IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MARYLAND

MALLINCKRODT INC.,	*	
	*	
Plaintiff,	*	
	*	
v.	*	Civil No. 14-CV-3607-DKC
	*	
UNITED STATES FOOD AND DRUG ADMINISTRATION, et al.,	*	
	*	
	*	
Defendants.	*	
	*	
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MEMORANDUM IN SUPPORT OF DEFENDANTS' MOTION TO DISMISS

Plaintiff Mallinckrodt's suit presents no cognizable case or controversy that is ripe for judicial review, in large part because the United States Food and Drug Administration's ("FDA") conduct does not constitute final agency action. FDA did not order Plaintiff to engage in or refrain from any action nor did the agency do anything which is binding on the parties. It is clear that any product in the Orange Book list is subject to additional regulatory action going forward and that is all that happened here. Thus, Plaintiff's claim is not ripe, and this Court lacks subject matter jurisdiction over Mallinckrodt's case.

Plaintiff also fails to state a claim for relief under the Administrative Procedure Act ("APA") or the U.S. Constitution. Absent final agency action, judicial review of a change in "therapeutic equivalence" or TE ratings is precluded under the APA and foreclosed by long-standing precedent in this district. Additionally, the change in a product's TE rating falls short of a property interest protected under the Fifth Amendment of the Constitution. The fact remains that Plaintiff's product is approved by the FDA and its approval has not been withdrawn.

Plaintiff seeks declaratory and injunctive relief requiring FDA to change the TE rating for Mallinckrodt's generic drug product, methylphenidate hydrochloride extended release, which is used to treat children and adults with Attention Deficit Hyperactivity Disorder. Plaintiff makes this bold request despite serious unresolved scientific questions about whether Mallinckrodt's product in fact provides the same continuous therapeutic effect as the brand-name product. *See* FDA Oct. 30, 2014, Memo, (attached to Pls.' TRO Br. at D.E. 8, Ex. D.).[1] All of Mallinckrodt's claims are premised on the misguided notion that a change in TE rating effectively outlaws its product. But, Mallinckrodt's product has not been withdrawn, is still approved, and continues to be marketed. FDA's well-established practice of publishing advisory TE ratings in Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book") is vastly different from the statutory drug approval withdrawal process contained in 21 U.S.C. § 355(e), despite Mallinckrodt's characterizations to the contrary. Accordingly, Plaintiff's Complaint should be dismissed pursuant to Federal Rules of Civil Procedure 12(b)(1) and 12(b)(6) for lack of subject matter jurisdiction and failure to state a claim upon which relief can be granted.

I. STATUTORY AND REGULATORY BACKGROUND

Under the Federal Food, Drug, and Cosmetic Act ("FDCA"), new drugs may be approved through the New Drug Application ("NDA") process, *see* 21 U.S.C. § 355(b)(1) & (b)(2), or the Abbreviated New Drug Application ("ANDA") process, *see* 21 U.S.C. § 355(j) -- the approval pathway for the Mallinckrodt product. There are important differences in the approval requirements for each pathway. Pharmaceutical companies seeking to market "pioneer" or "innovator" drugs must first obtain FDA approval by filing an NDA containing extensive scientific data demonstrating the safety and effectiveness of the drug. 21 U.S.C. § 355(a), (b).

[1] This document may be considered without converting this motion to dismiss into one for summary judgment because it is authentic and integral to the complaint. *See Philips v. Pitt Cnty. Mem'l Hosp.*, 572 F.3d 176, 180 (4th Cir. 2009).

Under the alternative pathway, the FDCA permits an applicant to submit an ANDA seeking approval for a generic version of a previously approved drug product. 21 U.S.C. § 355(j). The previously approved drug is called the reference listed drug ("RLD"), defined as "the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application." 21 C.F.R. § 314.3(b). ANDA applicants rely on FDA's finding of safety and effectiveness for the RLD and do not submit the same types of clinical investigations to demonstrate safety and effectiveness, as are necessary for approval of an NDA. Rather, an application for a generic version of the RLD must demonstrate that it is the same with respect to active ingredient(s), dosage form, route of administration, strength, conditions of use, and with certain exceptions, labeling. *See e.g.*, 21 U.S.C. § 355(j)(2)(A) & 355(j)(4); *see also* 21 C.F.R. § 314.94. An ANDA must also include sufficient information to demonstrate that the proposed product is bioequivalent to the RLD. *See, e.g.*, 21 U.S.C. § 355(j)(2)(A)(iv) & 355(j)(4)(F). A drug is considered to be bioequivalent if "the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug . . . ." 21 U.S.C. § 355(j)(8)(B)(i). FDA must approve the ANDA unless it finds that there is insufficient evidence of the foregoing or there is inadequate information to ensure the identity, strength, quality, and purity of the drug. *See e.g.*, 21 U.S.C. § 355(j)(2)(A) & 355(j)(4); *see also* 21 C.F.R. § 314.94.

