UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

ROBERT GUSTAVSEN et al.,	)	
	)	
on behalf of themselves	)	
and all others similarly situated,	)	
	)	
Plaintiffs,	)	
	)	Civil Action No. 1:14-cv-11961-MLW
v.	)	
	)	
ALCON LABORATORIES, INC. et al.,	)	
	)	
Defendants.	)	
	)	

DEFENDANTS' SUPPLEMENTAL MEMORANDUM IN SUPPORT OF OMNIBUS AND GENERIC DEFENDANTS' MOTIONS TO DISMISS FIRST AMENDED COMPLAINT

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Page(s)

CASES

STATUTES

RULES

REGULATIONS

OTHER AUTHORITIES

I. INTRODUCTION

At the October 30, 2015 hearing on Defendants' Motions to Dismiss Plaintiffs' First Amended Complaint ("FAC"), this Court requested that the parties submit supplemental briefs focusing on issues of preemption addressed during the hearing. Without restating all of the arguments from their motion papers, Defendants submit this brief focusing on the key points requiring that Plaintiffs' claims be dismissed with prejudice on preemption grounds. The Generic Defendants also briefly summarize their separate and independent bases for preemption specific to the generic products in this lawsuit.[1] If the Court concludes that Plaintiffs' claims are preempted, then the lawsuit must be dismissed in its entirety. Finally, Defendants explain why, even if Plaintiffs' claims were not preempted, the Massachusetts law claims should still be dismissed under the Chapter 93A statutory exemption.

II. PLAINTIFFS' CLAIMS ARE PREEMPTED IN THEIR ENTIRETY

A. Under The Supreme Court's Preemption Standard, Plaintiffs' Claims Are Preempted If Defendants Could Not Independently Make The Changes Plaintiffs Seek.

The Supreme Court has established the standard for impossibility preemption in prescription drug cases in three recent decisions: *Wyeth v. Levine*, 555 U.S. 555 (2009), *PLIVA, Inc. v. Mensing*, 131 S. Ct. 2567 (2011), and *Mutual Pharmaceutical Co. v. Bartlett*, 133 S. Ct. 2466 (2013). These cases provide that "[t]he question for 'impossibility' is whether the private party could ***independently*** do under federal law what state law requires of it." *Mensing*, 131 S. Ct. at 2579 (citing *Levine*, 555 U.S. at 573) (emphasis added). Thus, under the *Levine-Mensing-Bartlett* trilogy, if the manufacturer cannot take the action allegedly required by state law without obtaining FDA's prior approval, the state-law claim is preempted. As the First Circuit has now confirmed, this analysis applies equally to brand name and generic drugs. *In re Celexa & Lexapro Mktg. & Sales Pracs. Litig.*, 779 F.3d 34, 40-41 (1st Cir. 2015).

[1] Defendants' prior preemption arguments and authorities are set forth in Dkt. 51 at 8-18, Dkt. 83 at 4-11, and Dkt. 94. The Generic Defendants' prior preemption arguments and authorities are set forth in Dkt. 53 and Dkt. 85.

Here, Plaintiffs contend that state law requires Defendants to manufacture products that dispense eye drops no larger than 15 microliters ("µL"), about half the drop volume dispensed by Defendants' current FDA-approved products. FDA has never approved 15 µL drops for ophthalmic medications. As both sides agree, the question here is whether Defendants would need to seek prior FDA approval to sell redesigned products that dispense smaller drops, or whether such a change could be made by Defendants unilaterally. *See* 10/30/15 Hr'g Tr. at 63:6-8 ("MR. CORNFELD: Your Honor, the issue here is whether they could make the change to the container closure system to reduce the drop size on a CBE 30."). If such a change would require prior FDA approval, Plaintiffs' claims are preempted.

As explained below, the applicable regulations and binding FDA Guidance make clear that the changes Plaintiffs believe state law requires are "major changes" and thus could not be made without prior FDA approval.

B. The Changes Plaintiffs Contend Are Required By State Law Are "Major Changes" Requiring Prior FDA Approval.

"Major" changes to approved prescription drugs are defined in 21 C.F.R. § 314.70 (attached as **Exhibit A**) as follows:

> (b) *Changes requiring supplement submission and approval prior to distribution of the product made using the change (major changes).* (1) A supplement must be submitted for any change in the drug substance, drug product, production process, quality controls, equipment, or facilities that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product.

21 C.F.R. § 314.70(b)(1). Under this standard, FDA must pre-approve a proposed change anytime there is a "substantial ***potential***" for it to adversely affect the "identity, strength, quality, purity, or potency of the drug product" with respect to the drug product's safety or effectiveness. *Id*. (emphasis added). As FDA has explained, because federal law "bases the reporting category

on the ***potential*** for that change to have an adverse effect," prior approval is required for changes that have such potential "even if the applicant concludes that their studies and data demonstrate that the change has no adverse effect." *See* Supplements and Other Changes to an Approved Application, Final Rule, 69 Fed. Reg. 18,728, 18,736 (Apr. 8, 2004) (amending 21 C.F.R. § 314.70) (attached as **Exhibit B**). Thus, whether it "would" have an adverse effect on safety and effectiveness is for FDA to determine; if it "could" have such an effect, prior approval is required.

