DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
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Confirmation Copy by First Class Mail

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Re: Docket Number: FDA-2013-P-0076/CP1

Dear Mr. DuVal:

This responds to the petition you filed on January 16, 2013, which is both a petition for stay of action under 21 C.F.R. § 10.35 and a citizen petition under 21 C.F.R. § 10.30 (collectively referred to as "your petitions"). In your petition for stay of action, you request that the Commissioner of Food and Drugs ("Commissioner") suspend finalization and any use of the draft guidance entitled, "The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]" ("Draft 510(k) Program Guidance").[1,2] In your citizen petition, you request that FDA take certain actions listed in your petition related to FDA's administration of the 510(k) program since 2009. We have carefully reviewed your petitions, as well as the comments on the petitions and other information available to the Agency, and for the reasons outlined below, we deny your petitions.

I. Petition for Stay of Action

[1] Your petitions relate to the Draft 510(k) Program Guidance; however, the draft guidance has since been revised and finalized. A copy of the final guidance, "The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]" ("Final 510(k) Program Guidance") is available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm404770.htm

[2] The term "510(k) program" or "510(k) process" refers to the process for submitting and reviewing premarket notifications (i.e., 510(k) submissions). A manufacturer who intends to market a new device (including a modified version of a legally marketed device) intended for human use in the United States, for which a premarket approval application ("PMA") is not required, must submit to FDA a 510(k) submission at least 90 days before introducing the device into interstate commerce, unless the device is exempt for the 510(k) requirements (section 510(k) of the Federal Food, Drug, and Cosmetic Act ("FD&C Act"), 21 U.S.C. § 360(k)). FDA reviews 510(k) submissions to determine whether the device meets the criteria for market clearance (sections 510(k) and (n) of the FD&C Act). This decision is based on a determination of whether the device is substantially equivalent to a legally marketed (predicate) device (section 513(i) of the FD&C Act, 21 U.S.C. § 360c(i)). A device cannot be marketed until FDA clears the device by issuing an order which states that the device is substantially equivalent to its predicate (section 513(f)(1) of the FD&C Act, 21 U.S.C. § 360c(f)(1)).

Your petition for stay of action requests that the Commissioner stay finalization of the Draft 510(k) Program Guidance. Under 21 C.F.R. § 10.35(e), the Commissioner shall grant a stay in any proceeding if all of the following apply:

(1) The petitioner will otherwise suffer irreparable injury.
(2) The petitioner's case is not frivolous and is being pursued in good faith.
(3) The petitioner has demonstrated sound public policy grounds supporting the stay.
(4) The delay resulting from the stay is not outweighed by public health or other public interests.

Your petition for stay of action fails to demonstrate that it meets the above conditions for FDA to grant the petition and stay finalization of the Draft 510(k) Program Guidance.

Further, under 21 C.F.R. § 10.35(e), the Commissioner may grant a stay in any proceeding if a stay is in the public interest and in the interest of justice. As explained further below, we have determined that it is not in the public interest and in the interest of justice to stay finalization of the Draft 510(k) Program Guidance.

In your petition you request a stay of finalization of the Draft 510(k) Program Guidance because you claim that "the administrative practices and definitional interpretations that FDA has put into practice since 2009 in reviewing 510(k)s . . . have dramatically changed the manner in which the 510(k) program operates."[3] You also assert that FDA "ha[s] made such changes without conducting notice and comment rulemaking to effectuate such interpretative changes."[4] Your petition, however, rarely discusses the Draft 510(k) Program Guidance. In the few places in the petition where you discuss the contents of the Draft 510(k) Program Guidance, you claim that the Draft 510(k) Program Guidance narrows the interpretation of intended use to a focus on whether the new device's indication is different, and not whether the indication is a logical extension of the predicate device's intended use, and you believe that FDA's explanation of "different question of safety and effectiveness" with respect to different technological characteristics "appears to be a wholly new standard for the 510(k) program."[5]

Your petition's assertion that FDA has proposed a significantly narrowed interpretation of "new intended use" relative to longstanding interpretation that appears in the K86-3 Guidance is inapt. FDA's approach to evaluating intended use, as described in the Draft 510(k) Program Guidance, is consistent with the "Guidance on the CDRH [Center for Devices and Radiological Health] Premarket Notification Review Program, 510(k) Memorandum K86-3" ("K86-3 Guidance"), issued on June 30, 1986. In both documents, FDA explained that in evaluating intended use, FDA determines whether differences in the indications for use between the new device and the predicate device raise different questions of safety or effectiveness. The K86-3 Guidance explained, "For the purposes of determining whether or not the new device has the same

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[3] DuVal & Associates P.A., Citizen Petition and Petition for Stay of Action (Pet.) at 1.
[4] *Id.* In a comment to the docket for the DuVal & Associates P.A., Citizen Petition and Petition for Stay of Action, Washington Legal Foundation makes a similar assertion claiming that the Draft 510(k) Program Guidance indicates that "FDA has substantially altered its interpretation of the statute" and therefore, the Draft 510(k) Program Guidance "cannot be adopted unless FDA first complies with the APA's [Administrative Procedure Act] formal notice-and-comment procedures." Washington Legal Foundation (WLF) Comment at 19.
[5] Pet. at 25, 37.

intended use as a predicate device, the Center assesses any difference in label indications in terms of the safety and effectiveness questions they may raise."[6] The K86-3 Guidance also explained "as long as these label indications do not introduce questions about safety or effectiveness different from those that were posed by the predicate device's intended use, the new device may be found SE [substantially equivalent]."[7]

The Draft 510(k) Program Guidance explained, "Not every change in indications for use that may affect safety or effectiveness will result in a finding of a new intended use. Only a change in the indications for use that raises different questions of safety and effectiveness and precludes a meaningful comparison with the predicate device constitutes a new intended use."[8]

