DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

MAR 25 2013

Michael Carome, M.D.
Deputy Director
Public Citizen's Health research Group
1600 20th St. NW
Washington, DC 20009

Re: Citizen Petition Docket Number FDA-2011-P-0923

Dear Dr. Carome:

This letter is in response to your January 28, 2013 letter ("2013 letter") relating to the Food and Drug Administration's (FDA or "agency") response ("citizen petition response"), dated August 8, 2012, to the above referenced citizen petition and FDA's approval of changes to the labeling for the Stryker Corporation's ("Stryker") Wingspan Stent System with Gateway PTA Balloon Catheter ("Wingspan Stent System"). The citizen petition response is attached as Attachment A to this letter and referenced herein. In your 2013 letter, you outline your concerns with FDA's determination not to withdraw the Humanitarian Device Exemption (HDE) approval of the Wingspan Stent System, and FDA's decision to approve revised labeling for the device. You request that FDA reverse its decision and withdraw the HDE approval for this device.

FDA has reviewed your 2013 letter and continues to believe that withdrawal of the Wingspan Stent System HDE approval is not warranted. FDA has provided a discussion of the key points in your 2013 letter below.

I. Background

You submitted a citizen petition (FDA-2011-P-0923), dated December 21, 2011, and filed by FDA on December 22, 2011, and a supplement to this petition, dated January 12, 2012 (citizen petition and supplement, collectively, "petition"). In your petition, you requested that the agency (1) withdraw approval of the HDE for the Wingspan Stent System and (2) order Stryker to initiate a class I recall of all unused Wingspan Stent Systems. On March 23, 2012, FDA held a panel meeting of outside exerts, the Neurological Devices Panel, to seek expert scientific and clinical opinion on the risks and benefits of the Wingspan Stent System based on the available premarket and postmarket data ("Neurological Devices Panel Meeting").

On August 8, 2012, FDA denied your petition because FDA concluded that the information before the agency, including results from the prospective randomized controlled trial sponsored by the National Institutes of Health (NIH)/National Institute of Neurological Disorders and Stroke ("NINDS") *Stenting and Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis* ("SAMMPRIS"), did not constitute a basis for withdrawing the HDE approval or for ordering a Class I recall of the Wingspan Stent System. As discussed in the citizen petition response,[1] FDA believes that

[1] Citizen petition response, at 9-10.

the agency's actions addressed some of the underlying concerns in your petition. Specifically, on August 8, 2012, FDA approved Stryker's supplement to the Wingspan Stent System ("HDE supplement"). The approved changes include a revised Indications for Use ("revised indication"), new contraindications and warnings, and additional information in the clinical experience section of the Directions for Use. FDA also approved revised patient labeling that more clearly describes the risks of the device. In addition, the approved HDE supplement includes a new physicians' training program on the revised indication, the contraindications and warnings, and instructions for physicians on the selection of appropriate patients and on the technical aspects of successful device delivery and deployment. Finally, FDA ordered Stryker to conduct a postmarket surveillance study under section 522 of the FD&C Act. These changes are outlined in a FDA Safety Communication: Narrowed Indications for Use for the Stryker Wingspan Stent System, available at http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm314600.htm ("safety communication").

II. Discussion

1. *FDA's approval for a revised Indications for Use for the Wingspan Stent System*

FDA approval of an HDE application authorizes marketing of a humanitarian use device that is intended to benefit patients by treating or diagnosing a disease or condition that affects fewer than 4,000 individuals in the United States per year, subject to certain profit and use restrictions, under section 520(m) of the Federal Food, Drug, and Cosmetic Act ("FD&C Act") and implementing regulations at 21 CFR part 814 subpart H. An HDE is exempt from the effectiveness requirements of sections 514 and 515 of the FD&C Act, provided that the agency makes certain findings about the device.[2] FDA's approval of an HDE is based, among other things, on FDA's determination that the device will not expose patients to an unreasonable or significant risk of illness or injury, and that the probable benefit to health from the use of the device outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment.[3] In addition, the agency must determine that no comparable devices are available to treat or diagnose the disease or condition, and that the device would not be available to patients with the disease or condition unless the agency approves the HDE.[4]