The change Plaintiffs claim state law requires here fits squarely into the basic definition of a major change—a change potentially adversely affecting "identity, *strength*, quality, purity, or *potency* of the drug product as these factors may relate to the safety and effectiveness of the drug product." Cutting drop volume by half necessarily cuts the amount of active and inactive ingredients in half.[2] By definition, a drop volume reduction is therefore a reduction in the "strength . . . of the drug product." *See* Drugs@FDA Glossary of Terms, *available at* http://www.fda.gov/drugs/informationondrugs/ucm079436.htm ("The strength of a drug product tells how much of the active ingredient is present in each dosage."). Indeed, it is hard to imagine a change more likely to have the potential to adversely impact a drug's *strength* or *potency* than cutting the FDA-approved dose of medication delivered to patients by half.

Binding FDA Guidance addresses this exact circumstance, instructing that altering the dose delivered to patients is categorically a major change:

[2] In *Bartlett*, which found preemption under 21 C.F.R. § 314.70(b), the Supreme Court stated that any change to the "'qualitative or quantitative formulation of the drug product, including active ingredients'" is a "major" change. *Bartlett*, 133 S. Ct. at 2471.

B. Major Changes (Prior Approval Supplement)

The following are examples of changes considered to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.

1. Changes that may affect the controlled (or modified) release, metering or other characteristics (e.g., particle size) of the dose delivered to the patient, including the addition or deletion of a code imprint by embossing, debossing, or engraving on a modified-release solid oral dosage form.

* * *

* Insofar as this guidance adjusts reporting categories pursuant to section 506A of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.70, it does have binding effect.

FDA, CDER, Guidance for Industry, Changes to an Approved NDA or ANDA (April 2004) ("FDA Changes Guidance") (attached as **Exhibit C**) at 12. Plaintiffs cannot reasonably dispute that cutting the size of each drop in half, and thereby reducing the dose, would alter the "characteristics" of the dose.

Plaintiffs' sole response to Defendants' argument that cutting the drop volume in half would reduce by half the amount of active and inactive ingredients in each dose is that "changing the drop size would not affect the dose of these products. It would still be one drop." Dkt. 60 at 16. But it is the ***characteristics*** of the dose that matter. Plaintiffs apparently assume that because some of the medication labels describe the dose as "one drop," manufacturers are free to change the droppers to make each dose as large or small as they want and then sell them to treat glaucoma patients—all without FDA's prior approval. But the idea that manufacturers can increase or reduce the volume of drops unilaterally, and thereby provide patients with increased or reduced dosages, is directly contrary to federal regulations.

But if the Court needs further confirmation that the change Plaintiffs propose is a major change under Section 314.70(b)(1), the regulation goes on to provide specific examples of when a change meets this definition (e.g., 21 C.F.R. § 314.70(b)(2)(iii), (v), (vi)), which are then fleshed out by FDA in the Federal Register and the binding FDA Changes Guidance. If any one of these examples in the regulation subsections applies to the proposed changes at issue, then

preemption applies and Plaintiffs' claims must be dismissed. In fact, as explained below, the changes Plaintiffs propose are classified as major changes under multiple subsections.

- **21 C.F.R. 314.70(b)(2)(iii): Redesigning the container closure system for a sterile drug product is a "major" change requiring prior FDA approval**

By law, any change that "may affect drug substance or drug product sterility assurance" of a sterile product is a major change. 21 C.F.R. § 314.70 (b)(2)(iii). The medications here indisputably are sterile solutions.[3] Plaintiffs propose "changing the design and dimension of the dropper tip" to reduce these sterile solutions' drop volume. (FAC ¶ 130.)

In the April 2004 Federal Register, FDA states unequivocally that a change to the container closure system for a sterile drug product, "even if minimal," may affect drug product sterility assurance and thus requires pre-approval:

> aspect of the safety assessment. Changes in the container closure system, even if minimal, may affect the sterility assurance of the drug product and are a major change. For sterile drug
>
> * * *
>
> FDA declines to revise the regulation as requested. All container closure systems changes must be supported with data to demonstrate that various characteristics of the drug product and/or container closure system are unchanged or equivalent (e.g., physical, chemical). For a sterile drug product, however, data must also be provided to support that the sterility assurance level and the maintenance of sterility for the product has not been affected. Sterility of drug products is a fundamental and essential quality attribute of these drugs and is a critical aspect of the safety assessment. FDA would consider an

[3] *See* 21 C.F.R. § 200.50(a)(1) ("[A]ll preparations offered or intended for ophthalmic use . . . should be sterile."); *id.* §§ 200.50(a)(2)-(3), (c) (non-sterile ophthalmic medicines and droppers may be regarded as adulterated and misbranded under federal law).

assessment of the effects of a change in a container closure system for a sterile product to be inadequate if it did not include tests and data relating to sterility assurance and maintenance of sterility. FDA considers changes in the container closure system for sterile drug products to be changes that may affect the sterility assurance and/or maintenance of sterility of a drug and, therefore, may have significant potential to affect the safety of the drug. Therefore, FDA has identified this change as one that requires prior approval (see comment 34 of this document).