FDA considers drug products to be TE "only if they are pharmaceutical equivalents and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling." *See* Orange Book Preface at vii. Drug products are considered pharmaceutical equivalents if they contain the same active ingredients, are of the same dosage form and route of administration, and are identical in strength or

concentration. *See* 21 C.F.R. § 320.1(c); Orange Book Preface at vi-vii. Thus, products evaluated as TE can be expected, in the judgment of FDA, to have equivalent clinical effect. Orange Book Preface at xi. The Orange Book also sets forth general criteria for evaluating TE, including, among others, pharmaceutical equivalence and bioequivalence. *Id.*

FDA first published the above-described TE rating criteria in 1980, in the context of a notice-and-comment rulemaking amending FDA's disclosure regulations. *See* 45 Fed. Reg. 72582 (Oct. 31, 1980); *see also* 44 Fed. Reg. 2932 (Jan. 12, 1979) (proposed rule); codified in FDA's disclosure regulations at 21 C.F.R. § 20.117. This notice-and-comment rulemaking put sponsors and the public on notice that FDA will make TE ratings publicly available using the above criteria. The current thirty-fourth annual edition of the Orange Book is available at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/UCM071436.pdf. To provide timely consumer information on generic drugs, the Electronic Orange Book is updated daily as new generic approvals occur. *See* http://www.accessdata.fda.gov/ scripts/cder/ ob/default.cfm. The Electronic Orange Book is also updated monthly to reflect changes in other information. *See* http://www.fda.gov/Drugs/InformationOnDrugs/ucm 114166.htm.

A product's TE rating is designated by a two-letter code. The first letter of a TE code specifies whether FDA has evaluated a product as TE to another product, while the second letter provides additional information regarding the basis of FDA's evaluation. *See* Orange Book Preface at xiii. TE codes fall into two basic categories: (1) those that begin with the letter "A" (signifying that FDA considers the product to be TE to another product); and (2) those that begin with the letter "B" (signifying that, at the time of the rating, actual or potential bioequivalence problems have not been resolved by adequate evidence of bioequivalence). *See id.*

The Orange Book is informational and advisory. Orange Book Preface at xi. It is a mechanism for the public to gain access to existing agency information or records. *See* Orange Book Preface at xi ("To the extent that the [Orange Book] identifies drug products approved under [21 U.S.C. § 355], it sets forth information that the Agency is required to publish and that the public is entitled to under the Freedom of Information Act."). The Orange Book's TE ratings do not constitute determinations that any product violates the Act or its implementing regulations. *Id.* Nor does the Orange Book mandate which drug products may or may not be prescribed, purchased, dispensed, or substituted for one another. *Id.*

Consistent with its goal to provide the public with the agency's most current TE information, FDA may change a product's TE rating if the circumstances giving rise to the rating change or information available to the agency calls into question the data FDA assessed to evaluate a product's TE rating. Orange Book Preface at xiii. When TE rating changes apply to a single drug product, as opposed to an entire category of drug products, FDA does not initiate notice and comment rulemaking.[2] *Id.* at xiii, xii.

II. FACTS

On December 28, 2012, Mallinckrodt obtained FDA approval of a generic version of the RLD drug Concerta,[3] methylphenidate hydrochloride extended release ("ER") tablets, under

[2] Mallinckrodt's product is a generic version of Concerta, which is only one of many approved methylphenidate hydrochloride products. *See* http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Overview&DrugName=METHYLPHENIDATE%20HYDROCHLORIDE. FDA did not change the TE ratings for all these products but instead only for those referencing Concerta.

[3] Concerta is manufactured by Janssen Pharmaceuticals, Inc. *See* http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2000/21121ltr.pdf. Mallinckrodt manufactures one of the approved generic versions of Concerta. *See* http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Overview&DrugName=METHYLPHENIDATE%20HYDROCHLORIDE. Janssen also manufactures an "authorized generic" of Concerta, which is marketed by Actavis as a generic. *Id.* Because the Actavis drug is identical to Janssen's Concerta, it was not subject to the same TE concerns as Mallinckrodt's and the other generic manufacturer's products. *Id.*

ANDA202608. *See* http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2012/202608Orig1s000ltr.pdf. The product was approved for the treatment of ADHD in children and adults 6 years of age and older. *Id.* At the time of approval, the TE rating for Mallinckrodt's product in the Orange Book was AB, meaning that FDA considered Mallinckrodt's generic methylphenidate hydrochloride ER product to be TE to Concerta.

