IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLORADO
Chief Judge Wiley Y. Daniel

Civil Action No. 09-cv-00411-WYD-BNB

REGENERATIVE SCIENCES, INC.

Plaintiff,

v.

UNITED STATES FOOD AND DRUG ADMINISTRATION;
FRANK TORTI, M.D., in his Official Capacity as Commissioner of the United States Food and Drug Association;
MARY A. MALARKEY, in her Official Capacity as Director of the Office of Compliance and Biologics Quality Center for Biologics Evaluation and Research;
UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES;
CHARLES E. JOHNSON, in his Official Capacity as Acting Secretary of the United States Department of Health and Human Services;

Defendants.

ORDER OF DISMISSAL

I. INTRODUCTION

THIS MATTER is before the Court on Defendant's Motion to Dismiss Pursuant to Rules 12(b)(1) and 12(b)(6) of the Federal Rules of Civil Procedure filed April 29, 2009., seeking to dismiss Plaintiff Regenerative Sciences, Inc.'s ("Regenerative") Complaint. The Complaint seeks declaratory and injunctive relief barring the United States Food and Drug Administration ("FDA") from regulating Regenerative's use of Mesenchymal Stem Cells ("MSCs) in its Regenexx Procedure, marketed for the treatment of musculoskeletal and spinal injuries.

Defendants argue that dismissal of the Complaint is appropriate because the claim is not ripe for judicial review as FDA has taken no final agency action. Defendants

also argue that the Court lacks jurisdiction to enjoin FDA's enforcement under the Federal Food, Drug, and Cosmetic Act ("FD&C Act").

A response in opposition to the motion was filed on May 26, 2009. Regenerative argues that Defendants' motion does not meet the requirements for a Rule 12(b) dismissal and that Defendants' arguments in support of the motion fail as a matter of law. A reply was filed on May 26, 2009. For the reasons stated below, the motion to dismiss is granted.

II. BACKGROUND

Plaintiff Regenerative consists of two physicians who operate a small medical facility in Broomfield. They assert that their patients come to them when they are experiencing moderate to severe joint, muscle, tendon or bone pain due to injury or other conditions which traditionally could only be treated by invasive surgical procedures and rehabilitation. Regenerative performs the procedure known as the "Regenexx Procedure" which it asserts helps the patient avoid the need for surgery.

The Regenexx Procedure begins with one of Regenerative's physicians taking bone marrow from the back of a patient's hip through a needle. Blood is also taken from a vein in the patient's arm. The bone marrow and blood is then sent to Regenerative's laboratory (also located in Broomfield) where the MSCs are isolated from the bone marrow and then multiplied using the natural growth factors in the patient's blood. After approximately 1-2 weeks, the MSCs are placed back into the patient's injured area (i.e. knee, hip, rotator cuff). According to Regenerative, the MSCs then begin to repair the patient's degenerated or injured area.

The Public Health Service Act ("PHS Act") authorizes the FDA to regulate human cells, tissues, or cellular and tissue based products ("HCT/Ps"). Regenerative does not dispute that the MSCs used in the Regenexx Procedure meet the definition of HCT/Ps. HCT/Ps are defined as "articles containing or consisting of human cells or tissues that are intended for implantation, transportation, infusion, or transfer into a human recipient." 21 C.F.R. § 1271.3(d). Instead, Regenerative claims that this is a new definition created by the FDA in 2005 without affording the public with notice or the opportunity to comment and was an *ultra vires* act.

HCT/Ps are not subject to additional statutory requirements, such as biologies license application ("BLA") or investigational new drug ("IND") requirements, if all the criteria in 21 C.F.R. § 1271.10(a) are met. If any of the criteria are not met, HCT/Ps are regulated both by the PHS Act, 42 U.S.C. § 264, and under the FD&C Act and § 262 of the PHS Act, as devices, drugs and/or biological products. *See* 21 C.F.R. § 1271.20.

