because the agency's stated justification for the reclassification is "not sufficient to enable [the Court] to conclude" that the action "was the product of reasoned

decisionmaking." *Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 52 (1983). "The importance of reasoned decisionmaking in an agency action cannot be over-emphasized. When an agency . . . is vested with discretion to impose restrictions on an entity's freedom to conduct its business, the agency must exercise that discretion in a well-reasoned, consistent, and evenhanded manner." *Greyhound Corp. v. ICC*, 668 F.2d 1354, 1359 (D.C. Cir. 1981).

The 15-page memorandum described above is FDA's only proffered explanation for its action, and it contains numerous glaring errors that demonstrate the action was arbitrary and capricious.[4] *First*, FDA "relied on a selection of data, tests, and standards that did not always appear to be logical, obvious, or even rational." *See Dow AgroSciences LLC v. Nat'l Marine Fisheries Serv.*, 707 F.3d 462, 475 (4th Cir. 2013). Most notably, FDA relied on a collection of adverse event reports to support its decision. But FDA's own analysis shows that *most* of the cited reports were about *other* products — i.e., reports of efficacy concerns about drugs *other than* Mallinckrodt's

[4] Separate from the 15-page memo, FDA claimed there was a collection of data described by agency officials as "compelling," which FDA initially promised to provide to Mallinckrodt. *See* Saltarelli Decl. ¶ 21. Despite repeated requests from the company, FDA has refused to provide any additional rationale beyond the 15-page memo, including the materials FDA described as "compelling." *Id.* Of course, Mallinckrodt can only challenge FDA's action based on the reasons provided by the agency, and it is axiomatic that "a reviewing court may look only to [the] *contemporaneous* justifications in reviewing the agency action." *See Dow AgroSciences LLC v. Nat'l Marine Fisheries Serv.*, 707 F.3d 462, 467-68 (4th Cir. 2013) (citing *SEC v. Chenery*, 318 U.S. 80, 87-88 (1943)).

methylphenidate ER. Saltarelli Decl. ¶¶ 28-31. FDA cannot rationally use reports about other products to support a therapeutic equivalence determination about Mallinckrodt's product.

Second, the agency treated *all* "lack-of-effect" complaints — regardless of the factual scenario in which the complaints arose — as evidence of lack of therapeutic equivalence. Saltarelli Decl. ¶¶ 33-35. Common sense establishes that not all "lack-of-effect" complaints are evidence of lack of therapeutic equivalence between a brand drug and generic. In fact, *most* reporting scenarios are irrelevant to the issue of therapeutic equivalence between a brand drug and generic, because most do not involve a patient switching medication from the brand drug to the generic — the only scenario relevant to therapeutic equivalence. *Id.* Reports that arise in other scenarios — *e.g.*, patients who never took the brand drug but are taking the generic in the first instance and patients who are being co-administered medications that impact efficacy — provide no rational or logical support for any conclusions as to the therapeutic equivalence of Mallinckrodt's product. *Id.* Here FDA lumped all "lack-of-effect" complaints together, piled them on top of a mountain of reports about other products, and used this "data" as the foundation upon which to build its reclassification action. Because FDA "relie[d] on one unsubstantiated conclusion heaped on top of another," its action was arbitrary and capricious. *See Sorenson Commc'ns Inc. v. FCC*, 755 F.3d 702, 708 (D.C. Cir. 2014).

Third, FDA also relied on plainly inaccurate facts. FDA claimed, for example, that there was a "spike" in reported events for methylphenidate products in April 2013, and the agency speculated that this spike "may be attributable to the launch of [Mallinckrodt's] product," because, according to FDA, "the 1st marketing of the Mallinckrodt product was 3/25/2013." Saltarelli Decl. ¶ 32. But FDA's premise is simply false. As FDA's own memo states, Mallinckrodt's ANDA "was approved on 12/28/2012," and thus Mallinckrodt first began marketing and selling one strength of its product (27 mg strength) in December 2012 — more than three months before the alleged "spike." *Id*. FDA's speculative conclusion that the "spike" was caused by Mallinckrodt's initial entry into the market is just one example of FDA "offer[ing] an explanation for its decision that runs counter to the evidence before [it]." *See Motor Vehicle Mfrs. Ass'n*, 463 U.S. at 43.