Mallinckrodt's methylphenidate hydrochloride ER product, like Concerta, is intended to control ADHD symptoms by releasing the drug in the body over a 10- to 12-hour timeframe of daily living (such as a typical school or work day) and not to interfere with the ability of the patient to sleep at night. *See* FDA Oct. 30, 2014, Memo, at 1. In some individuals, however, evidence suggests that Mallinckrodt's product may deliver the drug in the body at a slower rate during the 7- to 12-hour range. *Id.* at 12-13. The diminished release rate may result in the product not having the desired therapeutic effect. *Id.*

Shortly after Mallinckrodt received approval for its product, FDA began to receive adverse event reports and complaints relating to the product's lack of effect. *See* http://www.fda.gov/Drugs/Drug Safety/ucm422569.htm. Between May 2013 and June 2014, FDA's Adverse Event Reporting System ("FAERS") database received reports of patients describing insufficient therapeutic effect, including nearly 200 adverse event reports specific to the Mallinckrodt product. *Id.*

Although the total number of lack-of-effect reports was small compared to the overall usage of methylphenidate hydrochloride products, FDA evaluated the overall number of complaints for Mallinckrodt's product relative to Concerta and authorized generic products and found substantially more complaints for two generic products (one of which was Mallinckrodt's). After learning of concerns with the products, the Office of Generic Drugs

("OGD") in FDA's Center for Drug Evaluation and Research ("CDER") formed a Tracked Safety Issue ("TSI") Committee to conduct a multi-disciplinary review of Mallinckrodt's product. This review included an evaluation of adverse event reports; a review of the data submitted with the ANDAs; FDA laboratory testing, including drug stability and dissolution testing; and broad interdisciplinary consultation with FDA physicians, pharmacists, chemists, and other agency scientists and experts to discuss the new information. *See* FDA Oct. 30, 2014, Memo, at 3-14. The TSI Committee ultimately recommended three agency actions: "[1] The therapeutic equivalence (TE) rating in the Orange Book be changed to BX[;] [2] The current guidance for Methylphenidate ER tablets be removed[; and 3] A Working Group be established to develop a new guidance that would ensure better predictability of therapeutic effect with pharmacokinetic testing." *Id.* at 11.

On November 12, 2014, FDA notified Mallinckrodt that the agency had reason to believe that Mallinckrodt's methylphenidate hydrochloride ER tablets may not be therapeutically equivalent to Concerta. *Id.* at 14. On November 13, FDA updated the Orange Book accordingly by changing the TE code for Mallinckrodt's product from AB to BX. This means that Mallinckrodt's product remains approved and can be prescribed, but the data that have been reviewed by the agency are insufficient to determine TE to Concerta.

As FDA informed Mallinckrodt on November 12, FDA expects Mallinckrodt to either: (1) voluntarily withdraw its product from the market under 21 C.F.R. § 314.150(d) and request that FDA withdraw approval of the ANDA; or (2) commit to complete new bioequivalence studies on its product within 6 months in accordance with FDA's Revised Draft Guidance on Methylphenidate Hydrochloride (Nov. 2014). *See* http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm320007.pdf.

III. STANDARD OF REVIEW

A motion to dismiss pursuant to Rule 12(b)(1) "tests a court's subject matter jurisdiction to adjudicate a case." *FTC v. AmeriDebt, Inc.*, 343 F. Supp. 2d 451, 459 (D. Md. 2004). Such a motion is properly granted "where a claim fails to allege facts upon which the court may base jurisdiction." *Davis v. Thompson*, 367 F. Supp. 2d 792, 799 (D. Md. 2005) (citations omitted). Plaintiff bears the burden of proving that subject matter jurisdiction properly exists in federal court. *See Evans v. B.F. Perkins Co., a Div. of Standex Int'l Corp.*, 166 F.3d 642, 647 (4th Cir. 1999). In considering a Rule 12(b)(1) motion, the court "may consider evidence outside the pleadings" to help determine whether it has jurisdiction over the case before it. *Richmond, Fredericksburg & Potomac R.R. Co. v. United States*, 945 F.2d 765, 768 (4th Cir. 1991); *see also Evans*, 166 F.3d at 647.