Further, the Draft 510(k) Program Guidance did not provide "a wholly new standard" for "different question of safety and effectiveness" with respect to different technological characteristics but merely clarified and elaborated on a factor presented in the K86-3 Guidance. Although the K86-3 Guidance specified that one of the factors affecting whether a new device with technological differences compared to the predicate may be not substantially equivalent (NSE) is whether "the new device poses the same type of questions about safety or effectiveness as a predicate device," the K86-3 Guidance did not clearly explain this factor.[9] To address this lack of clarity, the Draft 510(k) Program Guidance explained that a "different question of safety or effectiveness" is "a question raised by the technological characteristics of the new device that was not applicable in the 510(k) for the predicate device and poses an important safety or effectiveness concern for the new device."[10] Because comments suggest the need for additional clarity regarding this explanation, in the final guidance on "The 510(k) Program: Evaluating

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[6] K86-3 Guidance at 3.

[7] *Id.* The question in the K86-3 Guidance's Flowchart – whether the differences in indication "alter the intended therapeutic/diagnostic/etc. effect" – was meant to guide reviewers and industry in assessing whether the differences in indication raise different questions of safety or effectiveness.

[8] Draft 510(k) Program Guidance at 15. FDA further explained, "FDA may find changes in indications for use of a device to constitute a new intended use when the changes raise a safety or effectiveness issue that was not raised by the predicate device or when the changes have the potential to significantly increase a safety or effectiveness concern raised by the predicate device. In the first case, reliance on a predicate device is inadequate because the safety or effectiveness issue was not considered in reviewing the 510(k) for the predicate device. In the second case, although the safety or effectiveness issue may have been considered in the 510(k) for the predicate device, the finding of substantial equivalence for the predicate device cannot be generalized to the new indications for use because of a probable, significant change in the incidence or severity of the issue." *Id.* at 15. In its comment, WLF claims the Draft 510(k) Program Guidance "asserts emphatically that a proposed device creates a new intended use if it raises 'a safety or effectiveness issue' that was 'not considered in reviewing the 510(k) for the predicate device'" and that this "assertion . . . differs sharply from FDA's prior position." WLF Comment at 12. While FDA acknowledges that this explanation regarding new intended use has not been expressly provided in guidance before, this explanation does not represent a departure from a prior position. FDA believes its approach to evaluating intended use is appropriate and necessary to preserve the integrity of the 510(k) program, which, as explained in the Draft and Final 510(k) Program Guidances, is a classification program intended to classify devices according to risk by means of comparison to a predicate device.

[9] K86-3 Guidance at 4. *See* FDA, CDRH Preliminary Internal Evaluation -- Volume 1, at 52 (stating that the K86-3 Guidance does not fully articulate a clear standard that may be applied consistently by reviewers and managers in determining which "technological characteristics" to consider in their decision making, and how to determine whether such characteristics raise "different questions of safety and effectiveness."), available at http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/UCM220784.pdf.

[10] Draft 510(k) Program Guidance at 18.

Substantial Equivalence in Premarket Notifications [510(k)]" ("Final 510(k) Program Guidance"), FDA more clearly explains that a "different question of safety or effectiveness" is "a question raised by the technological characteristics of the new device that was not applicable to the predicate device, and poses a significant safety or effectiveness concern for the new device."[11] Regardless, FDA did not intend to change through the Draft 510(k) Program Guidance the standard for evaluating whether there is a "different question of safety and effectiveness" with respect to different technological characteristics, but to provide greater clarity by clearly articulating the appropriate standard.

Importantly, the Draft 510(k) Program Guidance maintained the factors provided in the K86-3 Guidance for purposes of determining whether technological changes are "consequential." Specifically, the K86-3 Guidance explained that CDRH "finds devices with new technological features to be NSE when the new feature could adversely affect safety or effectiveness in a way that is consequential under the conditions of intended use" and identified the following factors to determine whether the technological change is "consequential": whether "the new device poses the same type of questions about safety or effectiveness as a predicate device; there are accepted scientific methods for evaluating whether safety or effectiveness has been adversely affected as a result of the use of new technological characteristics; and there are data to demonstrate that new technological characteristics have not diminished safety or effectiveness."[12] These factors were captured in the Proposed 510(k) Decision-Making Flowchart provided in the Draft 510(k) Program Guidance. Specifically, the first factor was captured in Decision Point 4 (whether the new device raises different questions of safety and effectiveness relative to the predicate is another way of asking whether the new device poses the same type of questions about safety and effectiveness as the predicate device) and the other two factors were captured in Decision Points 5a ("Are the methods acceptable?") and 5b ("Do the data demonstrate equivalence and support the indications?") of the Flowchart in the Draft 510(k) Program Guidance.[13]

Additionally, contrary to your contention that the Draft 510(k) Program Guidance "require[s] that the manufacturer identify a 'clear purpose' for each aspect of device,"[14] FDA is not requiring that the manufacturer declare a clear purpose for each aspect of the device, but recommending that certain information be provided to help FDA better understand the device and the safety and effectiveness issues that may be raised by its technological characteristics relative to the predicate device, which may in turn help to reduce requests for additional information.[15] As noted in the Draft 510(k) Program Guidance, guidances "do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited."[16] Further, FDA's intent in describing the steps in reviewing the

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[11] Final 510(k) Program Guidance at 20.
[12] K86-3 Guidance at 4-5.
[13] Draft 510(k) Program Guidance at Appendix A.
[14] Pet. at 36.
[15] The discussion regarding the clear purpose for each aspect of the new device has been revised in the Final 510(k) Program Guidance. *See* Final 510(k) Program Guidance at 19.
[16] Draft 510(k) Program Guidance at 1. *See also* section 701(h)(1)(A) of the FD&C Act (guidance documents "shall not create or confer any rights for or on any person"), 21 U.S.C. § 371(h), and 21 CFR 10.115(d) ("Guidance documents do not establish legally enforceable rights or responsibilities. They do not legally bind the public or FDA.").

technological characteristics was not to "find reasons for more testing and/or reasons to deny an SE determination" as you contend,[17] but to provide transparency and facilitate consistent and efficient 510(k) reviews.