Fourth, beyond the agency's irrational and illogical use of reporting "data," FDA also relied on a fundamentally flawed methodology for predicting therapeutic equivalence. Specifically, FDA attempted to predict clinical effects based on the plasma concentration levels of Mallinckrodt's product. Saltarelli Decl. ¶¶ 36-43. FDA's modeling approach was based on the assumption that there is a direct and quantitative correlation between plasma concentration and clinical effects of methylphenidate. *Id.* ¶ 40. By FDA's own admission, this is "the first time such modeling has been used" to support a therapeutic equivalence decision. *See id.*, Ex. D at 8. It would be one thing if

FDA used a new method that was supported by existing science. It is another where, as here, FDA itself has rejected the key assumption underlying its untested method. In fact, FDA has publicly emphasized that "there is no authoritative literature information on the correlation of dose or plasma concentration with clinical effects of methylphenidate." *See id.* ¶ 41. FDA cannot rationally rely on a novel method when the agency has rejected the underlying premise of that method. *See Nat'l Ass'n of Clean Water Agencies v. EPA*, 734 F.2d 1115, 1145 (D.C. Cir. 2013), *reh'g en banc denied* ("We are hesitant to rubber-stamp EPA's invocation of statistics without some explanation of the underlying principles or reasons why its formulas would produce an accurate result, particularly when the [known data] . . . demonstrate flaws in the formula.").

Finally, FDA failed to consider or even acknowledge a host of relevant data that contradict the agency's conclusions. For example, FDA had in its possession actual data showing the Mallinckrodt product's clinical effects. Saltarelli Decl. ¶¶ 44-46. It appears the agency never utilized this data — and failed even to acknowledge its existence — but instead opted to *predict* the same information using the untested method described above. *Id*. In other words, FDA ignored actual data in favor of flawed, speculative guesses. Similarly, FDA ignored data in its possession that directly conflicts with the agency's speculative assertion that there are "concerns of possible in vivo [active drug ingredient] degradation." *Id.* ¶¶ 47-50. Of course, "an agency's refusal to consider evidence bearing on the issue before it constitutes arbitrary action within the meaning of § 706," and "an

agency cannot ignore evidence contradicting its position." *Butte Cnty. v. Hogen*, 613 F.3d 190, 194 (D.C. Cir. 2010)*; accord Sorenson Commc'ns Inc. v. FCC*, 755 F.3d at 710 (rejecting agency action where "there was contrary evidence" but agency "left th[o]se serious concerns unaddressed").

D. Mallinckrodt is Likely to Succeed on the Merits of its Claim That FDA Has Violated Notice and Comment Rulemaking Requirements

A major premise for FDA's reclassification action is that Mallinckrodt's methylphenidate ER tablets did not satisfy FDA's new "draft guidance" for bioequivalence regarding methylphenidate hydrochloride issued on November 6, 2014. *See* Saltarelli Decl. ¶ 19. Mallinckrodt is likely to succeed on the merits of its claim that FDA's reclassification action is invalid, because the "draft guidance" underlying that action violates notice and comment rulemaking requirements imposed by the Administrative Procedure Act.

The Administrative Procedure Act requires an agency to follow notice and comment requirements in promulgating a "legislative" rule, unless "the agency for good cause finds (and incorporates the finding and a brief statement of reasons therefore in the rules issued) that notice and public procedure thereon are impracticable, unnecessary, or contrary to the public interest." 5 U.S.C. § 553(b)(3)(B); *Am. Mining Cong. v. Mine Safety & Health Admin.*, 995 F.2d 1106, 1108-09 (D.C. Cir. 1993). FDA violated 5 U.S.C. § 553, because the "draft notice" is a "legislative" rule, and the agency neither

satisfied notice and comment requirements nor published findings establishing a "good cause" exemption.[5]

As Mallinckrodt has now learned to its detriment, the new "draft guidance" sets forth the substantive scientific standards under which FDA will — or will not — find methylphenidate hydrochloride drugs bioequivalent (and therefore approvable through an ANDA). The "draft guidance" meets the Administrative Procedure Act's definition of a "rule," because it is an "agency statement of general or particular applicability and future effect designed to implement . . . or prescribe law or policy. . . . ." 5 U.S.C. § 551(4). And the "draft guidance" also is a "legislative" rule, because it "*modifies* or *adds* to a legal norm based on the agency's *own authority*" and thereby "really adds content to the governing legal norms." *Syncor Int'l Corp. v. Shalala*, 127 F.3d 90, 95, 96 (D.C. Cir. 1997) (emphasis in original). The "draft guidance" adds content to the governing legal norms by changing the substantive criteria under which FDA will permit a drug to be marketed. In this case, the "draft guidance" provided the substantive basis for FDA's determination that methylphenidate ER may not be bioequivalent or therapeutically equivalent to Concerta®. Such an "agency action that sets forth legally binding