A motion to dismiss pursuant to Rule 12(b)(6) "tests the sufficiency of the complaint." *Vance v. CHF Int'l*, 914 F. Supp. 2d 669, 677 (D. Md. 2012). A complaint will survive a motion to dismiss only if it contains "sufficient factual matter, accepted as true, to state a claim to relief that is plausible on its face." *Id.* (quoting *Ashcroft v. Iqbal*, 556 U.S. 662, 678 (2009) (internal quotation marks omitted)). Thus, in reviewing a Rule 12(b)(6) motion, "a court must determine whether it is plausible that the factual allegations in the complaint are enough to raise a right to relief above the speculative level.'" *Id.* (quoting *Monroe v. City of Charlottesville*, 579 F.3d 380, 386 (4th Cir. 2009) (internal quotation marks omitted)). Although the court must "accept[] all well-pled facts as true and construe[] these facts in the light most favorable to the plaintiff," *Nemet Chevrolet, Ltd. v. Consumeraffairs.com, Inc.*, 591 F.3d 250, 255 (4th Cir. 2009) (citations omitted), the court need not accept as true "a legal conclusion couched as a factual allegation," "conclusory allegations devoid of any reference to actual events," or "allegations that are merely

conclusory, unwarranted deductions of fact or unreasonable inferences." *Vance*, 914 F. Supp. 2d at 677.

Because this Court lacks jurisdiction and Mallinckrodt has failed to state a claim, this case should be dismissed pursuant Rules 12(b)(1) and 12(b)(6).

IV. ARGUMENT

A. Mallinckrodt's Challenge Is Not Ripe for Adjudication

The primary purpose of the ripeness doctrine is "to prevent the courts, through avoidance of premature adjudication, from entangling themselves in abstract disagreements over administrative policies, and also to protect the agencies from judicial interference until an administrative decision has been formalized and its effects felt in a concrete way by the challenging parties." *Abbott Labs. v. Gardner*, 387 U.S. 136, 148-149 (1967), overruled on other grounds by *Califano v. Sanders*, 430 U.S. 99 (1977); *Nat'l Park Hospitality Ass'n v. Dep't of Interior*, 538 U.S. 803, 808 (2003). The APA likewise authorizes judicial review only with respect to "final agency action." 5 U.S.C. § 704. Thus, the requirement of final agency action is both part of the ripeness inquiry, as well as an independent basis for dismissal under the APA.

Ripeness turns upon two primary considerations: (1) "the fitness of the issues for judicial decision"; and (2) "the hardship to the parties of withholding court consideration." *Abbott Labs.*, 387 U.S. at 149; *accord Toilet Goods Ass'n, Inc. v. Gardner*, 387 U.S. 158, 162 (1967). A case is fit for adjudication "when the issues are purely legal and when the action in controversy is final and not dependent on future uncertainties." *Landsdowne on the Potomac Homeowners Ass'n, Inc. v. OpenBand at Lansdowne, LLC*, 713 F. 3d 187, 198 (4th Cir. 2013). Conversely, "a claim is not ripe when 'it rests upon contingent future events that may not occur as anticipated.'" *Naranjo*, 768 F.3d at 347 (quoting *Scoggins v. Lee's Crossing Homeowners Ass'n*, 718 F. 3d

262, 270 (4th Cir. 2013)). In evaluating the hardship prong, the court considers the immediacy of the threat and burden imposed on parties. *Naranjo*, 768 F.3d at 347; *Potomac Homeowners Ass'n*, 713 F.3d at 198. In light of the above considerations, Mallinckrodt's lawsuit is manifestly unripe for judicial review and should be dismissed.

1. Mallinckrodt's Action Is Not Fit for Judicial Decision

a. Mallinckrodt's Claims Raise Fact-Intensive Issues that Are Not Purely Legal In Nature

Mallinckrodt challenges FDA's scientific TE review of the company's methylphenidate hydrochloride ER tablets following concerns identified during the agency's post-marketing surveillance efforts. By its nature, scientific analysis cannot be evaluated as a purely legal question. In particular, "[t]herapeutic equivalence evaluations are a scientific judgment based upon evidence." Orange Book Preface at xi. A TE review entails a fact-intensive, scientific inquiry peculiarly suited to the expertise of FDA's staff of scientists, doctors, statisticians, and other public health experts. In conducting a TE evaluation, such experts must consider whether drugs products are pharmaceutical equivalents and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling. Orange Book Preface at vii. CDER OGD's ongoing review of Mallinckrodt's product has included an evaluation of adverse event reports; a study of data submitted with the ANDA; FDA laboratory testing, including drug stability and dissolution testing; and broad interdisciplinary consultation with a range of FDA experts.

At present, the data reviewed by FDA are insufficient to determine whether Mallinckrodt's product is therapeutically equivalent to Concerta. As noted above, FDA informed Plaintiff that the agency expects Mallinckrodt to either: (1) voluntarily withdraw its product from the market under 21 C.F.R. § 314.150(d) and request that FDA withdraw approval

of the ANDA; or (2) commit to complete new bioequivalence studies on its product within 6 months in accordance with FDA's Revised Draft Guidance on Methylphenidate Hydrochloride (Nov. 2014). *See* http://www.fda.gov/downloads/drugs/guidancecomplianceregulatory information/guidances/ucm320007.pdf. This necessarily means that FDA's TE review of Mallinckrodt's product is ongoing. Only after further study, with input from Mallinckrodt, should the company decide to provide the requested data, will FDA consider whether to take regulatory action, such as withdrawing Mallinckrodt's product from the market.