The PHS Act defines a biological product as a "virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product applicable to the prevention, treatment or cure of a disease or condition of human beings. 42 U.S.C. § 262(i). Biological products can also be contemporaneously regulated as drugs and are generally subject to the same requirements that apply to all drugs. *Id.*, § 262(j).

The FC&C Act defines "drug" to include, among other things, "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man." 21 U.S.C. § 321(g)(1)(B). A "new drug" is defined as (1) a drug that is "not generally recognized, among experts qualified by scientific training and experience . . . as safe and

effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof," or (2) a drug that, "as a result of investigations to determine the safety and effectively for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material time under such conditions." 21 U.S.C. § 321(p).

Under the FD&C Act, a "new drug" cannot be distributed in interstate commerce until the drug's sponsor receives FDA approval. 21 U.S.C. §§ 331(d), 355(b). For new drugs, the sponsor must seek approval to market a product by submitting a new drug application to FDA pursuant to the FD&C Act. *Id.*, § 355(a). For biological products the sponsor must seek FDA's approval by submitting a BLA pursuant to the PHS Act. 42 U.S.C. § 262(a). In both cases, approval depends upon a scientific showing, satisfactory to FDA, that the product is both safe and effective for its intended use. Further, before a sponsor can test a biological product or other new drug on humans, it must seek approval from FDA by submitting an IND pursuant to the FD&C Act, 21 U.S.C. § 355(i)(1); 21 C.F.R. § 312.2(a).

In this case the FDA sent a letter dated July 25, 2008, to Regenerative. It stated that the Agency's review of Regenerative's web site found that it touts the Regenexx procedure as a "groundbreaking procedure" to "regenerate bone and cartilage" and "relieve[] pain and restore[] mobility in people who "suffer from painful and debilitating orthopedic conditions." (Compl., Att. A at 1.) The letter advised Regenerative that, based on the information presented on the web site, it was promoting the "use of [MSCs] under conditions that cause these cells to be drugs" under section 201(g) of the FD&C Act (21 U.S.C. § 321(g)) and biological products, as defined in section 351(i) of the PHS

Act (42 U.S.C. § 262). The FDA letter also noted that the MSCs used in the Regenexx procedure to do not meet all of the criteria in 21 C.F.R. § 1271.10 that set forth the circumstances in which HCT/Ps such as MSCs are not subject to the BLA and IND requirements.

The letter further advised that because Regenerative's use of the MSCs in the Regenexx Procedure has not been authorized by the FDA, through either the BLA or IND process, its use "appears to violate the [FD&C] Act and the PHS Act and may result in FDA seeking relief as provided by law." (*Id*.) The letter concluded by requesting that Regenerative notify FDA in writing "of the steps you have taken or will take to address the violations noted above and to prevent their recurrence." In accordance with its policy, the FDA posted the letter on its web site so that it was available to the public.

On August 22, 2008, Regenerative submitted a response to the FDA letter, claiming that the MSCs are not drugs and biological products. (Compl., Att. E.) The letter set forth facts and arguments that supported its position that the MSCs should not be regulated by FDA.

On February 23, 2009, FDA commenced an inspection of Regenerative's facilities pursuant to the inspectional authority granted under the FD&C Act and the PHS Act. On February 26, 2009, three days after FDA began inspection, Regenerative filed this lawsuit. It also filed a motion for protective order claiming that FDA's inspection was allowing it to gather discovery in an unsupervised manner not permitted by the Federal Rules of Civil Procedures. The motion for protective order was denied.

Regenerative then brought this suit, alleging that the definitional regulation of HCT/Ps is too broad and that Congress did not intend to give FDA the authority to

regulate the use of HCT/Ps in the person from who they were obtained (autologous use). When viewed in the context of Plaintiff's medical practice, it is argued that what was at one time a regulatory scheme narrowly tailored to prevent the spread of communicable diseases from human tissue donors to human tissue recipients, became in 2005 a targeted effort of the FDA to regulate much more. Regenerative also asserts that the FDA does not have the authority to regulate the practice of medicine, even when it involves the manipulation of stem cells.