[5] FDA did initiate a notice and comment process for the "draft guidance." But the process was incomplete at the time FDA applied the "draft guidance" to Mallinckrodt; the comment period remains open until January 5, 2015. 79 Fed. Reg. 65,978 (Nov. 6, 2014).

requirements for a private party to obtain a permit or license is a legislative rule." *Nat'l Mining Ass'n v. McCarthy*, 758 F.3d 243, 251-52 (D.C. Cir. 2014).[6]

Furthermore, FDA's characterization of its legislative rule as a *non-binding* "draft guidance" or "recommendation" does not undermine the conclusion that it is a legislative rule. It is well established that it is the *substance* of the rule that controls whether a rule is legislative: "the agency's characterization of its own action is not controlling if it self-servingly disclaims any intention to create a rule with the 'force of law,' but the record indicates otherwise." *CropLife Am. v. EPA*, 329 F.3d 876, 883 (D.C. Cir. 2003). Courts therefore have not hesitated to invalidate agency pronouncements labeled as non-binding "guidances" where, as here, they actually are operating as legislative rules. *See, e.g., Syncor*, 127 F.3d at 93, 96 (notice characterized by FDA as a "guidance" was legislative rule subject to notice and comment requirements); *Appalachian Power Co. v. EPA*, 208 F.3d 1015, 1023, 1028 (D.C. Cir. 2000) (EPA "guidance" document was legislative rule subject to notice and comment requirements notwithstanding "boilerplate" disclaimer that "'[t]he policies set forth in this paper are intended solely as guidance, do not represent final Agency action, and cannot be relied upon to create any rights enforceable by any

[6] It is notable that in the Orange Book, FDA acknowledges that notice and comment is required "before making a change in a therapeutic equivalence code for an entire category of drugs." Orange Book at xxii. Here the "draft notice" was the basis for changing the code for the only two non-authorized generic manufacturers in the methylphenidate hydrochloride extended release category. *See* Kaczmarek Decl. ¶¶ 40, 56.

party.'") (citation omitted); *Natural Res. Def. Council v. EPA*, 643 F.3d 311, 320-21 (D.C. Cir. 2011) (EPA "guidance" was legislative rule).

E. Administrative Law Doctrines Do Not Preclude Judicial Review of FDA's Reclassification Action

In a challenge to federal agency action such as this, it is common for the government to seek dismissal on the ground that administrative law doctrines regarding "final agency action," "ripeness," and/or "exhaustion of administrative remedies" allegedly preclude judicial review. To the extent that the government attempts to avoid the merits by raising any of these defenses, Mallinckrodt is likely to prevail.

1. The "Final Agency Action" Doctrine Does Not Preclude Judicial Review

Four of the five counts in Mallinckrodt's Complaint allege claims under the Administrative Procedure Act, which provides a right to judicial review only for "final agency action for which there is no other adequate remedy in a court." 5 U.S.C. § 704.[7] In a November 12, 2014, conference call, an FDA official expressly *conceded* that the

[7] The remaining count in the Complaint (Count II) is a direct cause of action under the Due Process Clause and is not an Administrative Procedure Act claim. Because the "final agency action" doctrine is limited to Administrative Procedure Act claims, Count II is judicially reviewable regardless of whether there is a "final agency action." *See Trudeau v. FTC*, 456 F.3d 178, 188-89 (D.C. Cir. 2006) (direct cause of action under First Amendment was judicially reviewable even though "the absence of final agency action . . . cost [plaintiff] his APA cause of action"); *see also id.* at 191-97 (reviewing pleading sufficiency of First Amendment claim, in the absence of final agency action, under Fed. R. Civ. P. 12(b)(6)).

reclassification is a final agency action. Saltarelli Decl. ¶ 20. In addition, this Court has previously stated (in *dicta*) that "it would appear that an Orange Book designation constitutes a final agency action." *Zeneca Inc. v. Shalala*, No. CIV.A. WMN-99-307, 1999 WL 728104, at *11 n.13 (D. Md. Aug. 11, 1999), *aff'd*, 213 F.3d 161 (4th Cir. 2000).[8]

These views are fully consistent with other case law addressing final agency actions. For an agency action to be "final," it must satisfy two conditions, and both the reclassification action and the "draft guidance" satisfy these conditions.