As stated in FDA's approval letter and discussed in the citizen petition response, FDA approved the HDE application for the Wingspan Stent System on August 3, 2005, with the indications for use "in improving cerebral artery lumen diameter in patients with intracranial atherosclerotic disease, refractory to medical therapy, in intracranial vessels with ≥50% stenosis that are accessible to the system."[5] FDA's approval was based on FDA's review of the data from bench and animal testing, and on a clinical trial ("HDE study") provided in the Wingspan Stent System HDE application.[6] The HDE study was a prospective, single arm open label study of 45 subjects conducted at 12 international sites. The subjects were eligible for inclusion if they had evidence of recurrent stroke thought to be secondary to 50% or

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[2] Section 520(m)(2) of the FD&C Act.
[3] Section 520(m)(2)(C) of the FD&C Act.
[4] Section 520(m)(2)(B) of the FD&C Act.
[5] *See* Wingspan Stent System HDE approval letter, dated August 3, 2005, *available at* http://www.accessdata.fda.gov/cdrh_docs/pdf5/h050001a.pdf. *See also,* citizen petition response, at 3-6.
[6] For a more detailed discussion of these preclinical and clinical studies, see the citizen petition response, at 3-6.

greater intracranial stenosis, and refractory to medical therapy (e.g., anti-clotting agents such as warfarin and/or anti-platelet agents). The most recent stroke must have occurred 7 days or longer prior to enrollment. Of the 45 subjects enrolled, 44 were treated with the Wingspan Stent System and were considered evaluable subjects. The primary safety endpoint was composite ipsilateral stroke and/or death at 30 days. Procedure success was defined as stent success without stroke or death at discharge, and safety was evaluated by the incidence of adverse events at discharge, 30-day follow-up, and 6-month follow-up.

The results of the HDE study indicated that the Gateway PTA Balloon Catheter could be inflated safely to dilate the lesion, and that the stent could be deployed safely across the target lesion (44/45 lesions, 97.8% accessed). The primary outcome measure, ipsilateral stroke and/or death within 30 days of treatment, occurred in 4.5% of subjects (2 events in 44 treated subjects), which was a favorable outcome compared to an estimated risk of over 20% in patients without intervention. This latter estimate was based on the available published reports at the time of the HDE study[7]

FDA determined that the probable benefit for the population studied in the HDE study was an "increase in diameter of atherosclerotic arteries."[8] In addition, the type and frequency of observed adverse events, including stroke, for the indicated population were consistent with or lower than similar neurovascular procedures. Based on a review of this data, the agency concluded that the device "will not expose patients to an unreasonable or significant risk of illness or injury, and the probable benefit to health from using the [Wingspan Stent System] for improving cerebral artery lumen diameter in patients with intracranial atherosclerotic disease, refractory to medical therapy, in intracranial vessels with ≥50% stenosis that are accessible to the [Wingspan Stent System] outweighs the risk of illness or injury."[9]

As discussed in the citizen petition response,[10] the subpopulation in the SAMMPRIS study most comparable to that in the HDE study – subjects who had recurrent stroke (2 or more) despite being on medical therapy and whose most recent stroke was more than 7 days prior to stenting - was a relatively small subgroup of only 33 subjects out of the full SAMMPRIS population of 451 subjects. Further, only 16 of these 33 subjects had stenting. As indicated in the post-hoc table you provided in your 2013 letter, the comparison between the medical and stenting arms for this subgroup (12.2%/12.5%) suggests that outcomes were similar, i.e. that there was no additional risk of stroke or death for those implanted with the stent. However, this analysis of a sample of 16 vs. 17 was not a pre-specified analysis and therefore FDA considers it exploratory, and the results are not statistically confirmatory. In addition, the small size of this sample results in a very wide confidence interval, from which FDA cannot conclude that the result in the 16-subject subgroup is worse than the results seen in the HDE study. The discussion regarding the analysis of this limited data was included in the citizen petition response to explain that the results of the SAMMPRIS analysis were not considered by FDA to be adequate to refute the results of the HDE study because the SAMMPRIS study was neither intended nor powered to detect differences between the medical therapy and the stenting arms for this subpopulation. This is consistent with the

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[7] Thijs VN, Albers GW. Symptomatic intracranial atherosclerosis: outcome of patients who fail antithrombotic therapy. Neurology 2000;55(4):490-497. *See also* Prognosis of patients with symptomatic vertebral or basilar artery stenosis. The Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) Study Group. Stroke 1998;29(7):1389-1392; Chimowitz MI, Kokkinos J, Strong J et al. The Warfarin-Aspirin Symptomatic Intracranial Disease Study. Neurology 1995;45(8):1488-1493.