Ex. B (69 Fed. Reg. at 18,745, 18,751) (emphasis added).

FDA's binding Changes Guidance from April 2004 on changes to approved prescription drugs also provides that changing the design of a sterile product container is something FDA requires be pre-approved, stating as follows:

IX. CONTAINER CLOSURE SYSTEM

* * *

B. Major Changes (Prior Approval Supplement)

The following are examples of changes considered to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.

* * *

4. For sterile drug products, any change that may affect drug product sterility assurance, such as:[21]

* * *

- Changes in the size and/or shape of a container for a sterile drug product.

Ex. C (FDA Changes Guidance) at 20-21 (emphasis added).

At the October 30 hearing, Plaintiffs noted that the same FDA guidance document classifies changes in the size and/or shape of a container for a sterile drug ***substance*** as "moderate" changes not requiring prior approval. 10/30/15 Hr'g Tr. at 41:12-20. While true, that does not help Plaintiffs, who have missed the critical distinction between a drug ***substance*** and a

drug ***product***. FDA defines a "drug product" as follows:

> *Drug product* means a finished dosage form, for example, tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients.

21 C.F.R. § 314.3(b) (attached as **Exhibit D**). The "drug product" is the "finished dosage form," i.e., the medications used by patients, such as the products Plaintiffs used and are complaining about in this lawsuit.

"Drug substance," conversely, is defined as follows:

> *Drug substance* means an active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body, but does not include intermediates use in the synthesis of such ingredient.

Id. "Drug substance" thus refers to the raw active ingredient, not the finished product received by the end user. The container for the drug ***product*** is therefore the container closure system or dropper bottle used by patients. The container for the drug ***substance*** is a manufacturing storage container. A change to the size or shape of a container for the finished sterile drug product (as sold to patients) is a major change requiring prior approval, while a change to the size or shape of a container for a drug substance (used for storage during manufacturing) is not.

The Court also asked the parties to address two issues regarding changes to containers of sterile products. First, the Court noted that FDA has left open the possibility that, through guidance, it "may identify certain container closure system changes for sterile drug products that can be reported other than by submission of a prior approval supplement." 10/30/15 Hr'g Tr. at 41:23-42:1. The possibility that FDA guidance "may" in the future allow certain changes without prior agency approval should have no bearing on the Court's preemption analysis.

Preemption must be decided based on what the law *is*, not what it might eventually be. As the Supreme Court found in *Mensing*: "We can often imagine that a third party or the Federal Government ***might*** do something that makes it lawful for a private party to accomplish under federal law what state law requires of it. … If these conjectures suffice to prevent federal and state law from conflicting for Supremacy Clause purposes, it is unclear when, outside of express pre-emption, the Supremacy Clause would have any force." *Mensing*, 131 S. Ct. at 2579 (italics in original). The above cited FDA Changes Guidance remains in effect and FDA has not issued any other guidance on the subject. Courts defer to FDA's interpretation of its own regulations unless the interpretation is "plainly erroneous or inconsistent with the regulation." *Id.* at 2575. Accordingly, the Court should follow FDA's binding Guidance here.

Second, the Court asked about the significance of FDA's statement in the Federal Register that "an applicant could submit a comparability protocol that would allow it to implement post-approval changes in sterile container closure systems without a prior approval supplement." 10/30/15 Hr'g Tr. at 42:1-4 (quoting 69 Fed. Reg. at 18,745). Even assuming Defendants could submit a comparability protocol for these container changes, this does not alter the preemption analysis because the protocol itself must receive prior FDA approval:

> (e) *Protocols.* An applicant may submit one or more protocols describing the specific tests and studies and acceptance criteria to be achieved to demonstrate the lack of adverse effect for specified types of manufacturing changes on the identity, strength, quality, purity, and potency of the drug product as these factors may relate to the safety or effectiveness of the drug product. Any such protocols, if not included in the approved application, or changes to an approved protocol, must be submitted as a supplement requiring approval from FDA prior to distribution of a drug product produced with the manufacturing change. The supplement, if approved, may subsequently justify a reduced reporting category for the particular change because the use of the protocol for that type of change reduces the potential risk of an adverse effect.