Plaintiff seeks a judicial declaration pursuant to 28 U.S.C. § 2201 *et.seq.*, that (1) the FD&C Act does not give the FDA jurisdiction to regulate the practice of medicine; (2) FDA's decision that Regenerative's manipulation of MSCs in its Regenexx Procedure make the MSCs drugs for which an IND is required or biological products for which a BLA is required is arbitrary and capricious; and (3) 21 C.F.R. § 1721.3(d) is *ultra vires*. Plaintiff also seeks an order enjoining the FDA from regulating the Regenexx medical Procedure via FDA's July 25, 2008, and costs and attorneys' fees.

III. ANALYSIS

A. Standard of Review

A motion to dismiss under Rule 12(b)(1) can be either a facial attack on the sufficiency of the allegations of the complaint as to subject matter jurisdiction or a challenge to the actual facts upon which subject matter jurisdiction is based. *Ruiz v. McDonnell*, 299 F.3d 1173, 1180 (10th Cir. 2002). In this case, Defendants are raising a facial attack on the sufficiency of the allegations as to subject matter jurisdiction.

Defendants also move to dismiss the Complaint under Fed. R. Civ. P. 12(b)(6). When considering a motion to dismiss pursuant to Rule 12(b)(6), the Court "assumes the

truth of the plaintiff's well-pleaded factual allegations and view[s] them in the light most favorable to the plaintiff." *Ridge at Red Hawk, L.L.C. v. Schneider*, 493 F.3d 1174, 1177 (10th Cir. 2007). "To survive a motion to dismiss, a complaint must contain sufficient factual matter, accepted as true, to 'state a claim to relief that is plausible on its face.'" *Ashcroft v. Iqbal*, ___ U.S., 129 S. Ct. 1937, 1949 (2009). Plausibility, in the context of a motion to dismiss, means that the plaintiff pled facts which allow "the court to draw the reasonable inference that the defendant is liable for the misconduct alleged." *Id*. If the allegations state a plausible claim for relief, such claim survives the motion to dismiss. *Id*. at 1950.

B. Whether Dismissal is Appropriate of the Claims for Declaratory Judgment and Injunctive Relief

FDA asserts that the Court does not have jurisdiction under the Administrative Procedure Act ("APA"), 5 U.S.C. § 704, to review Plaintiff's complaint alleging that the definitional regulation of HCT/Ps is too broad and not authorized by Congress. This regulation was issued under a provision of the PHS Act that provides for regulations "necessary to prevent the introduction, transmission, or spread of communicable diseases." 42 U.S.C. § 264(a). In Regenerative's view, autologous use of HCT/Ps cannot possibly cause communicable diseases and that, therefore, FDA's definitional regulation is *ultra vires*. FDA asserts in response that this is a factual issue that cannot be resolved until FDA brings an action against Regenerative. Since such an action has not yet been brought, FDA argues that this case is not ripe.

Ripeness is a justiciability doctrine designed "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*, *Califano v. Sanders*, 430 U.S. 99, 105 (1977). To determine whether administrative action is ripe for judicial review, the Court evaluates: (1) the fitness of the issues for judicial decision and (2) the hardship to the parties of withholding court consideration. *Id.* at 149.

When applying this two-prong test, the Court examines four factors: (1) whether the issues in the case are purely legal; (2) whether the agency action involved is "final agency action" within the meaning of the APA; (3) whether the action has or will have a direct and immediate impact upon the plaintiff; and (4) whether the resolution of the issues will promote effective enforcement and administration by the agency. *See Park Lake Res., L.L.C. v. U.S. Dep't of Agric.*, 197 F.3d 448, 450 (10th Cir. 1999). The plaintiff bears the burden of establishing that its case is ripe for judicial review. *Coal. for Sustainable Res., Inc. v. U.S. Forest Serv.*, 259 F. 3d 1244, 1250 (10th Cir. 2001) After applying the *Abbott Labs* test, I conclude that Regenerative has failed to meet its burden of showing that this case is ripe.