If the Court were to involve itself in this matter now to determine whether data reviewed by FDA are sufficient to determine whether Mallinckrodt's product is TE to Concerta, FDA would not have had the "full opportunity to apply its expertise and correct errors or modify positions in the course of" its administrative evaluation. *Estee Lauder, Inc. v. FDA*, 727 F. Supp. 1, 4 (D.D.C. 1989). A consideration such as this "weigh[s] strongly in favor of dismissal when the court is asked to rule on a factual question 'particularly within the agency's bailiwick as opposed to a purely legal question within the primary competence of the courts.'" *Estee Lauder*, 727 F. Supp. at 4 (quoting *Pub. Citizen Health Research v. FDA*, 740 F.2d 21, 31 (D.C. Cir. 1984)); *see generally Ciba Corp. v. Weinberger*, 412 U.S. 640, 643-44 (1973) (FDA's expertise in resolving scientific questions is the reason it has primary jurisdiction over classifying products under the FDCA).

Cases challenging a determination that involves technical and scientific matters benefit from the development of a full agency record prior to judicial review. *See Biotics Res. Corp.*, 710 F.2d 1375, 1377 (9th Cir. 1983); *see also CSG Exploration Co. v. FERC*, 930 F.2d 1477, 1486 (10th Cir. 1991). In such situations, the court should "decline reviewing anything less than a final administrative determination." *Biotics*, 710 F.2d at 1377. Mallinckrodt's claims present

precisely the circumstance in which judicial review should be had only after a full administrative record has been compiled by the agency, which can only happen after FDA has made a final decision.

b. The TE Rating Change Is Not Final Agency Action and Thus Not Subject to Judicial Review

The plaintiff bears the burden identifying specific federal conduct and explaining how it qualifies as final agency action. *Lujan v. Nat'l Wildlife Fed'n*, 497 U.S. 871, 882 (1990). Mallinckrodt has not met, and cannot meet, that burden here.

To be reviewable under the APA, the agency conduct in question must (1) constitute "agency action" and (2) be "final." *Golden & Zimmerman, LLC v. Domenech*, 599 F.3d 426, 431 (4th Cir. 2010). The APA defines "agency action" as including "the whole or a part of an agency rule, order, license, sanction, relief, or the equivalent or denial thereof, or failure to act." 5 U.S.C § 551(13). The TE rating for Mallinckrodt's product does not constitute agency action, as the court in *Pharmaceutical Manufacturers Association v. Kennedy*, 471 F. Supp. 1224 (D. Md. 1979) concluded. In that case, the court dismissed a suit filed by the Pharmaceutical Manufacturers Association ("PMA") challenging FDA's publication of TE ratings. 471 F. Supp. at 1225. The court held that although the TE ratings may adversely affect PMA members, the ratings did not "order[] any PMA member to engage in or refrain from any action" nor did the agency "do[] anything which is binding on the parties." 471 F. Supp. at 1231 (internal citation omitted). Accordingly, there was no judicially reviewable agency action under the APA. *Id.* Similarly, the FDA's change in the TE rating for Mallinckrodt's product is not a reviewable agency action.

Even if FDA's change to a product's TE rating could be considered agency action, it would not be "final." Final agency action "mark[s] the consummation of the agency's decision-

making process" and is "one by which rights or obligations have been determined, or from which legal consequences will flow." *Bennett v. Spear*, 520 U.S. 154, 178 (1997) (internal quotations omitted). TE ratings do not determine the legal rights of any drug manufacturer or distributor, nor impose any requirement or restriction upon any person. *See* Orange Book Preface at xi.

The legal consequences of agency action are "'a function of the agency's intention to bind either itself or regulated parties.'" *Tozzi v. HHS*, 271 F.3d 301, 310 (D.C. Cir. 2002) (quoting *Kennecott Utah Copper Corp. v. United States Dept. of Interior*, 88 F.3d 1191, 1223 (D.C. Cir. 1996)). As FDA explained in the original Orange Book notice-and-comment rulemaking, TE ratings are advisory, informational, and non-binding. *See e.g.*, Orange Book Preface at xi, xii-xiii; 45 Fed. Reg. 72584-89; *see also PMA*, 471 F. Supp. at 1231 (affirming that TE ratings are advisory).