Ex. A (21 C.F.R. § 314.70(e)) (emphasis added). Thus, any protocol Defendants might submit to FDA describing the studies and other testing that would be needed to redesign their containers to deliver microdrops of 15 µL would have to be approved by FDA "prior to distribution of [the] drug product produced with the manufacturing change." *Id.* For preemption purposes, the outcome is the same: Defendants cannot make the changes Plaintiffs' state-law claims require without prior FDA approval, and so the claims are preempted.

- **21 C.F.R. 314.70(b)(2)(vi): Changes to container closure systems that control drug product delivery are "major" changes requiring prior FDA approval**

FDA must also pre-approve all "[c]hanges in a drug product container closure system that controls the drug product delivered to a patient …." 21 C.F.R. § 314.70(b)(2)(vi). While the provision discussed above (§ 314.70(b)(2)(iii)) is focused on sterile products only and ensuring that product sterility is maintained, this provision covers all drug products and focuses on ensuring patients are receiving the approved dosage of medication. FDA has explained what kinds of container closure systems "control[] the drug product delivered to a patient," and why the design of these systems is "critical" in ensuring patients receive adequate doses:

> For some drug products, the container closure system itself, rather than a person, regulates the amount of drug product that is administered to a patient. These container closure systems are considered to "control drug delivery." For example, a patient that uses a metered dose inhalation product as instructed cannot control the amount of drug product the container closure system delivers or verify that the appropriate amount has been administered. Where a drug product container closure system controls drug delivery, FDA requires information to be submitted to support that the container closure system can accurately and repeatedly deliver the required amount of drug product. The design and operation of these container closure systems is critical to ensure that the patient receives the correct dose. A drug

product may not be safe or effective if a patient receives too much or too little of the drug product. Changes in these systems are considered to have a substantial potential to adversely affect the identity, strength, quality, purity, or potency of the drug as they may relate to the safety or effectiveness of a drug product. Container closure systems for drug products where a person controls the amount of drug product administered and/or which allow for verification that the appropriate amount has been administered (e.g., number of tablets, milliliters of liquid) are not considered container closure systems that "control drug delivery."

Ex. B (69 Fed. Reg. at 18,739) (emphasis added).

FDA's binding Changes Guidance provides a similar explanation:

IX. CONTAINER CLOSURE SYSTEM

* * *

B. Major Changes (Prior Approval Supplement)

The following are examples of changes considered to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.

* * *

3. A change in the primary packaging components for any drug product when the primary packaging components control[20] the dose delivered to the patient (e.g., the valve or actuator of a metered-dose inhaler).

* * *

[20] A container closure system that is considered to control the dose delivered to the patient is a container closure system where the system itself, rather than a person, regulates the amount of drug product ultimately delivered to a patient. A container closure system where a person controls the amount of drug product administered or that allows verification that the appropriate amount has been administered (e.g., number of tablets, milliliters of liquid) is not considered a container closure system that controls the dose delivered to the patient.

Ex. C (FDA Changes Guidance) at 20 & n.20.

Plaintiffs' only response to why this subsection does not preempt their claims is that the patient, rather than the container closure system, controls delivery of Defendants' eye medications because the patient squeezes the bottle and dispenses one drop. Under Plaintiffs'

interpretation, the patient ***always*** controls drug delivery if the patient is holding the product. But that is not what "controls drug delivery" means. Otherwise, an inhaler would not be a container closure system that controls drug delivery, which FDA clearly says it is. *See* 69 Fed. Reg. at 18,739 (quoted on pp. 9-10). And just as a patient using a metered-dose inhaler cannot verify how many microns of medicine there are in each "puff," neither can a patient dispensing eye drops verify how many microliters of medicine are in each drop. In both examples, it is the ***container closure system*** that controls the amount of drug delivered. Per FDA's explanation, this contrasts with drug delivery that the patient controls by, for example, counting out the number of tablets, or pouring a certain number of milliliters of liquid into a dispensing cup. Indeed, Plaintiffs' lawsuit is expressly premised on the allegation that "the size of the drop is determined by . . . the dimensions of the plastic dropper tip." (FAC ¶ 10); (*see also id.* ¶ 107) ("the design of eyedropper tips . . . determines the [drop] size and flow rate of the bottle"); (*id.* ¶¶ 128-33.) Plaintiffs' own allegations thus demonstrate, consistent with the regulations and FDA Changes Guidance, that an eye dropper is a container closure system that controls drug delivery. Accordingly, any changes to the droppers are "major" and require prior FDA approval.