1. Fitness

A claim is fit for review by this Court if the issues raised are primarily legal and the administrative action is final. *Friends of Marolt Park v. U.S. Dep't of Transp.*, 382 F.3d 1088, 1094 (10th Cir. 2004); *State of Cal., Dept. of Educ. v. Bennett*, 833 F.2d 827, 833 (9th Cir. 1987). In determining whether an agency action is final, the court inquires: (1) whether the impact of the action is "direct and immediate;" (2) whether the action marks

the consummation of an agency's decision-making process; and (3) whether the action settles the rights and obligation of parties, or gives rise to legal consequences." *Gordon v. Norton*, 322 F.3d 1213, 1220 (10th Cir. 2003).

One of the hallmarks of finality in this context is whether "legal consequences will flow" from the agency actions. *Bennett v. Spear*, 520 U.S. 154, 178 (1997). The requirement of finality is interpreted pragmatically. *Abbott Labs.*, 387 U.S. at 149-150. A court looks to whether the agency action represents the final administrative word to insure that judicial review will not interfere with the agency's decision-making process." *Bennett*, 833 F.2d at 833.

In the present case, the FDA asserts that its enforcement action against Regenerative does not constitute a legal question, nor is it a "final agency action" as defined under the APA. In response, Regenerative contends that it is not asking the Court to decide on a particular FDA enforcement action, rather, it is challenging the unlawful creation of a new definition of HCT/P under the regulation promulgated in 2005. Plaintiff explains in its response brief that it challenges 21 C.F.R. § 1271.3(d) as being unlawful for two reasons. First, it asserts that the regulation was not changed pursuant to the APA's notice and comment rulemaking procedures. Second, Regenerative asserts that the change in the regulation was made in excess of the FDA's jurisdiction, and thereby purports to give jurisdiction to the FDA never afforded to it by Congress.

Viewing the pleadings in a light most favorable to Regenerative, I agree that it has pled such a claim. Specifically, Claim Six of the Complaint pleads that FDA's definition of HCT/Ps is *ultra vires*. "An 'agency action' includes any 'rule,' defined by the Act as 'an agency statement of general or particular applicability and future effect designed to

implement, interpret, or prescribe law or policy.'" *Abbott Labs*, 387 U.S. at 149. Here, Regenerative is challenging the validity of a promulgated regulation which it claims was in excess of FDA's jurisdiction. In *Toliet Goods Ass'n, Inc. v. Gardner*, 387 U.S. 158, 164 (1967), the Supreme Court recognized that a claim presents a purely legal question when it challenges whether a regulation is "totally beyond the agency's power under the statute." Therefore, when fashioned in the light most favorable to the plaintiff's pleading, the Court concludes that this claim requires no further fact-finding and therefore is fit for judicial review.

However, the remainder of Regenerative's claims all involve fact-finding specific to the Regenexx procedure and whether the MSCs used in the Regenexx procedure implicate the Part 1271 regulations under the PHS Act. Specifically, Plaintiff asserts the following additional claims: (1) the Regenexx Procedure constitutes the practice of medicine and is beyond the scope of the FDA's regulatory authority and jurisdiction; (2) the PHS Act does not give the FDA jurisdiction over the practice of medicine and the FDA should be enjoined from regulating the Regenexx Procedure; (3) the FDA Act does not give the FDA jurisdiction over the Regenexx Pocedure because it is the practice of medicine; and (4) FDA's decision that Regenerative's manipulation of MSCs makes the MSCs "drugs" for which an IND is required or biological products for which a BLA is required is arbitrary and capricious.

I agree with FDA that these claims will require a factual inquiry into whether FDA can regulate autologous use of human cells, tissues, or cellular or tissue-based products ("HCT/Ps") and their functions. I also agree with FDA that the claims do not involve a

final FDA action interpreting and applying Part 1271 "to a specific set of circumstances" as required for the action to be ripe and fit for review. As the Supreme Court has stated:

> [A] regulation is not ordinarily considered the type of agency action 'ripe' for judicial review under the [Administrative Procedure Act (APA)] until the scope of the controversy has been reduced to more manageable proportions, and its factual components fleshed out, by some concrete action applying the regulation to the claimant's situation in a fashion that harms or threatens to harm him.