The Draft 510(k) Program Guidance, as it explains, was not intended to implement significant policy changes to the current 510(k) review process but rather to enhance the predictability, consistency, and transparency of the 510(k) program by describing in greater detail the regulatory framework, policies, and practices underlying FDA's 510(k) review,[18] initially set forth in the K86-3 Guidance published over 27 years ago. In addition to providing greater detail, the Draft 510(k) Program Guidance also updated certain terminology set out in amendments to the Federal Food, Drug, and Cosmetic Act ("FD&C Act") subsequent to the issuance of the K86-3 Guidance.[19] The Draft and Final 510(k) Program Guidances do not represent significant shifts in policy or existing interpretations and are not intended to result in major changes in review outcomes but, instead, are intended to improve the consistency of the 510(k) program by interpreting or explaining certain concepts not clearly articulated in the K86-3 Guidance.

You allege that FDA has made "changes without conducting notice and comment rulemaking to effectuate such interpretive changes."[20] As mentioned above, while the Draft 510(k) Program Guidance includes interpretations of certain concepts that were not clearly articulated in the K86-3 Guidance, it did not significantly change existing interpretations. Therefore, *Paralyzed Veterans of America v. D.C. Arena, L.P.*, 117 F.3d 579 (D.C. Cir. 1997) and similar cases do not apply. FDA properly issued the Draft 510(k) Program Guidance without conducting notice-and-comment rulemaking.

Moreover, FDA followed the process provided by Congress in section 701(h) of the FD&C Act, 21 U.S.C. § 371(h), and as implemented through regulation in 21 C.F.R. § 10.115, in providing guidance on the Agency's 510(k) program. Therefore, the Draft 510(k) Program Guidance was properly issued in accordance with applicable laws and regulations. Additionally, under 21 C.F.R. § 10.115(k), FDA reviews its existing guidance documents to determine whether they need to be changed or withdrawn. As previously mentioned, the K86-3 Guidance was published over 27 years ago. Following a preliminary internal evaluation of the 510(k) program, in 2010 FDA determined that greater clarity regarding certain aspects of the 510(k) review was needed (the preliminary internal evaluation is discussed further below in the response to your citizen petition).[21] As part of this effort and in accordance with 21 C.F.R. § 10.115(k), FDA determined that it was appropriate and also in the public interest to update the K86-3 Guidance to improve the transparency, consistency, and predictability of the 510(k) program.

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[17] Pet. at 36.
[18] Draft 510(k) Program Guidance at 1.
[19] *Id.* at 9. The Safe Medical Devices Act of 1990 (Pub. L. No. 101-629) added section 513(i) to the FD&C Act, which codified FDA's review practice and policies in applying the "substantial equivalence" review standard.
[20] Pet. at 1. In its comment, WLF also claims that "the New 510(k) Guidance is a 'legislative' rule and cannot be adopted unless FDA first complies with the APA's notice-and-comment procedures." WLF Comment at 19.
[21] FDA, Plan of Action for Implementation of 510(k) and Science Recommendations, available at http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/UCM239450.pdf.

In conclusion, FDA has determined that you have not established that staying the finalization of the Draft 510(k) Program Guidance is warranted under 21 C.F.R. § 10.35(e). As explained above, FDA believes that finalizing the Draft 510(k) Program Guidance is in the public interest to enhance the predictability, consistency, and transparency of the 510(k) program. Further, the Draft 510(k) Program Guidance did not significantly change existing interpretations and was appropriately issued under section 701(h) of the FD&C Act and FDA's good guidance practices regulation in 21 C.F.R. § 10.115. For the reasons discussed above, FDA is denying your request to stay finalization of the Draft 510(k) Program Guidance.

II. Citizen Petition

This responds to your citizen petition, which requests four discrete actions and contains a number of unsupported allegations related to FDA's administration of the 510(k) program since 2009. The requested actions, and FDA's response to each request, are discussed in greater detail below. For the reasons explained below, FDA is denying your citizen petition.

1. First Request: Honor and Apply Pre-2009 Definitions of the 510(k) Program

Your petition requests that FDA "honor and faithfully apply pre-2009 definitions of the 510(k) program with past 510(k) guidance documents unless and until newer guidance documents can be more carefully vetted by the public at large."[22] In particular, the petition lists five guidance documents and a report which you request that FDA should return to using and not abandon. These documents are:

a. "Guidance for Industry: General/Specific Intended Use, issued on November 4, 1998;"
b. "Guidance on the CDRH Premarket Notification Review Program 6/30/86 (K86-3);"
c. "Deciding When to Submit a 510(k) for a Change to an Existing Device (K97-1);"
d. "The New 510(k) Paradigm Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications – Final Guidance";
e. "Report: Review of the Regen Menaflex®: Departures From Processes, Procedures, And Practices Leave The Basis For A Review Decision In Question, Preliminary Report, September 2009" (insofar as it prohibits FDA from using "clinical utility/benefit" as a criterion for a SE determination);" and
f. "The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles; Final Guidance for FDA and Industry" and other associated Least Burdensome guidance documents.[23]

Four of these guidance documents (items a, c, d, and f from the list above) reflect FDA's current thinking and remain fully in effect.[24] Initially, the Draft 510(k) Program Guidance was intended to supersede the K86-3 Guidance and The New 510(k) Paradigm – Alternate Approaches to

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[22] Pet. at 11.
[23] *Id.*
[24] Regarding item f from the list above, FDA notes that the other least burdensome guidance document that remains fully in effect is the guidance on "Suggested Format for Developing and Responding to Deficiencies in Accordance with the Least Burdensome Provisions of FDAMA" (Nov. 2000), available at http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm073679.htm.