- **21 C.F.R. 314.70(b)(2)(v): Any change to the dosage description in the labeling is a "major" change requiring prior FDA approval**

Unless expressly excepted, any changes to drug labeling are major changes requiring prior approval. 21 C.F.R. § 314.70(b)(2)(v). The FDA-approved label for Pfizer's Xalatan states how much of the active ingredient, latanoprost, is contained in each drop, noting that "[o]ne drop contains approximately 1.5 µg of latanoprost" and that "[t]he recommended dosage is one drop (1.5 µg) in the affected eye(s) once daily in the evening."[4] Unless Plaintiffs are proposing that the formulation of the drug be altered—which would itself be a major change (*see* 21 C.F.R. § 314.70(b)(2)(i))—Plaintiffs' proposal to reduce the volume of the drops by half or more would

[4] Xalatan Label, *available at* http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm? setid= cc16fa68-4b68-4cdb-8e52-30c803292c22 (referenced at FAC ¶ 152 n.81). Documents referenced in the complaint may be considered on a Rule 12 (b)(6) motion. *Clorox Co. Puerto Rico v. Proctor & Gamble Comm. Co.*, 228 F.3d 24, 32 (1st Cir. 2000).

necessarily reduce the amount of latanoprost in each drop by that amount. Accordingly, Plaintiffs' claims would require Pfizer to change its labeling related to dosage and administration, which would require FDA pre-approval. Plaintiffs do not dispute that Pfizer would need to change its label or that this would require prior approval. That should end the inquiry. Plaintiffs' claims against Pfizer are preempted for this reason as well.

For each of these independent reasons, Defendants cannot unilaterally reduce the drop volume/dosage for their eye medications without first obtaining FDA approval. Plaintiffs' claims directly conflict with federal law and are thus preempted.

C. Plaintiffs Cannot Otherwise Avoid Preemption

1. Plaintiffs' efforts to introduce documents about unrelated container changes have no bearing on the preemption analysis.

Plaintiffs attached to their Opposition certain FDA correspondence with Allergan obtained from FDA's website in an effort to suggest that FDA has not always required prior approval for changes to sterile drug product containers. *See* Dkt. 60 at 19-20 & n.17. Plaintiffs suggested at the hearing that this presents a factual issue warranting denial of Defendants' motion. It does not.

Setting aside Plaintiffs' failure to show that these modifications altered drop size (they did not), identifying instances where a regulator may not have followed the letter of the regulations on prior occasions has no bearing on the preemption analysis. Anyone who looks long enough is likely to find instances where a federal agency took action inconsistent with a regulation. And Defendants could identify dozens of examples where they were required to seek prior FDA approval for far less serious changes to their products than those at issue here. But the analysis is not about counting up how many times Defendants did or did not have to seek prior approval for changes to their products. Preemption is instead a ***legal*** issue based on the application of federal regulatory requirements to the particular proposed change. *See Mensing*, 131 S. Ct. at 2580 (preemption is based on the "'ordinary meaning' of federal law"). Indeed, as the Supreme Court has made clear, if the possibility that a federal agency might grant an

exception to federal requirements were sufficient to overcome preemption, it "would render conflict pre-emption largely meaningless because it would make most conflicts between state and federal law illusory. We can often imagine that a third party or the Federal Government ***might*** do something that makes it lawful for a private party to accomplish under federal law what state law requires of it. … If these conjectures suffice to prevent federal and state law from conflicting for Supremacy Clause purposes, it is unclear when, outside of express pre-emption, the Supremacy Clause would have any force." *Id.* at 2579 (italics in original).

2. Supreme Court authority forecloses any argument that Plaintiffs' damages claims are immune from preemption.

At the hearing, the Court also questioned why Defendants would need to redesign their medications instead of just paying damages to Plaintiffs and continuing to sell their medications in their current design. 10/30/15 Hr'g Tr. at 34:5-6. Plaintiffs have never argued that their damages claims should be treated differently than their injunctive relief claims for purposes of the preemption analysis, and with good reason. The Supreme Court squarely addressed this question in *Bartlett*. Justice Breyer argued in dissent that it was not "literally impossible" for the defendant to comply with state and federal law "because it could escape liability 'either by not doing business in the relevant State or by paying the state penalty, say damages, for failing to comply with, as here, a state-law tort standard." *Bartlett*, 133 S. Ct. at 2477 n.3. Justice Sotomayor similarly suggested that the defendant could "remove the drug from the market, or pay compensation as a cost of doing business." *Id.* at 2491 (Sotomayor, J., dissenting). The majority rejected both options, finding "our pre-emption cases presume that a manufacturer's ability to stop selling does not turn impossibility into possibility" and *Mensing* "forecloses any argument that impossibility is defeated by the prospect that a manufacturer could 'pa[y] the state penalty' for violating a state-law duty; that prospect would have defeated impossibility in [*Mensing*] as well." *Id*. at 2477 n.3 (citations omitted). State-law claims cannot "require a manufacturer to choose between leaving the market and accepting the consequences of its actions (in the form of a fine or other sanction)." *Id*. at 2479. Accordingly, Plaintiffs cannot

defeat impossibility preemption by arguing that Defendants simply could pay damages in lieu of redesigning their medications.