Lujan v. Nat'l Wildlife Fed'n, 497 U.S. 871, 891 (1990).

Although Regenerative acknowledges FDA's authority to "control communicable diseases," it asks this Court to find, as a matter of law, that Congress intended to foreclose the possibility that FDA would regulate any autologous use of HCT/Ps – regardless of the type of HCT/Ps, the intended use of the HCT/Ps, the degree to and circumstances under which the HCT/Ps are manipulated prior to implantation, and regardless of how these factors may contribute to the transmission of diseases. Pl. Opp. at 3, 11. As a result of the posture of this litigation, such a task would be unduly complex and speculative. The Court would have to assess the likelihood of the transmission of a wide range of diseases, under diverse methods for processing numerous types of HCT/Ps with various autologous uses, to determine at this stage whether FDA's regulation defining HCT/Ps, 21 C.F.R. § 1271.3(d), is "ultra vires" in all possible circumstances. Only a final FDA action interpreting and applying Part 1271 (including its exceptions) to a specific set of circumstances would reduce this amorphous inquiry to a controversy of "more manageable proportions." *See Nat'l Parks Hospitality Ass'n v. Dep't of Interior*, 538 U.S. 803, 811-12 (2003) (holding that a legal question is not always a final agency action that is ripe for review).

Similarly, the July 25, 2008, FDA warning letter is not a "final agency action" as defined under the APA. Instead, it is a "tentative or interlocutory action" which does not constitute a final agency action. *Schering-Plough Healthcare Prods., Inc. v. Schwarz Pharma, Inc.,* 547 F. Supp. 2d 939, 946 (E.D. Wis. 2008) (FDA letters indicating in the opinions of the officials who wrote the letter that the defendants' products were misbranded were not final agency actions); *Clinical Reference Lab., Inc. v. Sullivan*,791 F. Supp. 1499, 1501, 1502-1503 (D. Kan. 1992) (regulatory letters including a letter of warning from the FDA, stating that risk assessment protocol for HIV-1 violated the FD&C Act and demanding a cease of activities was not final agency action, as "[s]uch letters do not bind the agency to the views expressed in them"), *aff'd in part, rev'd in part on other grounds*, 21 F.3d 1026 (10th Cir. 1994); *see also See Mobil Exploration & Producing U.S., Inc. v. Dep't of Interior*, 180 F.3d 1192, 1198 (10th Cir. 1999) (letter from MMS advising that it was conducting a review of a party's valuation of crude oil for royalty purposes and requesting information was not final agency action as it "served only to initiate further proceedings by which the MMS could determine whether the party owed royalties and "was not the consummation of the agency's decisionmaking process"); *Dietary Supplement Coal., Inc. v. Sullivan*, 978 F.2d 560, 563 (9th Cir. 1992) ("regulatory letters do not constitute final agency action"), *cert. denied*, 508 U.S. 906 (1993). Based on the foregoing, I find that Claims One Through Five are not fit for judicial review.

2. Hardship

Even though the Court is persuaded that Claim Six presented by Regenerative is fit for judicial review, Regenerative has failed to demonstrate the required hardship that would result from the Court's withholding consideration of this as well as all of

Regenerative's claims. Courts are clear in holding that "the hardship element of the *Abbott Labs* standard is not met unless a litigant shows that withholding review would result in 'direct and immediate' hardship and would entail more than possible financial loss." *Gordon*, 322 F.3d at 1219; *see also Principal Life Ins. Co. v. Robinson*, 394 F.3d 665, 670 (9th Cir. 2005); *W. Oil & Gas Ass'n v. Sonoma County*, 905 F.2d 1287, 1291 (9th Cir. 1990). The costs to the plaintiff must be significant, or the agency must have taken "concrete action" impairing plaintiff's interest to cause a true hardship. *See Utah v. U.S. Dep't of Interior*, 535 F.3d 1184, 1197-98 (10th Cir. 2008).