Mallinckrodt cannot identify any legal consequences that flow from its product's TE rating change. Instead, Plaintiff emphasizes the effects of intervening acts of third parties, such as state legislators and pharmacists, none of which stem from FDA action. In other words, according to Mallinckrodt, whether legal consequences flow from agency conduct depends not on the agency's conduct, but on the ever-changing actions or decisions of others in response to the agency's conduct.[4]

Courts have routinely rejected similarly attenuated reviewability theories. In *Industrial Safety Equipment Association v. EPA*, 837 F.2d 1115 (D.C. Cir. 1988), the D.C. Circuit held that an advisory agency report stating that certain asbestos-protection respirators were recommended

[4] Mallinckrodt also relies on dicta from an unpublished opinion in this district to argue that the legal effect of a TE rating has changed over time. *See* Pls.' TRO Br. at 32 (citing *Zeneca Inc. v. Shalala*, No. Civ. A. WMN-99-307, 1999 WL 728104 (D. Md. Aug. 11, 1999)). But the court in *Zeneca* did not reach the conclusion that the legal consequences of TE ratings have changed, and the facts in that case were materially different than those here. In *Zeneca*, the plaintiff challenged "*FDA's decision to list*," or in other words, approve and add to the Orange Book, the drug product at issue. 1999 WL 728104 at 11 n.13. Approving an ANDA undoubtedly constitutes final agency action. Changing an approved drug's TE rating, in no way affecting its approval status, does not. And nothing in *Zeneca* suggests otherwise.

for use by employers, while others were not recommended did not have legal consequences. The agency report, the court pointed out, "establishes no rule that the regulated industry must obey," and "any effect it might have on respirator manufacturers is indirect and arises from the reactions and choices of industry customers and workers." *Indus. Safety*, 837 F.2d at 1121. Likewise, in *Aerosource, Inc. v. Slater*, 142 F.3d 572 (3d Cir. 1998), the FAA issued a warning letter to the aviation community about problems with a repair contractor's work. The Third Circuit decided that the warning letter was not final agency action because it did not impose "legal consequences" on the contractor, which was not required to "comply with any directive." *Id.* at 581; *see also Asbetec Constr. Servs. v. EPA*, 849 F.2d 765, 768-69 (2d Cir. 1988) (agency order was not final agency action even though it led to plaintiff's "diminished opportunities" and "stigma" in obtaining contracts since the order did not affect the plaintiff's duties or obligations).

Mallinkcrodt relies on *Tozzi v. United States Department of Health and Human Services*, 271 F.3d 301 (D.C. Cir. 2002), for the proposition that agency action is final and reviewable if it triggers an effect under state law. Pls.' TRO Br. at 33-34. This argument misreads *Tozzi*. The court in *Tozzi* found reviewable the United States Department of Health and Human Services ("HHS")'s publication of a list of human carcinogens. 271 F.3d at 303. In that case, HHS' list altered the chemical dioxin's designation from a "reasonably anticipated" carcinogen to a "known" carcinogen. *Id.* In reaching the conclusion, the court relied on several indicia of reviewability. First, the court considered that HHS did not intend its listing to be binding and offered it for "informational purposes only." *Id.* at 310. Second, the court noted that the Public Health Service Act ("PHSA") required HHS to publish a proposed notice of the dioxin designation and a final summary of its decision in the Federal Register. *Id.* Removing the substance from the listing, the court pointed out, also required notice and comment under the

PHSA. *Id.* Third, HHS' listing triggered legal obligations under both federal and state law, including regulations promulgated by HHS. *Id.*

The second and third considerations in *Tozzi* were "equally important" to the court in reaching its conclusion on the listing's legal effect and reviewability. *Id.* Neither consideration is presented by the facts here. A change in TE rating for a single product like Mallinckrodt's methylphenidate hydrochloride ER tablets does not require notice and comment. *See* Orange Book preface at xxiii § 1.10 ("Change of the Therapeutic Equivalence Evaluation for a Single Product"); *see also Tozzi*, 271 F.3d at 310 ("Where the agency characterizes its action as non-binding or does not publish in the Federal Register, we have found the action unreviewable."). Whereas the PHSA required the agency in *Tozzi* to publish the dioxin designation in the Federal Register, no statute or other authority requires FDA to engage in any similar "elaborate procedure" here. *See* 271 F.3d at 310. And, contrary to Mallinckrodt's representations, *Tozzi* did not hold that agency conduct constituted final agency action because it had some consequence by operation of state law. Nor should the Court here.