III. PLAINTIFFS' CLAIMS AGAINST THE GENERIC DEFENDANTS ARE PREEMPTED SEPARATE AND INDEPENDENT OF THE PREEMPTION GROUNDS APPLICABLE TO ALL DEFENDANTS

In addition to the preemption grounds applicable to all Defendants, Plaintiffs' claims against the Generic Defendants should also be dismissed on separate and independent preemption grounds applicable to the Generic Defendants alone, because the Generic Defendants are subject to an ongoing federal "duty of sameness." That means generics must be a "copy" of their brand name equivalents. Because the brand name products dispense drops greater than 15 microliters, it is impossible for the Generic Defendants to comply with any purported state law duty to provide drops no greater than 15 microliters without violating their duty of sameness.

A. The Generic Defendants Are Subject To A Federal Duty Of Sameness.

The legal obligation of the Generic Defendants to keep their generic drugs the same as the reference listed drugs ("RLDs") on which they are modeled is spelled out in the Hatch-Waxman Amendments to the FDCA, which provide in relevant part:

> (2)(A) An abbreviated application for a new drug shall contain—
>
> (i) information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the new drug have been previously approved for a drug listed under paragraph (7) (hereinafter in this subsection referred to as a "listed drug");
>
> * * *
>
> (iii) information to show that the route of administration, the dosage form, and the ***strength*** of the new drug are the same as those of the listed drug referred to in clause (i) … ;
>
> * * *
>
> (iv) information to show that the new drug is ***bioequivalent*** to the listed drug referred to in clause (i) … ;

21 U.S.C. § 355(j)(2)(A)(i), (iii)-(iv) (emphasis added).

In addition, as discussed above (*see* Section II.B, *supra*), 21 C.F.R. § 314.70(b)(2) requires prior FDA approval for any change that "has a substantial potential to have an adverse

effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product," including changes "in the qualitative or ***quantitative formulation*** of the drug product," and changes "requiring completion of studies … to demonstrate the ***equivalence*** of the drug product as manufactured without the change or to the reference listed drug[.]" 21 C.F.R. § 314.70(b)(2) (emphasis added).

In *Mensing* and *Bartlett*, the Supreme Court construed these statutory and regulatory provisions to mean that "generic drug manufacturers have an ongoing federal duty of 'sameness.'" *Mensing*, 131 S. Ct. at 2575; *see also Bartlett*, 133 S. Ct. at 2471. Each generic drug is "designed to be ***a copy***" of its RLD, "and thus identical in active ingredients, safety and efficacy." *Mensing*, 131 S. Ct. at 2574 n.2 (emphasis added). Where an alleged state-law duty would require a generic manufacturer to make changes to a generic drug that would cause it to cease being a "copy" of its RLD, the duty of sameness necessitates conflict preemption. That was the outcome in *Mensing*, where the Court held that the duty of sameness preempted a state-law failure to warn claim that would have required a generic manufacturer to change the labeling of its generic drug to deviate from the RLD, because the manufacturer could not "independently do under federal law what state law requires of it." 131 S. Ct. at 2579 (citing *Wyeth*, 555 U.S. at 573). "[W]hen a party cannot satisfy its state duties without the Federal Government's special permission and assistance, which is dependent on the exercise of judgment by a federal agency, that party cannot independently satisfy those state duties for pre-emption purposes." *Id.* at 2581. Or, as expressed in *Bartlett*, which extended *Mensing* to design defect claims, where "federal law forbids an action that state law requires, the state law is 'without effect.'" *Bartlett*, 133 S. Ct. at 2476-77 (quoting *Maryland v. Louisiana*, 451 U.S. 725, 746 (1981)). So it is with respect to Plaintiffs' claims against the Generic Defendants in this case.

B. It Is Impossible For The Generic Defendants To Comply With Their Alleged State-Law Duties Without Violating The Federal Duty Of Sameness.

Plaintiffs' First Amended Complaint demands that the Generic Defendants change "the design" and "the dimensions" of the plastic dropper tip of their FDA-approved generic eye

medications in order to reduce their drops to a volume no larger than 15 µL per drop. (FAC ¶¶ 10, 75, 107, 128-130, 135, 137-38.) Plaintiffs' own allegations describe this as a reduction in drop volume for most medications to ***less than half*** the current volume of their corresponding RLDs, from an average size of 39 µL to 15 µL. (*Id*. ¶¶ 9, 90-101, 104, 109, 115, 117.) And Plaintiffs' Prayer for Relief includes a demand for "declaratory and injunctive relief … including a preliminary and permanent injunction enjoining Defendants from continuing the unlawful practices as set forth herein." (*Id*. Prayer for Relief ¶ 6.)

The Generic Defendants cannot comply with an alleged state-law duty to change the design and dimensions of their droppers to reduce drop volume from an average of 39 µL to 15 µL, without violating their federal duty of sameness. Such a change would violate federal law by, at a minimum, changing the strength, bioequivalence, and quantitative formulation of the Generic Defendants' products as compared to their corresponding RLDs.