[8] Wingspan Stent System "Summary of Safety and Probable Benefit," *available at* http://www.accessdata.fda.gov/cdrh_docs/pdf5/H050001b.pdf, at 13.

[9] Id. at 13.

[10] Citizen petition response, at 7-8.

FDA's approach to these types of analyses that are not pre-specified and for which the studies are not adequately powered.

On the other hand, although the HDE study did not have a concurrent comparator, the 30 day stroke rate in the HDE study was very low in comparison to the rate of stroke expected in this subpopulation for whom therapeutic options had been exhausted. FDA therefore considers the HDE study adequate to support that there is a probable benefit for the specific population in the revised indication, which more strictly limits the Wingspan Stent System to the subpopulation of patients included in the HDE study.

As discussed in the citizen petition response,[11] the data from the SAMMPRIS study did inform the agency of important information about the use of the Wingspan Stent System, which has been incorporated into the revised indication. In addition, the revised labeling specifically contraindicates use of the Wingspan Stent System in those circumstances in which the SAMMPRIS data suggested unreasonable risk, i.e. treatment of a transient ischemic attack and treatment of stroke with an onset of symptoms within 7 days or less of treatment. FDA also reviewed a subgroup analysis of the Comparison of Warfarin and Aspirin for Symptomatic Intracranial Stenosis (WASID) study, which showed that the risk of a stroke was highest in those with 70-99% stenosis as compared to those with less than 70% stenosis (which was the basis for selecting a population with a degree of stenosis of 70%-99% in the SAMMPRIS study),[12] and concluded that the probable benefit to risk comparison is most favorable when use of the Wingspan Stent System is limited to those with 70% or greater stenosis. The revised indication for the Wingspan Stent System was therefore further restricted to this group. Finally, in reviewing the data from the SAMMPRIS study, FDA concluded that enhanced physician training would help mitigate the short term risk of stroke or death due to the procedure with the device. The revised labeling for the Wingspan Stent System therefore includes a training program for practitioners.[13]

On August 8, 2012, FDA approved the HDE supplement for the Wingspan Stent System after making the determination, based on a review of all available information before the agency, including the HDE study, and subsequent data from published postmarket studies, including the SAMMPRIS study, that the Wingspan Stent System will not expose the indicated patients to an unreasonable or significant risk of illness or injury and that the probable benefit to health from using the Wingspan Stent System outweighs the risk of illness or injury, when taking into account the probable risks and benefits of currently available alternative forms of treatment for this narrowed subpopulation. The Wingspan Stent System's revised indication is limited to:

> improving cerebral artery lumen diameter in patients 22 to 80 years old with recurrent (2 or more) strokes refractory to a comprehensive regimen of medical therapy and due to atherosclerotic disease of intracranial vessels with 70-99% stenosis that are accessible to the system. The most recent stroke must have occurred more than 7 days prior to treatment with the Wingspan Stent System. Patients are eligible for treatment with the Wingspan Stent System if their Modified Rankin Score (mRS) is 3 or less at the time of treatment.[14]

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[11] See the citizen petition response, at 8.

[12] Kasner SE, Chimowitz MI, Lynn MJ et al. Predictors of ischemic stroke in the territory of a symptomatic intracranial arterial stenosis. Circulation 2006;113(4):555-563.

[13] See the Wingspan Stent System Directions for Use, *available at* http://www.stryker.com/stellent/groups/public/documents/adacct/148220.pdf, at 5,

[14] See the Wingspan Stent System Directions for Use, *available at* http://www.stryker.com/stellent/groups/public/documents/adacct/148220.pdf, at 2. The approved revised labeling also

You contend in your 2013 letter that many of the subjects enrolled in the in the SAMMPRIS study share one or more characteristics required under the revised indication, and therefore the SAMMPRIS study results are "generalizable to patients covered under that indication." However, patients eligible for use of the Wingspan Stent System under the revised indication must have had two or more strokes despite a comprehensive regimen of medical therapy and therefore are not, as you have suggested, comparable to most of the subjects in the SAMMPRIS trial. There is currently no other approved treatment for use in this subpopulation of patients.