First, to be a final agency action, "'the action must mark the consummation of the agency's decisionmaking process — it must not be of a merely tentative or interlocutory nature.'" *Holistic Candlers & Consumers Ass'n v. FDA*, 664 F.3d 940, 943 (D.C. Cir. 2012) (quoting *Bennett v. Spear*, 520 U.S. 154, 177-78 (1997)). FDA's November 12 concession acknowledges the finality of the agency's action. Saltarelli Decl. ¶ 20. And for good reason. As the Orange Book itself states, the classifications are those of "the

[8] In so stating, this Court distinguished an earlier decision of this Court holding that the proposed precursor to the Orange Book was not a final agency action. The Court noted that the earlier decision did not account for the "increased significance attributed to an Orange Book listing over the years since this Court decided" the earlier case. *Id.* (citing *Pharm. Mfrs Ass'n v. Kennedy*, 471 F. Supp. 1224 (D. Md. 1979)). In fact, at the time of the earlier case, the Orange Book did not even exist yet. The Orange Book arose from the fundamental transformation of the generic drug approval process that Congress enacted in 1984. *See supra* note 2.

Agency" — not some sort of low-level tentative determination. [Orange Book at v].[9] In addition, because the "draft guidance" operates as a substantive standard governing methylphenidate hydrochloride ANDA approval, the "draft guidance" is neither tentative nor interlocutory.

Second, to be a final agency action, the action must be "'one by which rights or obligations have been determined, or from which legal consequences will flow.'" *Holistic Candlers*, 664 F.3d at 943 (quoting *Bennett*, 520 U.S. at 177-78). Legal consequences obviously flow directly from the reclassification to BX, which triggers — and is intended by FDA to trigger — legal consequences under state pharmacy laws as described above. *See supra* at 14 n.2 (describing FDA's intent to provide uniform therapeutic equivalency standards for the states). The D.C. Circuit has found a directly parallel action to be "final" because of similar effects on other laws. *Tozzi v. U.S. Dep't of Health & Human Services*, 271 F.3d 301, 310 (D.C. Cir. 2002) (EPA listing of human carcinogens that "trigger[ed] obligations under OHSA, Department of Labor and state regulations" was reviewable final agency action). The "draft guidance" similarly triggers

[9] While FDA is currently considering a request by Mallinckrodt for a meeting to discuss the parties' dispute, that potential dialog does not undermine the finality of the agency's action. "The mere possibility that an agency might reconsider in light of 'informal discussion' . . . does not suffice to make an otherwise final agency action nonfinal." *Sackett v. EPA*, 132 S. Ct. 1367, 1372 (2012).

legal consequences by setting the substantive standards used to determine whether FDA will approve an ANDA for methylphenidate hydrochloride.[10]

2. The "Ripeness" Doctrine Does Not Preclude Judicial Review

The "ripeness" doctrine also does not preclude judicial review. The ripeness doctrine "probes the fitness for review of the legal issue presented, along with (in at least some cases) 'the hardship to the parties of withholding court consideration.'" *Teva Pharms. USA, Inc. v. Sebelius*, 595 F.3d 1303, 1308 (D.C. Cir. 2010) (quoting *Nat'l Park Hospitality Ass'n v. Dep't of Interior*, 538 U.S. 803, 808 (2003)).

The "fitness" prong generally addresses "'whether the issue is purely legal, whether consideration of the issue would benefit from a more concrete setting, and whether the agency's action is sufficiently final.'" *Teva Pharms.*, 595 F.3d. at 1308 (citation omitted). The issues presented here — matters of constitutional right, statutory interpretation, arbitrary and capricious agency action and procedural correctness — obviously are purely legal. There is no more concrete setting than the present, in which

[10] The "draft guidance" is a "final agency action" notwithstanding its label as a non-binding "draft." The substance of the action — not the document's title or the agency's disclaimer — is what controls. FDA's action is "final" because it meets the two conditions described above even though the agency characterizes it as a purely "informational" document with no legal effect. *See Tozzi*, 271 F.3d at 310 (EPA listing of human carcinogens allegedly "'for informational purposes only'" was reviewable final agency action).

the agency's action has effectively taken Mallinckrodt's drug off the market. And FDA itself has conceded that its action is final. Saltarelli Decl. ¶ 20.