Demonstrating Substantial Equivalence in Premarket Notifications ("New 510(k) Paradigm Guidance"); however, the Final 510(k) Program Guidance only supersedes the K86-3 Guidance. As explained in the response to your petition for stay above, the Draft 510(k) Program Guidance did not represent a significant change in existing interpretations and it was in the public interest to update and replace the K86-3 Guidance. Therefore, FDA is denying your request to reinstate the K86-3 Guidance. FDA intends to address Special and Abbreviated 510(k)s in a separate guidance and until that guidance is issued, the recommendations on these types of submissions in the existing New 510(k) Paradigm Guidance remain in effect.

To the extent that you are alleging in your request above that opportunity for public input was not provided for the Draft 510(k) Program Guidance, this allegation is without merit. FDA issued the Draft 510(k) Program Guidance in accordance with the FD&C Act and its implementing regulations, which generally require that FDA issue a draft guidance for public comment.[25] FDA announced the availability of the Draft 510(k) Program Guidance for public comment in the *Federal Register* on December 28, 2011.[26] Although the typical comment period for a draft guidance is 90 days, the comment period for the Draft 510(k) Program Guidance, which began on December 28, 2011 and ended on April 26, 2012, was 120 days. FDA received many comments on the Draft 510(k) Program Guidance and carefully reviewed them before finalizing the guidance. Your petitions, as well as the comments on the petitions, were also considered as comments on the Draft 510(k) Program Guidance and were included in this review. Therefore, the issuance of the Draft 510(k) Program Guidance complied with all applicable laws and regulations, and the Agency provided ample opportunity for meaningful public comment.

You also request that FDA follow the report entitled, "Review of the ReGen Menaflex®: Departures from Processes, Procedures, and Practices Leave the Basis for a Review Decision in Question" ("ReGen Report") (Sep. 2009) "(insofar as it prohibits FDA from using 'clinical utility/benefit' as a criterion for a SE [substantial equivalence] determination)." We note that this document is a report that contains findings and recommendations concerning FDA's review and clearance of a specific device, ReGen Biologics, Inc.'s Collagen Scaffold (CS) device for meniscal repair (also referred to as the Menaflex®). Therefore, this document is not a guidance, and does not contain recommendations to industry and FDA staff typically provided in a guidance.

Furthermore, you allege that since 2009 FDA has "essentially rewritten the 510(k) program" through "a collection of definitional interpretations and administrative practices" which you specify in section II.B. of your petition.[27] Your allegations regarding the 510(k) program, as specified in section II.B of your petition, are addressed below. In addition to your allegations regarding the 510(k) program, you also allege that "FDA does not seem to understand, or misapplies, the standard for a *de novo* review."[28] You did not provide any facts to support this allegation, with which FDA disagrees. As you may be aware, the Food and Drug Administration Safety and Innovation Act (FDASIA), which was enacted on July 9, 2012, amended, among

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[25] See section 701(h) of the FD&C Act; 21 C.F.R. § 10.115.
[26] 76 FR 81510.
[27] Pet. at 12-13.
[28] *Id.* at 12, 19.

other sections, the *de novo* provision in section 513(f) of the FD&C Act.[29] FDA is currently working on a new draft *de novo* guidance, on which you and others will have an opportunity to provide comments, in accordance with 21 C.F.R. § 10.115, when the draft guidance is published.

You also allege that FDA is "diverting as many 510(k) applications as possible to the *de novo* path" and that *de novo* "is becoming a substitute for 510(k) review."[30] You did not provide any facts to support this allegation, but we note that FDASIA streamlined the process for review of *de novo* applications, facilitating use of this pathway by novel low-to-moderate risk devices. Nonetheless, *de novo* submissions remain relatively rare. While FDA typically receives 3,000 to 4,000 510(k) submissions annually, the Agency received only about 15 *de novo* submissions per year between 2004 and 2011 and 46 in 2013, the first full year for which we have data following enactment of FDASIA.

With respect to the 510(k) program, you allege that FDA is "unilaterally amend[ing] the statutory standards for the 510(k) program" by allowing review staff "to inappropriately consider statutes and regulatory matters extraneous to the SE decision."[31] FDA disagrees with this allegation. You provide a couple of isolated examples without any references for the FDA to determine their accuracy. Regardless, they do not support your allegation that the Agency has a policy or practice that amends the 510(k) program. There is no Agency policy or practice allowing review staff to "inappropriately consider statutes and regulatory matters extraneous to the SE decision," and there is nothing in the Draft or Final 510(k) Program Guidance that supports your allegation. FDA's 510(k) program reflects the statutory framework and the Agency's implementation of that framework through regulation, guidance, and administrative practice. To the extent that a sponsor has questions or concerns about the review of a particular submission, the sponsor should contact the appropriate CDRH review division/branch for clarification or resolution. Your allegation that "past reviewer whistleblowing . . . makes many in management reluctant to overturn reviewers" is without merit and contradicted by your claim that "not infrequently management overturns [the decision of the review staff]."[32]

You also allege that FDA is allowing review staff "to inappropriately consider clinical utility/benefit and, in the case of in vitro diagnostics, clinical truth and operational truth, as part of the SE criteria."[33] FDA disagrees with this allegation. You refer to the 2009 ReGen Report as support for your allegation but as discussed above, the ReGen Report, which is focused on a specific device that was ultimately found NSE, is not guidance. Further, if you are claiming that the ReGen Report says that FDA cannot consider clinical utility/benefit as part of a substantial equivalence evaluation, that is not what the Report says. The Report discusses the possibility of considering clinical benefit in the context of a 510(k) review when comparing the risks and benefits of the new device to the predicate device.[34] FDA notes that it has issued a draft guidance that displayed on July 14, 2014, which discusses when it is appropriate to consider

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[29] Pub. L. No. 112-144, 126 Stat. 1054.
[30] Pet. at 18.
[31] *Id.* at 13, 29-33.
[32] *Id.* at 13, 17, 49-51.
[33] *Id.* at 12, 27-29.
[34] ReGen Report at 15-16.

risks and benefits as part of a substantial equivalence evaluation.[35] You and others have an opportunity to provide comments on the draft guidance, in accordance with 21 C.F.R. § 10.115.