Strength. FDA defines "strength" as "how much of the active ingredient is present in each dosage." Drugs@FDA Glossary of Terms, available at http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm; *see also* 21 C.F.R. § 210.3(b)(16) (defining "strength" as "concentration of the drug substance," including on a "unit dose/volume basis" and/or as the "potency, that is, the therapeutic activity of the drug product"). Plaintiffs propose to reduce the amount of the active pharmaceutical ingredient in each drop of the Generic Defendants' drugs (i.e., the volume of active ingredient per unit dose) by more than half, thereby necessarily altering the strength of each dose of the medications as compared to their respective RLDs.

Bioequivalence. FDA defines "bioequivalence" as "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study." 21 C.F.R. § 320.1(e). Here, reducing the dose size of the Generic Defendants' drugs to 15 µL from their corresponding RLDs' alleged average size of 39 µL would necessarily reduce

the quantity of active ingredient and active moiety[5] available at the site of the drug action in the same proportion, by definition ***not*** bioequivalent to their RLDs. At a minimum, establishing the bioequivalence of the Generic Defendants' drugs at a different dose size would require submission to FDA of a "complete study report" of an "appropriately designed study" establishing bioequivalence. 21 C.F.R. §§ 314.94(a)(7), 320.1(e), 320.21(b)(1). This is precisely the kind of "special permission and assistance" the Supreme Court held requires a finding of preemption. *Mensing*, 131 S. Ct. at 2581.

Quantitative Formulation. "Quantitative formulation" encompasses "both active and inactive ingredients" of the drug. 21 C.F.R. § 314.200(e)(2). Here, Plaintiffs would use state law to change—indeed, to reduce by more than half—the quantity of active and inactive ingredients in each drop instilled in the patient's eye. The measure of a "major change" is any change with a "substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product." 21 C.F.R. § 314.70(b)(1). Dramatically reducing the quantity of active and inactive ingredient in each dose of a generic drug as compared to its RLD is inescapably a major change. As *Bartlett* observed, "A drug's usefulness and its risk of danger are both direct results of its chemical design and, most saliently, its active ingredients." 133 S. Ct. at 2475.

Thus, because the changes Plaintiffs seek would make it impossible for the Generic Defendants to comply with federal law, Plaintiffs' state-law claims against the Generic Defendants are separately and independently preempted under *Mensing* and *Bartlett*. Indeed, in considering essentially identical claims, the U.S. District Court for the District of New Jersey in *Cottrell v. Alcon*, No. 14-5859, 2015 WL 3889367 (D.N.J. June 24, 2015), dismissed the claims

[5] "Moiety" means the "[f]unctional group" of a given substance. *Stedmans Medical Dictionary* (27th ed. 2000). This Court may take judicial notice of dictionary definitions, including those contained in medical dictionaries. *See* Fed. R. Evid. 201(b); *Pyles v. Merit Systems Protection Bd.*, 45 F.3d 411, 415 (Fed. Cir. 1995) (taking judicial notice of medical and English language dictionaries); *Cox v. Allin Corp. Plan*, 70 F. Supp. 3d 1040, 1044 n.2 (N.D. Cal. 2014) (taking judicial notice of *Stedmans Medical Dictionary*).

for lack of standing, but also noted that if plaintiffs sought to amend, their allegations "highlight the issue of preemption" under *Mensing* and *Bartlett* with respect to the Generic Defendants. *Id*. at *7 n. 7. Plaintiffs' claims here likewise highlight the issue of preemption, and for the foregoing reasons are preempted as to the Generic Defendants.

IV. PLAINTIFFS' CHAPTER 93A CLAIMS ARE BARRED BECAUSE THE STATUTE ITSELF EXEMPTS CONDUCT THAT IS PERMITTED BY THE REGULATORY AUTHORITY

Even if federal law did not preempt Plaintiffs' claims, the FDA's regulatory scheme would require dismissal of Plaintiffs' Massachusetts claims on state-law grounds as to all Defendants. The safe harbor provision of Chapter 93A states:

> Nothing in this chapter shall apply to transactions or ***actions otherwise permitted under laws as administered by any regulatory board*** or officer acting under statutory authority of the commonwealth or of the United States.
>
> For the purpose of this section, the burden of proving exemptions from the provisions of this chapter shall be upon the person claiming the exemptions.

Mass. Gen. Laws ch. 93A, § 3 ("Section 3") (emphasis added).[6] The exemption prevents lawsuits exactly like this one—where companies have been selling products for years under the safe harbor of federal agency approval, here the FDA's.