The "hardship" prong is "not a *sine qua non* of ripeness" and is "'largely irrelevant in cases . . . in which neither the agency nor the court have a significant interest in postponing review.'" *Teva Pharms.*, 595 F.3d at 1310 (quoting *Electric Power Supply Ass'n v. FERC*, 391 F.3d 1255, 1263 (D.C. Cir. 2004)). However, the hardship prong is obviously met here, given the substantial irreparable harm, discussed below, that Mallinckrodt will suffer unless this Court intervenes.

3. The "Exhaustion of Administrative Remedies" Doctrine Does Not Preclude Review

The "exhaustion of administrative remedies" doctrine also does not preclude judicial review. In an Administrative Procedure Act case such as this, exhaustion of administrative remedies "is a prerequisite to judicial review *only* when expressly required by statute or when an agency rule requires appeal before review and the administrative action is made inoperative pending that review." *Darby v. Cisneros*, 509 U.S. 137, 154 (1993) (emphasis in original); *see also* 5 U.S.C. § 704. The Orange Book (and the reclassification procedure followed here) are not even mentioned in the FFDCA or in FDA's regulations, so there obviously are no such binding statutory or regulatory remedies to exhaust. This Court has authority to review FDA's actions and is likely to reject them on the merits as explained above.

II. MALLINCKRODT WILL BE IRREPARABLY HARMED WITHOUT PRELIMINARY RELIEF

FDA's reclassification decision effectively takes Mallinckrodt's number one product off the market and therefore is inflicting substantial, ongoing, and imminent additional losses on the company. An explanation of these losses requires reference to confidential business information discussed in the Declaration of Walt Kaczmarek, which Mallinckrodt has filed under seal.[11] We respectfully request the Court to review this Declaration for a detailed explanation of the losses and irremediable harm that Mallinckrodt faces. As explained below, the nature and severity of these injuries constitutes irreparable harm and justifies immediate preliminary relief from the Court.

"The basis of injunctive relief in the federal courts has always been irreparable harm and inadequacy of legal remedies." *Sampson v. Murray*, 415 U.S. 61, 88 (1974) (citation omitted). As the Fourth Circuit has explained, the "key word" in this analysis is "irreparable." *Hughes Network Sys., Inc. v. InterDigital Commc'ns Corp.*, 17 F.3d 691, 694 (4th Cir. 1994) (quoting *Sampson*, 415 U.S. at 90). Injuries are irreparable when no "adequate compensatory or other corrective relief will be available at a later date, in the ordinary course of litigation." *Id.* FDA's reclassification is inflicting multiple types of harm that cannot be remedied later. It is fundamentally unfair for Mallinckrodt to be

[11] We respectfully request that the government similarly file under seal any responsive discussion of the information set forth in the Kaczmarek Declaration and the Saltarelli Declaration, which also has been filed under seal.

subjected to such drastic harm, which can be avoided by entering a temporary restraining order to preserve the status quo pending further litigation. The Kaczmarek Declaration describes harm that is irreparable for at least four major reasons.

First, FDA's BX rating eviscerates Mallinckrodt's *number one product*. Kaczmarek Decl. ¶ 26 (methylphenidate ER is company's most profitable product and number one generic drug). Mallinckrodt's annual sales of methylphenidate ER exceed *$209 million*, and total sales since launch exceed *$388 million*. *Id*. ¶¶ 27-28. In terms of both sales and profitability, methylphenidate ER is critical to the company's business. *Id*. ¶ 27.

FDA's sudden reclassification of this product leaves Mallinckrodt with a product that pharmacists either cannot (because it is illegal under state law) or will not dispense, and therefore Mallinckrodt's distributor customers will no longer purchase, especially as more AB rated product becomes available. *Id*. ¶¶ 30-32. Because the FDA's reclassification of an approved generic drug from AB to BX is unprecedented in the company's business, Mallinckrodt cannot precisely determine the total economic loss that it will incur each day that this product is BX rated.[12] What is known with certainty is that Mallinckrodt is immediately incurring enormous losses, as customers immediately begin

[12] "'[I]rreparable injury is suffered when monetary damages are difficult to ascertain or are inadequate.'" *Multi-Channel TV Cable Co. v. Charlottesville Quality Cable Operating Co.*, 22 F.3d 546, 551 (4th Cir. 1994) (quoting *Danielson v. Local 275, Laborers Int'l Union*, 479 F.2d 1033, 1037 (2d Cir. 1973)).

to curtail orders for this product and likely will return existing inventory for a refund. *Id.* ¶¶ 30, 33.