Moreover, neither the fact that some state pharmacy statutes incorporate FDA's TE ratings nor any purported harm sustained as a result of Mallinckrodt's product's TE rating render an agency action final. As the D.C. Circuit has held, materials promulgated by a federal agency and later adopted as part of a local government's permitting process do not create a binding effect and are thus not subject to judicial review. *Nat'l Ass'n of Home Builders v. Norton*, 415 F.3d 8, 14-16 (D.C. Cir. 2005); *cf.* TRO Br. at 33 (emphasizing the legal consequences that flow from the Mallinckrodt TE listing under state pharmacy laws). Likewise, "an agency's action is not final agency action merely because it betokens harm." *See, e.g.*, *Sierra Club v. Peterson*, 185 F.3d 349, 377 (5th Cir. 1999) (citation omitted).

Because the TE rating change for Mallinckrodt's product did not represent the consummation of FDA's process (which remains ongoing), did not determine any legal rights or obligations, and did not trigger legal consequences, the rating change did not constitute final agency action that is ripe for review or is reviewable under the APA. *See Utility Air Reg. Grp. v. EPA*, 320 F.3d 272, 277-79 (D.C. Cir. 2003) (ripeness determination is jurisdictional); *Reliable Automatic Sprinkler Co. v. CPSC*, 324 F.3d 726, 731 (D.C. Cir. 2003) (where there is no final agency action, there is no cause of action under the APA, and dismissal is appropriate under Fed. R. Civ. P. 12(b)(6)).[5]

2. Any Alleged Hardship Experienced by Mallinckrodt Is Outweighed by the Impact of Judicial Review on Effective and Efficient Agency Administration

Although Mallinckrodt has tried to demonstrate financial hardship absent judicial review, the company concedes that it continues to sell large quantities of its methylphenidate hydrochloride ER tablets. Mallinckrodt's claims of constructive withdrawal are further undermined by the undisputed fact that FDA has not taken action to withdraw approval of Mallinckrodt's product. Mallinckrodt's product remains on the market and can be purchased, prescribed, and dispensed. *See* Orange Book Preface at xi; *see also id.* ("[Orange Book TE] evaluations do not constitute determinations that any product is in violation of the Act or that any product is preferable to any other."). FDA has imposed no mandatory requirements or obligations on Plaintiff. *See id.*; *cf. Abbott Labs*, 387 U.S. at 151-52 (hardship warranting judicial review resulted from agency requirement compelling plaintiff to affix labeling to its

[5] Even assuming that an FDA employee represented to Mallinckrodt that its drug product's TE rating constituted final agency action, which FDA disputes, any such unofficial statement of a subordinate FDA official "does not bind or otherwise obligate or commit the agency to the views expressed." 21 C.F.R. § 10.85(k); *see also* TRO Br. at 31. Moreover, courts have consistently held that statements of subordinate agency officials and other similar informal statements do not represent final agency action and are not reviewable. *See, e.g.*, *Holistic Candlers & Consumers Ass'n v. FDA*, 664 F.3d 940 (D.C. Cir.) (warning letters, even in combination with FDA's website posting and FDA representatives' statements, were insufficient to supply the finality necessary for review of agency action).

products under the threat of criminal sanction for non-compliance). Only further future action by FDA would have such a result, demonstrating again that the issues Mallinckrodt raised are not ripe for review and "fail to overcome the finality and fitness problems inherent in attempts to review tentative positions." *Estee Lauder*, 727 F. Supp. at 5; *see also Charter Fed. Sav. Bank v. Office of Thrift Supervision*, 976 F.2d 203, 208 (4th Cir. 1992) ("[A]ction giving rise to the controversy [must be] final and not dependent upon future uncertainties or intervening agency rulings.").

Assuming, *arguendo*, that Mallinckrodt could show that withholding judicial review would result in direct and immediate hardship, which it cannot, judicial adjudication is outweighed by the impact it would have on effective and efficient agency administration. *See USPS v. Gregory*, 534 U.S. 1, 10 (2001) (such agency's decisions are entitled to "a presumption of regularity"). To provide timely consumer information on generic drugs, the Electronic Orange Book is updated daily as new generic approvals occur, *see* http://www.accessdata.fda.gov/ scripts/cder/ ob/default.cfm, and monthly to reflect changes in other information. *See* http://www.fda.gov/Drugs/InformationOnDrugs/ucm 114166.htm. FDA must be able to "change a product's TE rating if the circumstances giving rise to the rating change or information available to the agency calls into question the data FDA assessed to evaluate a product's TE rating." *See* Orange Book Preface at xiii. Immediate judicial review of a TE rating change in the Orange Book would frustrate the agency's ability to provide current information and advise the public on drug product approval, withdrawals, pharmaceutical equivalence, and bioequivalence. FDA's fulfillment of its public health mission would be impeded if every time FDA advised the public of a potential TE issue, suit could be filed against the agency. Specifically, with respect to Mallinckrodt's claims, judicial review would interrupt

FDA's ongoing process to reach a final determination on its product's TE, a scientific matter within FDA's expertise. *See FTC v. Standard Oil Co. of Cal.*, 449 U.S. 232, 242 (1980) (If courts were to examine agency positions that have not been finalized, that would "lead[] to piecemeal review which at the least is inefficient and upon completion of the agency process might prove to have been unnecessary.").