Further, FDA disagrees with your allegation that the Agency is "[d]ictating and being prescriptive about the non-clinical and clinical performance data that must be generated by an applicant, instead of reviewing at face value the data that are submitted to determine if it supports a SE decision," as well as your allegation that FDA "ignores its own Least Burdensome guidance documents."[36] FDA does review the data submitted in a 510(k) for a device that is eligible for 510(k) review but may request additional data if the data submitted are insufficient to support a substantial equivalence determination. FDA's process for requesting data is consistent with the least burdensome provision in section 513(i)(1)(D) of the FD&C Act and the principles discussed in the guidance, "The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles."[37] As explained above, this guidance as well as the guidance on "Suggested Format for Developing and Responding to Deficiencies in Accordance with the Least Burdensome Provisions of FDAMA" remain fully in effect.[38]

FDA's process for requesting performance data, including clinical performance data, is described in greater detail in the Draft and Final 510(k) Program Guidances. Specifically, as described in the Draft and Final 510(k) Program Guidances, FDA's data requests typically follow a stepwise analytical process to ensure the information requested reflects the least burdensome approach to establishing substantial equivalence.[39] First, FDA considers whether descriptive information about the technological characteristics, such as the materials, design, and specifications, of the new device is sufficient.[40] When this information is not sufficient to support a substantial equivalence determination, FDA then considers whether non-clinical performance testing data would be sufficient. Non-clinical animal and/or biocompatibility studies are typically requested when other forms of non-clinical bench performance testing are not sufficient to demonstrate substantial equivalence. When non-clinical performance testing data are insufficient, or available scientific methods are not acceptable (e.g., they are not clinically validated or supported by a valid scientific rationale), FDA may request clinical performance data to support a substantial equivalence determination. For 510(k)s reviewed in the Office of Device Evaluation, FDA currently requests clinical data for less than 10 percent of the 510(k) submissions. Clinical data provided in support of any marketing application, including a 510(k) when those data are relevant to a substantial equivalence determination, should constitute valid

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[35] Available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm404770.htm.

[36] Pet. at 13, 40-49.

[37] Available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm085994.htm.

[38] Available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073679.htm. In your petition, you also refer to the draft guidance entitled, "Evidence Models for the Least Burdensome Means to Market" (Sep. 1999), and indicate that FDA should "revitalize" the use of this draft guidance and "apply [it] to current device reviews." Pet. at 49. FDA notes that this draft guidance was never finalized, was never in effect, and was eventually withdrawn. 70 FR 824, 890 (Jan. 5, 2005).

[39] Draft 510(k) Program Guidance at 20 (noting that FDA follows the "least burdensome" provisions); Final 510(k) Program Guidance at 22.

[40] Very few 510(k) submissions rely solely on descriptive information about materials, design, specifications, and other technological characteristics.

scientific evidence as defined in 21 C.F.R. § 860.7(c)(2) and must comply with the Investigational Device Exemptions (IDE) regulations in 21 C.F.R. Part 812 as applicable.

Your allegation that FDA is "reinterpreting" general/specific use "so narrowly that FDA now considers almost every new indication for a 510(k) device to be a new intended use" is without merit.[41] In contrast to your unsupported allegation, NSE decisions based on a new intended use are relatively rare.[42] Also, as explained above, FDA's "Guidance for Industry: General/Specific Intended Use," which identifies the general principles the Agency considers in determining when a specific indication for use is reasonably included within a general indication for use of a device for purposes of determining substantial equivalence, remains fully in effect. Further, FDA disagrees with the allegation of inappropriately applying the criteria provided in the guidance on General/Specific Intended Use in the context of the example described in the petition.[43]

FDA also disagrees with your allegation that the Agency is "[m]ore restrictively interpreting when a device has a new technological characteristic and when those technological characteristics raise new questions of safety and effectiveness."[44] As explained further in the response to your petition for stay above, the Draft and Final 510(k) Program Guidances do not overturn key interpretations regarding substantial equivalence but provide more detail concerning existing interpretations, and in some cases, interpret concepts that have not previously been explained in guidance.

The need to update the K86-3 Guidance arose from a process that entailed multiple opportunities for public input. In 2009 FDA undertook a preliminary internal evaluation of the 510(k) program and determined that greater clarity regarding certain aspects of the 510(k) review and other program improvements were needed to enhance the predictability, consistency, and transparency of the program.[45] FDA issued a report on its preliminary evaluation and solicited input from stakeholders through multiple meetings and the public docket, as discussed further

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[41] Pet. at 12, 20-27. Your allegations regarding the Draft 510(k) Program Guidance with respect to intended use, pet. at 24-25, are addressed in the response to your petition for stay above.

[42] Less than 10 percent of 510(k)s are found NSE and approximately 10 percent of the NSE decisions are due to a new intended use. *See* "Initial Results of 510(k) Audit: Analysis of Not Substantially Equivalent (NSE) Determinations" (June 2011), available at http://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cdrh/cdrhreports/ucm259173.htm.

[43] Pet. at 26-27. Generally, FDA does not disclose the details of 510(k)s that have been found not substantially equivalent.