Further, even assuming that the full scope of economic loss could be quantified, there would be no way for Mallinckrodt to recoup or recover that loss, because no compensatory remedy exists against the government. This case asserts claims under the Administrative Procedure Act, and the government is protected from a damages remedy by sovereign immunity. *See* 5 U.S.C. § 702 (waiving sovereign immunity under Administrative Procedure Act only for "relief other than money damages"); *City of Houston v. HUD,* 24 F.3d 1421, 1428 (D.C. Cir. 1994) (money damages not available under Administrative Procedure Act). As a result, Mallinckrodt cannot collect economic losses from the government as compensatory damages. The imminent losses that Mallinckrodt faces accordingly constitute irreparable harm. *See, e.g.*, *Rum Creek Coal Sales, Inc. v. Caperton*, 926 F.2d 353, 362 (4th Cir. 1991), *abrogated on other grounds by Real Truth About Obama*, 575 F.3d 342 (2009) (plaintiff will "face probable irreparable harm from the alleged violation of a federally protected right and will be prevented from recovering monetary compensation from the State"); *see also Smoking Everywhere, Inc. v. FDA*, 680 F. Supp. 2d 62, 77 n.19 (D.D.C. 2010) ("even if the claimed economic injury did not threaten plaintiffs' viability, it is still irreparable because plaintiffs cannot recover money damages against FDA"); *Feinerman v. Bernardi*, 558 F. Supp. 2d 36, 38, 51 (D.D.C. 2008) ("any loss of income suffered by a plaintiff is

irreparable *per se*" if the plaintiff "cannot recover damages from the defendant due to the defendant's sovereign immunity" (internal citations omitted)); *Clarke v. Office of Fed. Hous. Enter. Oversight*, 355 F. Supp. 2d 56, 66 (D.D.C. 2004) (economic losses constitute irreparable harm where government likely immune from suit); *Brendsel v. Office of Fed. Hous. Enter. Oversight*, 339 F. Supp. 2d 52, 66-67 (D.D.C. 2004) (harm irreparable where defendant was "immune from suit because there is no relevant waiver of sovereign immunity permitting it to be sued on these claims"); *cf. United States v. N.Y.*, 708 F.2d 92, 93-94 (2d Cir. 1983) (harm irreparable where any judgment against State of New York would be uncollectible because of Eleventh Amendment immunity).

Second, FDA's reclassification will irreparably harm Mallinckrodt's customer relationships, reputation, and good will, all of which are essential to its business. Mallinckrodt sells its generic version of methylphenidate ER primarily to a few large wholesale customers, who purchase the drug on behalf of major retailers, including drug store chains. Kaczmarek Decl. ¶¶ 8-10. Because of the importance of maintaining an available inventory to fill patient prescriptions in those stores, it is critically important to customers for Mallinckrodt to provide an uninterrupted supply of drugs as they are ordered. *Id*. ¶¶ 11-12. In addition, Mallinckrodt's customers assume and expect that any generic drug they purchase is Orange Book rated AB, as therapeutically equivalent and substitutable for the corresponding brand drug. *Id*. ¶ 21. Customers will reject BX rated

product from Mallinckrodt, and FDA's sudden reclassification undermines customer confidence in Mallinckrodt and its products. *Id*. ¶¶ 30-39.

FDA's reclassification prevents Mallinckrodt from continuing to supply the product that customers and pharmacists want — *i.e.*, "AB" rated methylphenidate ER. FDA's action creates serious doubt in the minds of customers whether Mallinckrodt reliably can deliver products that are effective and interchangeable with brand drugs. *Id*. ¶¶ 37-39. Because of the critical importance of uninterrupted supply, FDA's sudden BX reclassification is threatening the lifeblood of Mallinckrodt's business — its customer relationships. *Id*. ¶¶ 34-39. As a result of FDA's reclassification, and corresponding doubt regarding whether the company can reliably supply brand-equivalent generic products, Mallinckrodt is likely to lose existing customers and may be unable to procure new customers, for all of its entire generic product line. *Id*. ¶¶ 39-40. Once Mallinckrodt loses customers for this product, those customers will establish new supply relationships and be unlikely to return to Mallinckrodt. *Id*. ¶¶ 41-43.