In addition, you provide a table of post-hoc subgroup analyses in your 2013 letter, which you believe demonstrates that for each of the criteria that FDA has chosen to use to narrow the indication for the Wingspan Stent System, the trend is toward greater risk of stroke or mortality for the stenting group. These analyses are a subset of the exploratory analyses conducted by FDA and presented at the Neurological Devices Panel Meeting. In those and other subgroup analyses, FDA identified a number of baseline patient characteristics such as the degree of stenosis, time from stroke symptom onset and the type of ischemic event which, taken alone or in various combinations, appeared to have been associated with a higher 30 day risk of stroke or death with aggressive medical management and intracranial stenting compared to aggressive medical management alone. This analysis suggests that the overall risks reported in SAMMPRIS are not equally applicable to all patient subgroups. The results of those subgroup analyses of the SAMMPRIS data strongly indicate that the risk of the intracranial stenting procedure was incrementally reduced as the population was restricted to the population in the HDE study, including those (i) who had failed medical management, (ii) whose qualifying event was a stroke as opposed to a transient ischemic attack, and (iii) who had a history of stroke prior to a qualifying stroke. In addition, the data also indicates that there was a significant reduction in risk when the procedure was performed following an interval of more than 7 days after the qualifying stroke. The approved HDE supplement requires patients to meet all the criteria in the revised indication, not individual criteria as you suggest. As stated above, the comparison between the medical and stenting arms for this subgroup suggests that outcomes were similar (12.2%/12.5%). However, this analysis of a sample of 16 vs. 17 was not a pre-specified analysis and therefore FDA considers it exploratory, and the results are not statistically confirmatory.

2. *FDA Safety Communication*

Your letter expressed concern that FDA has not adequately informed physicians of the key safety findings of the SAMMPRIS study, and cites language from the safety communication. FDA believes that information regarding the SAMMPRIS study and its results is provided in a clear and transparent manner in multiple sources to physicians. Specifically, the Directions for Use (DFU) for the Wingspan Stent System provides a discussion of the SAMMPRIS study and its results in the "clinical experience" section.[15]

FDA also recommends in the safety communication that neurologists "[b]ecome familiar with the design and results of the SAMMPRIS trial." Your letter remarks that the safety communication did not link to

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includes new contraindications and warnings, including contraindications for the treatment of TIA (which was not previously restricted in the label) and ischemic events with an onset of symptoms within 7 days of treatment.

[15] See the Wingspan Stent System Directions for Use, *available at* http://www.stryker.com/stellent/groups/public/documents/adacct/148220.pdf, at 4-5.

the SAMMPRIS results. The agency agrees that the safety communication should directly link to the SAMMPRIS study results. On January 31, 2013, FDA updated the safety communication website for Wingspan Stent System to include the correct link to the SAMMPRIS study.

3. *Off-Label Use*

Your letter raises a concern that the Wingspan Stent System will be used off-label for patients "who will undoubtedly be harmed by it." FDA believes that the revised labeling provides physicians and patients with sufficient information regarding the approved use and the risks of the device. The revised labeling clearly indicates that the Wingspan Stent System is indicated for medically refractory patients who meet specific criteria, including, among other criteria, having had "recurrent (2 or more) strokes."[16] The revised labeling also specifically contraindicates use of the Wingspan Stent System in those circumstances in which the SAMMPRIS data suggested unreasonable risk, and provides information on a physician training program. In addition, the safety communication now provides a link to the SAMMPRIS study, and the DFU provides information on the SAMMPRIS study results. Further, the approved HDE supplement includes revised patient labeling that describes the SAMMPRIS study results and the risks of the device.

You contend in the 2013 letter that FDA fails to provide a definition of "aggressive medical management" in the safety communication, which may leave substantial room for interpretation. FDA has left this term undefined in order to allow physicians to consider all relevant medical therapies as they advance.

Thank you for contacting us regarding this matter. If you have any further questions, please let us know.

Sincerely,

Jeffrey Shuren, M.D., J.D.
Director
Center for Devices and
Radiological Health

[16] See the Wingspan Stent System Directions for Use, *available at* http://www.stryker.com/stellent/groups/public/documents/adacct/148220.pdf, at 2.

Attachment A
Citizen Petition