[44] *Id.* at 13, 33-38. Based on the discussion in your petition, it appears that you are alleging that FDA is finding more devices NSE due to technological differences raising different questions of safety and effectiveness. FDA disagrees. In contrast to your unsupported allegation, although devices reviewed under the 510(k) program commonly have technological differences from their predicate devices, FDA rarely makes a finding of NSE based on technological differences raising different questions of safety and effectiveness, and NSE findings on this basis have not increased in recent years. *See* "Initial Results of 510(k) Audit: Analysis of Not Substantially Equivalent (NSE) Determinations" (June 2011) (less than 10 percent of 510(k)s are found NSE and generally, less than 10 percent of the NSE decisions are due to technological differences raising different questions of safety and effectiveness), available at http://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cdrh/cdrhreports/ucm259173.htm.

[45] FDA, CDRH Preliminary Internal Evaluation -- Volume 1, available at http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/UCM220784.pdf.

below in section II.3.[46] After soliciting input from stakeholders, in January 2011 FDA published a plan of action for improving the 510(k) program and explained that there would be additional opportunity for public input where appropriate.[47] As part of its plan of action, FDA implemented a robust training program for reviewers to help improve the review of, and ensure a more consistent approach to, 510(k) submissions (the training program is discussed further below in section II.2).

In November 2012, FDA reported that since the Agency began implementing its plan of action, there have been improvements in 510(k) review performance.[48] For example, the average time it takes to clear a 510(k) began declining for the first time since 2005, and the backlog of 510(k)s pending for more than 90 FDA days dropped significantly.[49] Additionally, FDA reported that without lowering the bar for clearance, the percentage of submitted 510(k)s that were cleared has increased since 2010.[50] These results would not be expected if the changes you allege in your citizen petition were in place. FDA expects that improvements to the 510(k) program will continue as the Agency continues to implement its plan of action, including finalization of the 510(k) Program Guidance.

Your petition also challenges a specific review practice and claims that the practice is new.[51] In particular, the petition coins the term "stage-gating" reviews,[52] to refer to FDA's practice of declining to review performance data if it is clear from an initial review of the 510(k) that the new device does not have the same intended use as the predicate device or that the different technological characteristics of the new device raise different questions of safety and effectiveness than the predicate. This practice is not new but longstanding and in fact, predates the K86-3 Guidance, which states: "If it is clear from an initial review that a new device has an intended use or technological feature that makes it NSE, the Center will not review or require performance information in the 510(k). Instead the applicant will be notified that the device is NSE, and any performance data will be reviewed in a PMA [premarket approval application] or reclassification petition."[53] The section of the K86-3 Guidance to which you refer describes the use of performance data in situations where it is "*not* clear from an initial review that the device has an intended use or technological change that makes it NSE" (emphasis added).[54] If it is clear, based typically on descriptive information, that the device does not meet the substantial equivalence standard because it has a new intended use or different technology that raises different questions of safety and effectiveness, then review of the performance data under the substantial equivalence standard is not appropriate. FDA believes this policy is optimal as it

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[46] *Id.*
[47] FDA, Plan of Action for Implementation of 510(k) and Science Recommendations, available at http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/UCM239450.pdf.
[48] FDA, Improvements in Device Review, Results of CDRH's Plan of Action for Premarket Review of Devices (Nov. 2012), available at http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm329008.htm.
[49] *Id.* at 2.
[50] *Id.*
[51] Pet. at 12-13, 16-17, 38-40.
[52] *Id.*
[53] K86-3 Guidance at 6. The K86-3 Guidance did not mention *de novo* because the *de novo* classification process in section 513(f)(2) of the FD&C Act, 21 U.S.C. § 360c(f)(2), was added later by the Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2340.
[54] Pet. at 39 (citing the K86-3 Guidance).

prevents costly and unnecessary review of data when simple factual information shows that the device is not eligible for review under 510(k). For example, if no legally marketed predicate device exists to allow an evaluation of substantial equivalence, reviewing performance data cannot overcome a finding of NSE and doing so may delay constructive communication from FDA that will enable the sponsor to seek an appropriate market pathway.

Further, the petition challenges a recent draft guidance that you allege imposes new "requirements."[55] Specifically, the petition requests that FDA withdraw the draft guidance entitled, "Guidance for Industry and FDA Staff – Total Product Life Cycle: Infusion Pump – Premarket Notification [510(k)] Submissions," because you claim it "impose[s] assurance case requirements on infusion pump manufacturers."[56] Consistent with 21 C.F.R. § 10.115, the draft guidance offers *recommendations* that the information and content of a 510(k) submission, required under 21 C.F.R. Part 807, be structured as an assurance case report.[57] The draft guidance clearly explains, "FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required."[58] FDA also notes that the draft guidance invited comments and suggestions.[59]

In sum, FDA's 510(k) program reflects the statutory framework and the Agency's implementation of that framework through regulation, guidance, and administrative practice. While there have been improvements to the 510(k) program to enhance predictability, consistency, and transparency of 510(k) review, there has not been a significant change to the key interpretations regarding substantial equivalence. To the extent that a sponsor has questions or concerns about the review of a particular submission, FDA encourages the sponsor to contact the appropriate CDRH review division/branch.