Similarly, FDA's reclassification is inflicting harm on Mallinckrodt's reputation, earned through nearly 150 years of industry leadership, as a company known for quality products, business integrity, and service — to patients and customers. *Id*. ¶¶ 44-45. This reputational harm, moreover, would take years to recover from and may never be fully corrected. *Id*. ¶¶ 46-47. As courts have recognized, such damage to customer relationships, business reputation, and good will constitutes irreparable harm. *See, e.g.*,

Multi-Channel TV Cable Co., 22 F.3d at 552 (holding that loss of goodwill demonstrates irreparable injury); *Merrill Lynch, Pierce, Fenner & Smith, Inc. v. Bradley*, 756 F.2d 1048, 1055 (4th Cir. 1985) (district court did not abuse its discretion in granting preliminary injunction pending arbitration where plaintiff faced "irreparable, noncompensable harm in the loss of its customers"); *Corporate Healthcare Fin., Inc. v. BCI Holdings Co.*, Civil No. CCB-05-3391, 2006 WL 1997126 (D. Md. July 13, 2006) (irreparable harm where plaintiff suffered potential loss of goodwill due to defendant's continuing breach of restrictive covenant).

Third, FDA's reclassification will destroy Mallinckrodt's market share for methylphenidate ER, starting immediately. Kaczmarek Decl. ¶ 40. The generic drug industry is fiercely competitive. *Id*. ¶ 13. Mallinckrodt competes against Kremers Urban and Actavis (the authorized generic) for sales of methylphenidate ER. *Id*. ¶¶ 13-14. As a result of FDA's reclassification, Mallinckrodt's market share will plummet each day, until it reaches 0%, for this product. *Id*. ¶ 40. Indeed, industry watchers already have predicted that Actavis is likely to capture market share at the expense of its generic competitors, Mallinckrodt and Kremers Urban, according to a recent article. *Id*. ¶ 41, Ex. A. The article states that as a result of "FDA's decision to reclassify Mallinckrodt's Concerta generic as not making the grade in equivalence," Actavis "stands in line to recapture an estimated $400 million, or maybe even more, in additional sales." *Id*.

FDA's reclassification is causing immediate and irremediable harm with respect to the company's *number one product*. Mallinckrodt is unable to compete in the market and is losing market share every day. This harm to market share and competitive injury to Mallinckrodt constitutes irreparable harm. *See, e.g., Grand River Enter. Six Nations, Ltd. v. Pryor*, 481 F.3d 60, 67 (2d Cir. 2007) ("It is well-established that a movant's loss of current or future market share may constitute irreparable harm."); *Novartis Consumer Health, Inc. v. Johnson & Johnson-Merck Consumer Pharms. Co.,* 290 F.3d 578, 596 (3d Cir. 2002) ("this loss of market share constitutes irreparable harm"); *Serono Labs., Inc. v. Shalala*, 974 F. Supp. 29, 35 (D.D.C. 1997) (same), *vacated on other grounds*, 158 F.3d 1313, 1326 (D.C. Cir. 1998); *Bracco Diagnostics, Inc. v. Shalala*, 963 F. Supp. 20, 29 (D.D.C. 1997) (same).

Finally, FDA's unanticipated reclassification undermines Mallinckrodt's ability to manage its business and imposes operational harm. Kaczmarek Decl. ¶ 48. To operate efficiently and cost-effectively, Mallinckrodt needs to manage its entire supply chain. This process includes, for example, coordinating with suppliers and customers with respect to the volume of products manufactured for Mallinckrodt, ordered by Mallinckrodt, offered for sale to customers, and shipped to and from Mallinckrodt, on a constant basis. *Id.* ¶ 49. FDA's reclassification makes it difficult, if not impossible, for Mallinckrodt to know exactly what products will be needed each day, as the demand and orders for its products come to an end. *Id.* ¶ 50. As a result of FDA's reclassification,

and the ensuing turmoil to Mallinckrodt's business, the company is left to guess how to manage existing inventory, supply relationships, and customer allocations for methylphenidate ER. *Id*. ¶ 51. Because this negative impact and cost on Mallinckrodt's business cannot be quantified in monetary terms, it is an additional irreparable harm. *See, e.g., Multi-Channel TV Cable Co.*, 22 F.3d at 551.