Without a doubt the container closure systems used by Defendants were affirmatively "permitted" by the FDA, and thus are exempt from challenge under Section 3. The safe harbor applies when Defendants show that the regulatory scheme "affirmatively permits the practice which is alleged to be unfair or deceptive." *Fleming v. Nat'l Union Fire Ins. Co.*, 837 N.E.2d 1113, 1121 (Mass. 2005). Unlike preemption—which focuses on whether the regulations ***prohibit*** Defendants from unilaterally redesigning their container closure systems—the Section 3

[6] Massachusetts is one of many states whose consumer fraud statute contains a regulatory safe harbor. Many of the states identified in the FAC enacted similar safe harbors. *See, e.g.*, Ark. Code Ann. §44-88-101(3); Ga. Code Ann. §10-1-374(a)(1); Ind. Code Ann. §24-5-0.5-6; Me. Rev. Stat. Ann. Tit. 5, §208; Minn. Stat. §325D.461; N.Y. Gen. Bus. Law § 349(d) (McKinney); Ohio Rev. Code Ann. §1345.12(A); Okla. Stat. Ann. Tit. 15, §754(2); Or. Rev. Stat. §646.612(1); R.I. Gen. Laws §6-13.1-4; S.C. Code Ann. §39-5-40(a); S.D. Codified Laws §37-24-10; Tenn. Code Ann. §47-18-111.

inquiry is whether FDA ***permits*** Defendants to sell the products with their current container closure systems.

For Section 3 to apply, the regulatory agency must affirmatively approve the conduct plaintiffs challenge, and Massachusetts courts uniformly dismiss Chapter 93A claims where defendants make this showing:

- *Animal Legal Def. Fund Boston, Inc. v. Provimi Veal Corp*., 626 F. Supp. 278, 283-84 (D. Mass. 1986) *aff'd*, 802 F.2d 440 (1st Cir. 1986): Defendants' sale of veal where the calves were fed antibiotic-rich, iron-depleted yield was protected by the Section 3 safe harbor because the United States Department of Agriculture's regulatory scheme affirmatively permitted defendant's use of medicated animal feeds.

- *DePasquale v. Ogden Suffolk Downs, Inc.*, 564 N.E.2d 584, 587 (Mass. App. Ct. 1990): Regulations promulgated by racing commission affirmatively permitted horse-racing track to deny plaintiff his gambling winnings where plaintiff could not produce the winning ticket.

- *Bierig v. Everett Square Plaza Associates*, 611 N.E.2d 720, 728 (Mass. App. Ct. 1993): Landlord's rent levels were exempt from Chapter 93A where the Massachusetts Housing Finance Agency had permitted landlord to charge both market-level and below-market level rents.

- *Riccio v. Ford Motor Credit Co.*, 238 F.R.D. 44, 47 (D. Mass. 2006): Ford's practice to include excise tax in the amount on which sales tax was calculated was one permissible way it could calculate sales tax under Department of Revenue regulations and therefore the conduct was exempt from Chapter 93A despite Ford's failure to disclose to consumers that the regulations also permitted Ford to separately state the excise and sales taxes.[7]

This case is like *Provimi*, *DePasquale*, *Bierig*, and *Riccio*. Defendants submitted their container-closure systems to FDA for review and approval as part of a comprehensive application that included specifications, dosing regimen, and volume for the drug and container closure system, and FDA reviewed and affirmatively permitted Defendants to market their container closure systems as currently designed. *See* "Search by Drug Name" at

[7] *Provini* and *Riccio* both relied on Section 3 to grant defendants' motions to dismiss. Although Section 3 is an affirmative defense, the Court may consider an affirmative defense on a Rule 12(b)(6) motion: "As a general rule, a properly raised affirmative defense can be adjudicated on a motion to dismiss so long as (i) the facts establishing the defense are definitively ascertainable from the complaint and the other allowable sources of information, and (ii) those facts suffice to establish the affirmative defense with certitude." *Rodi v. S. New England Sch. Of Law*, 389 F.3d 5, 12 (1st Cir. 2004); *see also Fleming*, 837 N.E.2d at 1113 (stating that the Section 3 safe harbor may be decided on a motion to dismiss).

http:www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Search_Drug_Name (containing approval history for all products referenced in FAC)[8]; *see also* 21 U.S.C.§§ 355(a), (b), (j); 21 C.F.R. § 200.50. Indeed, FDA's regulatory scheme makes it impossible for Defendants to market their currently designed container closure systems ***without*** FDA's affirmative permission.

Accordingly, because FDA affirmatively permitted Defendants to sell their container closure systems as designed and approved, Defendants are entitled to the protection of the Section 3 safe harbor and Plaintiffs' Chapter 93A claims should be dismissed.

V. CONCLUSION

For all these reasons, and the reasons set forth in Defendants' and the Generic Defendants' prior briefing and at oral argument, the Court should dismiss Plaintiffs' First Amended Complaint with prejudice.

[8] The Court may take judicial notice of these FDA records. *See* Dkt. 51 at 19 n.13.

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CERTIFICATE OF SERVICE

I hereby certify that this document filed through the CM/ECF system will be sent electronically to the registered participants as identified in the Notice of Electronic Filing and paper copies will be sent to those indicated as non-registered participants on November 5, 2015.

Dated: November 5, 2015

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