2. Second Request: Specific Annual Training Program for FDA Review Staff

Your petition further requests that FDA "ensure there is an effective training annual program for FDA review staff, Branch Chiefs and Division Directors, and the Director of the Office of Device Evaluation, the Office of Chief Counsel and the CDRH Ombudsman, conducted by the Food and Drug Law Institute [FDLI], with participation from AdvaMed [Advanced Medical Technology Association] and the Medical Device Manufacturer's Association (MDMA), that teaches Agency personnel the content of all FDA regulations and guidance documents (in place or in draft form before December 31, 2008) and the content of FDASIA [Food and Drug Administration Safety and Innovation Act]," with special emphasis on Least Burdensome

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[55] Pet. at 31-32.
[56] *Id.* Your assertion in section II.B of your petition that FDA is "[i]nappropriately applying risk mitigation and 'assurance case' principles to the criteria for 510(k) clearance," pet. at 13, appears to relate to this draft guidance.
[57] FDA Draft Guidance, "Guidance for Industry and FDA Staff – Total Product Life Cycle: Infusion Pump – Premarket Notification [510(k)] Submissions" (Apr. 2010), at 9.
[58] *Id.* at 4.
[59] *Id.* at 1.

requirements, and attention to the impact of Agency delays and decision making on innovation and investment in innovation.[60]

Enhancing staff training is one of the action items listed in FDA's Plan of Action for Implementation of 510(k) and Science Recommendations to increase the predictability and transparency of regulatory pathways and to strengthen the 510(k) process.[61] At CDRH, new reviewers complete mandatory training which includes coursework on relevant laws and regulations, writing deficiency communications, and conducting quality reviews. A comprehensive knowledge assessment is given at the completion of the coursework. CDRH "Master Reviewers" [62] also conduct an audit process of beginning reviewers' work to ensure a standardized approach to reviewing medical device submissions. After ten months, a reviewer is required to take the Reviewer Certification Program (Level 1), which comprises 20 subject areas, including the Least Burdensome principles, the 510(k) and PMA programs, and provisions of the Medical Device User Fee Amendments of 2012 (MDUFA III) in FDASIA, Pub. L. No. 112-144, 126 Stat. 1002. The Reviewer Certification Program also provides instruction on the guidance documents that address various premarket submissions, including 510(k), PMA, IDE application, *de novo*, and Humanitarian Device Exemption application.[63]

Part of the training offered to all CDRH staff, and particularly targeted to those involved in premarket review, is the Office of Device Evaluation (ODE) Vendor Day Program. The ODE Vendor Day Program is held 3 to 4 times a year and allows device manufacturers to display and provide to FDA reviewers product demonstrations highlighting the scientific basis for their products.[64] Additionally, FDA has implemented the Experiential Learning Program which allows staff to travel to manufacturing sites, hospitals and clinical sites to gain better understanding of how devices are developed, tested, and used.[65] CDRH has also implemented the Entrepreneurs-in-Residence (EIR) program.[66] This program has brought together world-class entrepreneurs and innovators with CDRH employees to develop solutions in areas that affect innovation. These training opportunities and programs are part of FDA's commitment to foster innovation.[67]

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[60] Pet. at 11-12.

[61] FDA, Plan of Action for Implementation of 510(k) and Science Recommendations, available at http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/UCM239450.pdf.

[62] A master reviewer is a type of peer reviewed regulatory review scientist/engineer at the GS 14/15 level.

[63] There are approximately 1,600 CDRH guidance documents currently in effect, and providing training for premarket review staff on all of the existing guidance documents would not be practical or appropriate. CDRH trains staff on the guidance documents that are applicable to their role in the Center. Accordingly, CDRH provides training for premarket review staff on the key cross-cutting premarket guidance documents.

[64] Information about the ODE Vendor Day Program can be found on FDA's website at http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHOffices/ucm116102.htm.

[65] 78 FR 19711.

[66] Information about the Entrepreneurs-in-Residence program at CDRH can be found on FDA's website at http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHInnovation/InnovationPathway/ucm286138.htm.

[67] FDA recognizes that the United States is a global leader in device innovation and is committed to continuing to foster an environment that will facilitate device innovation without compromising device safety and effectiveness. To support the development of innovative products, CDRH launched its Medical Device Innovation Initiative. Information about the Initiative, including proposals to help facilitate the development and regulatory evaluation of

CDRH has focused close attention on the training of its staff – particularly its review staff – and believes the training programs described in this response will further the goals of consistency and predictability in premarket review, enhance understanding of innovative technologies, and create new opportunities for review staff to understand the perspective of industry. Importantly, these training programs present many opportunities to learn from the perspectives of AdvaMed, MDMA, and other industry groups, as well as directly from member companies. While FDA believes these training opportunities provide valuable learning experiences for review staff, we do not believe mandating new annual training that can only be conducted by FDLI or device industry groups, such as AdvaMed or MDMA, is warranted.

3. Third Request: Institute Bi-Annual Meetings with Newly Constituted Independent Industry Group

You also request that FDA "conduct ongoing bi-annual FDA/industry sessions with an independent industry group, whose members would be equally chosen by AdvaMed, MDMA and LifeScience Alley and whose purpose would be to exchange ideas with CDRH staff on how the 510(k) program is operating and where there are issues and what improvements might be considered (this group would review case studies and apply lessons of the experience that pre-revenue, small and large companies have had going through FDA for clearance)."[68] FDA has already been working with industry and the public to help identify areas where FDA can improve the 510(k) program.

In its review of the 510(k) program, FDA welcomed industry and public input on problems and suggested areas for improvement. The Agency held a public meeting on February 18, 2010 where industry and the public could express their views on the 510(k) program. Prior to the meeting FDA published a notice in the *Federal Register* announcing the meeting and requesting comments on the 510(k) program.[69] In addition, in August 2010, FDA released for public comment the preliminary reports from the 510(k) Working Group and the Task Force on the Utilization of Science in Regulatory Decision Making.[70] FDA reviewed and considered all 55 recommendations filed in response to these documents. FDA also held a number of MDUFA III reauthorization meetings with industry. At one such meeting, on August 9, 2011, AdvaMed, MDMA, and the Medical Imaging and Technology Alliance (MITA) were present when the 510(k) program was the only topic discussed.[71] In addition, CDRH officials actively participated in discussions with the 510(k) Coalition, a stakeholder group which includes industry

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innovative devices, is available at http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHInnovation/ucm2024881.htm.

[68] Pet. at 12.

[69] Strengthening the Center for Devices and Radiological Health's 510(k) Review Process; Public Meeting; Request for Comments, 75 FR 4402 (Jan. 27, 2010).