III. THE BALANCE OF EQUITIES AND THE PUBLIC INTEREST JUSTIFY RELIEF

The balance of equities and the public interest further justify issuing the temporary restraining order. *First*, FDA's own statements indicate that there is no significant governmental or public interest in taking Mallinckrodt's methylphenidate ER off the market. It is very significant that this is *not* a case in which the agency has restricted access to a drug because of a public safety issue. To the contrary, FDA has stated that it "has not identified any serious safety concerns" and has told patients who have not yet been deprived of access to the drug that they "should not make changes to their treatment except in consultation with their health care professional." *See* Saltarelli Decl. Ex. B. The issue identified by FDA is a "concern" about efficacy, not a concern about safety. *Id*. And FDA's statements indicate that even the efficacy concern is not significant; FDA admits that number of reports of an efficacy concern "is *very small* compared to the overall usage of the products." *Id*., Ex. C (emphasis added).

Second, FDA's reclassification action is exacerbating a shortage of methylphenidate hydrochloride, thereby potentially harming patients rather than

protecting them. Even before FDA's reclassification action, the agency had listed methylphenidate as "Currently in Shortage." Kaczmarek Decl. ¶ 52, Ex. B. According to FDA's website, "Currently in Shortage" signifies "[a] situation in which the total supply of all clinically interchangeable versions of an FDA-regulated drug is inadequate to meet the current or projected demand at the user level. In general, FDA's Drug Shortage Program focuses on shortages of medically necessary products that have a significant effect on public health." *Id*. ¶ 52, Ex. C.

FDA's reclassification action regarding Mallinckrodt's drug (together with a parallel action regarding a competitor's drug) will effectively eliminate approximately 50% of the (already short) supply for methylphenidate ER drugs. *Id*. ¶ 56. Because of time needed to ramp up production levels, and because of additional delay if DEA quota approval is needed, it would take a number of weeks or months for other manufacturers to increase supply in an attempt to correct this substantial undersupply. *Id*. ¶ 57-58. Existing limited supplies of the drug are already fully allocated, moreover, likely leaving some distributors without product to supply to drug stores. *Id*. ¶ 54. For some period of time, substantial numbers of patients likely will have a difficult time obtaining methylphenidate ER as a therapy for ADHD. *Id*. ¶ 59. If patients cannot obtain methylphenidate ER and must switch to other types of methylphenidate products, it could harm their symptom control. Saltarelli Decl. ¶ 17.

Third, FDA's BX rating will almost certainly impose tremendous cost increases on the health care system and on patients. It is well known that a reduced generic drug supply will result in increased generic drug prices, sometimes including dramatic and abrupt price increases. Kaczmarek Decl. ¶ 60. Already, in response to FDA's reclassification, virtually all of Mallinckrodt's customers have expressed concerns to Mallinckrodt regarding product shortages, the likelihood of substantial price increases, and the inability to supply methylphenidate ER tablets needed to treat patients. *Id*. ¶ 55. The price of Actavis' product is likely to increase dramatically. Without other generic competition, an authorized generic product is often priced much higher — within approximately ten percent of the price of the brand product. *Id*. ¶ 62.

In addition, if the brand manufacturer is able to take its own "authorized" generic off the market (as sometimes happens if the authorized generic is the only generic on the market), then costs will escalate even further. *Id*. ¶ 61, 63-64. First, at the wholesale level, the cost of the brand product is likely to run hundreds of millions of dollars more in the course of a year, and to some extent those cost increases will be passed through to pharmacies and the payors. *Id*. ¶ 63. Second, at the retail level, in a brand-only market individual patient co-pays would likely skyrocket (in some examples, from a $10 co-pay to a nearly $175 co-pay, or from a $15 co-pay to a $50 co-pay). *Id*. ¶ 64. FDA's reclassification decision, therefore, could result in enormous collective additional costs imposed on the health care system. *Id*. ¶ 65.

Finally, a temporary restraining order would further the public interest by remedying unlawful action by FDA. The D.C. Circuit has recognized that "there is an overriding public interest . . . in the general importance of an agency's faithful adherence to its statutory mandate." *Jacksonville Port Auth. v. Adams*, 556 F.2d 52, 59 (D.C. Cir. 1977); *see also Bracco Diagnostics, Inc.*, 963 F. Supp. at 30 (there is "a strong public interest in requiring an agency to act lawfully, consistent with its obligations under the APA . . ."). All that Mallinckrodt requests is for FDA to satisfy its legal duties under the governing statute and the Administrative Procedure Act. The Court should issue the temporary restraining order, because it is in the public interest for FDA to act lawfully.

CONCLUSION

The Court should grant the Motion for Temporary Restraining Order.

Respectfully submitted,

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