For these reasons, Mallinckrodt's claims are unripe and therefore not justiciable. Accordingly, its complaint must be dismissed.[6]

B. Mallinckrodt Fails to State a Due Process Claim under the Constitution

Even if Mallinckrodt could establish jurisdiction to pursue this action, its remaining claims would nonetheless fail.[7] Mallinckrodt challenges its product's TE rating change under the Fifth Amendment's Due Process Clause. Complt. Counts I & II ¶¶ 33-46. The Due Process Clause of the Fifth Amendment provides: "No person shall . . . be deprived of life, liberty, or property, without due process of law . . . ." U.S. Const., Am. V. Mallinckrodt's claim is predicated on Mallinckrodt having a constitutionally protected property right in its TE rating, which it does not. *Cf. Bd. of Regents of State Colleges v. Roth*, 408 U.S. 564, 569-70 (1972) (Fifth Amendment requires procedural due process only where a person is deprived of a protected interest in liberty or property). Mallinckrodt argues that drug approval serves as the

[6] Mallinckrodt also challenges FDA's issuance of the Revised Draft Guidance on Methylphenidate Hydrochloride (Nov. 2014). The Court need not accept as true Plaintiff's conclusory allegations that FDA improperly relied on the draft guidance to change the TE rating for Mallinckrodt's product. *See, e.g.*, Complt. ¶ 57; *see also Vance*, 914 F. Supp. at 677. The draft guidance is not relevant. Contrary to Mallinckrodt's characterizations, and as evidenced by the FDA review memorandum embraced by Mallinckrodt's Complaint, the draft guidance was not a basis for the agency's decision to change the TE rating for Mallinckrodt's product. FDA Oct. 30, 2014, Memo, at 14; Complt. ¶ 57. Rather, the draft guidance was created separately, though spurred by the same set of facts and analyses that led the agency to update the TE rating for Mallinckrodt's product. *See* Ex. FDA Oct. 30, 2014, Memo, at 11. Because FDA did not rely on the draft guidance in changing the TE rating here, this claim is also premature and should be dismissed for lack of jurisdiction.

[7] This section addresses Counts I and II of the Complaint. Mallinckrodt, however, also has failed to state claims for relief brought under the APA. For the reasons discussed in section IV.A.1.b *supra*, FDA has not taken final agency action, and dismissal of those counts is also appropriate under Rule 12(b)(6). *See* Complt. Counts I, III, IV, & V ¶¶ 33-39, 47-53, & 61-66.

source for its purportedly protected property interest and that the agency deprived Mallinckrodt of that property interest when it changed the TE rating. Complt. ¶¶ 34-35. But, in order for that property interest to be deprived, the agency would have had to withdraw the drug's approval under 21 U.S.C. § 355(e). Withdrawal entails, among other things, notice and an opportunity for a hearing to the applicant and a formal determination by the Secretary that a drug product meets the criteria set forth in 21 U.S.C. § 355(e), such as that drug is not shown to be safe. The agency has taken no such action.

Mallinckrodt does not allege otherwise. Rather, Mallinckrodt argues that, FDA has "effectively" withdrawn its approval, because its generic Concerta is not selling as well as it was with an AB rating. *See, e.g.*, Pls.' TRO Br. at 15. Even assuming that Mallinckrodt has experienced a diminished share of the market, such decline in sales does not constitute withdrawal of a drug approval. Mallinckrodt's ANDA for methylphenidate hydrochloride ER tablets remains currently approved, and Mallinckrodt continues to commercially market its product. *See* http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2012/202608Orig1s000ltr.pdf Mallinckrodt's repeated reliance on "constructive withdrawal" as a "legitimate claim of entitlement" is misplaced.[8]

A change in the TE rating by itself is a far cry from a cognizable property interest. While certain state laws may limit the purchase or substitution of Mallinckrodt's product following the TE rating change, that does not somehow vest Mallinckrodt with a constitutional property interest. The TE rating change in and of itself has not prohibited or limited the product's sale or purchase, or altered its legal status under the FDCA.

V. CONCLUSION

[8] If Mallinckrodt fails to demonstrate bioequivalence and the agency takes further action, all appropriate procedural protections will apply.

For the foregoing reasons, Defendant's motion to dismiss should be granted.

Dated: December 23, 2014

Respectfully submitted,

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