[70] Center for Devices and Radiological Health 510(k) Working Group Preliminary Report and Recommendations, and Task Force on the Utilization of Science in Regulatory Decision Making Preliminary Report and Recommendations; Availability; Request for Comments, 75 FR 47307 (Aug. 5, 2010).

[71] Minutes for this meeting can be found on FDA's webpage at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceUserFeeandModernizationActMDUFMA/ucm272699.htm.

representatives. On September 16, 2011, FDA held a public meeting to encourage public comment on the recommendations proposed in the Institute of Medicine (IOM) report "Medical Devices and the Public's Health, The FDA 510(k) Clearance Process at 35 Years" which was released in July 2011.[72] Additionally, recognizing the wide public interest in the Draft 510(k) Program Guidance, FDA provided a longer than usual comment period on this draft guidance to ensure that all stakeholders had enough time to provide meaningful comment.[73] FDA received 26 sets of comments from individuals/entities providing more than 400 comments on specific content/aspects of this draft guidance and considered the recommendations provided in the comments as the Agency worked on finalizing the 510(k) Program Guidance. These interactions between the Agency and the public/industry reveal that FDA is in frequent contact with its stakeholders and regularly encourages the exchange of views and ideas.

Additionally, FDA committed to participating with industry in a comprehensive assessment of the process for the review of device applications, including 510(k)s.[74] The comprehensive assessment is to be conducted by an independent consulting firm and the scope of the assessment will include:

- Identification of process improvements and best practices for conducting predictable, efficient, and consistent premarket reviews that meet regulatory review standards;
- Analysis of the elements of the review process, including for 510(k)s, that consume or save time to facilitate a more efficient review process;
- Assessment of FDA methods and controls for collecting and reporting information on premarket review process resource use and performance;
- Assessment of effectiveness of FDA's Reviewer Training Program implementation; and
- Recommendations for ongoing periodic assessments and any additional, more detailed or focused assessments.[75]

FDA intends to incorporate the findings and recommendations from the comprehensive assessment, as appropriate, into its management of the premarket review program, including the 510(k) program.

Therefore, for the reasons discussed above, the Agency does not believe that constituting an additional industry group to have bi-annual discussions with FDA about the 510(k) program is necessary.

4. Fourth Request: Expand Use of Outside Individuals and Entities to Review 510(k)s

Finally, the petition asks that FDA take several actions that would expand the role of individuals and entities outside FDA in the 510(k) review process. In particular, the petition requests that FDA "consider contracting with more experienced part-time reviewers who have past Agency and/or industry experience with filing and/or reviewing 510(k)s" and entrust more reviews of

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[72] 76 FR 50230 (Aug. 12, 2011).
[73] 76 FR 81510 (Dec. 28, 2011).
[74] MDUFA III Commitment Letter at 12-13, available at http://www.fda.gov/downloads/MedicalDevices/NewsEvents/WorkshopsConferences/UCM295454.pdf.
[75] *Id.*

devices to FDA's third party review program regardless of whether they involve clinical data and "establish procedures making it more difficult for Center review staff to overturn recommendations of third party reviewers."[76]

FDA does, occasionally, hire experienced reviewers on a contractual basis to perform review work. These arrangements depend upon the interest of the reviewer and FDA's needs within a given review specialty, and there are certain restrictions that must be considered, e.g., conflict of interest laws.[77]

As for your request that FDA entrust more reviews of devices to FDA's third party review program, under section 523 of the FD&C Act, 21 U.S.C. § 360m, FDA does, subject to certain statutory limits, accredit third parties to review 510(k) submissions and make recommendations to FDA regarding the initial classification of devices under section 513(f)(1) of the FD&C Act, 21 U.S.C. § 360c(f)(1).[78] Specifically, section 523(a)(3)(A) of the FD&C Act states:

> In general- An accredited person may not be used to perform a review of—
> (i) a class III device;
> (ii) a class II device which is intended to be permanently implantable or life sustaining or life supporting; or
> (iii) a class II device which requires clinical data in the report submitted under section 510(k) for the device, except that the number of class II devices to which the Secretary applies this clause for a year, less the number of such reports to which clauses (i) and (ii) apply, may not exceed 6 percent of the number that is equal to the total number of reports submitted to the Secretary under such section for such year less the number of such reports to which such clauses apply for such year.

FDA believes the third party review program provides an important review avenue for devices that are eligible, but is unable to expand the program beyond the limitations set forth in the FD&C Act. Further, section 523 of the FD&C Act requires that FDA make its own determination with respect to the initial classification of a device within 30 days after receiving the recommendation of an accredited third party.[79] Therefore, FDA is denying your request to "establish procedures making it more difficult for Center review staff to overturn recommendations of third party reviewers." However, the Agency believes the third party review program is important and will continue to implement it in accordance with the FD&C Act and its implementing regulations.

III. Conclusion

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[76] Pet. at 12.
[77] *See, e.g.*, 18 U.S.C. §§ 203, 205, 209; 5 C.F.R. Part 2635, Subpart H; 21 C.F.R. § 5501.106(c).
[78] For more information on FDA's Third Party Review Program which implements section 523 of the FD&C Act, see "Implementation of Third Party Programs Under the FDA Modernization Act of 1997; Final Guidance for Staff, Industry, and Third Parties" (Feb. 2001), available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094450.htm; *see also* http://www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/premarketsubmissions/thirdparyreview/default.htm.
[79] Section 523(a)(2)(B) of the FD&C Act.

For the foregoing reasons, FDA is denying your petition for stay of action filed under 21 C.F.R. § 10.35 to stay finalization of the Draft 510(k) Program Guidance, and is denying your citizen petition filed under 21 C.F.R. § 10.30 requesting several actions related to the administration of the 510(k) program.

Sincerely,

Leslie Kux
Assistant Commissioner for Policy