Here, Regenerative argues that if it complied with the new regulation, it would experience "tremendous hardship." Analogizing its case to *Abbott Labs*, Regenerative contends that the new regulation forces its medical practice to make the "Hobson's choice between obeying the order or incur the risks of noncompliance," such as the possibility of "warning letter, seizure, injunction, criminal prosecution, and the disqualification of Regenerative's licensed physicians as clinical investigators." It argues that its position is stronger and more urgent than the petitioners in *Abbott Labs* because the parties in *Abbott Labs* had not been advised of any potential violation, whereas Regenerative has already received a warning letter from the FDA on July 28, 2008.

I find Regenerative's reliance on *Abbott Labs* unavailing. In that case, a regulation was promulgated that required manufacturers of prescription drugs to print the 'established name' of the drug 'prominently...for any proprietary name or designation for such drug,' on labels and other printed material. *Abbott Labs*, 387 U.S. at 138. A group of drug manufacturers challenged this regulation and the Supreme Court granted pre-enforcement review based on the finding that the impact was "sufficiently direct and

immediate." *Id.* at 139, 152. However, the Court also qualified the scope of the review to regulations that were "clear-cut" and "made effective immediately upon publication." *Id.* at 152. This is not the case here. The new regulation, as the FDA explains, encompasses a tiered, risk-based framework that regulate a variety of HCT/Ps. Depending on how the HCT/Ps are characterized, they can either fall in or out of the ambit of the new regulation. Here, the issues disputed are precisely whether the MSCs used in Regenerative's Regenexx procedure are intended for non-homologous uses and therefore subject to the regulation. Even the FDA concedes that the determination of which regulations and statutes should govern Regenerative's use of HCT/Ps is uncertain at this juncture. Therefore, the regulation as it applies to Regenerative's use of HCT/PS is far from "clear-cut" and *Abbott Labs* is inapposite.

Secondly, as FDA correctly noted, the July 28, 2008 letter has had no immediate impact on Regenerative. The letter on its face only concludes that Regenerative "appear" to violate the PHS Act and "may" result in FDA seeking relief as provided by law, but it does not compel Regenerative to change its conduct. Indeed, FDA was only beginning its investigation into whether there was a violation of the PHS Act when this lawsuit was commenced and the agency's decisionmaking process has not been consummated. Further, while Regenerative asserts that its practice of medicine may be impacted, its argument is conclusory and speculative. Finally, as to Regenerative's argument that it may face seizure, criminal prosecution and public humiliation, the perceived threat of enforcement action is felt no more strongly by Regenerative than by any other entity anticipating a disagreement with FDA over whether or how its activities should be regulated. The fact remains that Regenerative has not shown any specific

concrete action taken by the FDA that has harmed it or any specific losses it has suffered as a result of FDA action. Therefore, the Court concludes that Regenerative's risk of future FDA enforcement actions is too speculative to warrant judicial intervention and it has failed to demonstrate hardship.

Because Regenerative did not meet its burden on the hardship prong, the Court need not decide whether the resolution of Regenerative's claims will promote effective enforcement and administration of the FDA. I also need not consider Defendant's argument that Plaintiff improperly pled subject matter jurisdiction.

IV. CONCLUSION

In conclusion, after having evaluated the fitness of the claims for judicial review and the hardship to Regenerative of withholding consideration, the Court finds that the claims and issues presented here are not ripe for judicial review and dismissal is appropriate. It is therefore

ORDERED that Defendant's Motion to Dismiss Pursuant to Rules 12(b)(1) and 12(b)(6) of the Federal Rules of Civil Procedure (doc. # 25) is **GRANTED**. It is

FURTHER ORDERED that Plaintiff's Motion for a Stay of Administrative Action Pursuant to 5 U.S.C. § 705 (doc. # 29) is **DENIED AS MOOT**.

Dated: March 26, 2010

BY THE COURT:

s/ Wiley Y. Daniel
Wiley Y. Daniel
Chief United States District Judge