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Food and Drug Administration
Department of Health and Human Services
WO 2200
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WO 66, Room 5442
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Re: Citizen Petition Docket Number FDA-2011-P0923

Dear Drs. Hamburg and Shuren:

We write in response to Nancy Stade's letter, dated August 8, 2012, which denies our citizen petition urging the Food and Drug Administration (FDA) to immediately withdraw approval of the Humanitarian Device Exemption (HDE) for the Stryker Wingspan Stent System with Gateway PTA Balloon Catheter (hereafter referred to as the Wingspan Stent System) and order a class I recall for all unused Wingspan Stent Systems.[1] Instead of withdrawing the device, the FDA — based on seriously flawed reasoning and a disregard for the best available scientific evidence assessing the safety and effectiveness of the Wingspan Stent System — has approved new, narrowed labeling proposed by Stryker, the Wingspan Stent System's manufacturer.[2]

[1] The Food and Drug Administration. Response to Public Citizen's petition on Wingspan Stent System. August 8, 2012. http://www.citizen.org/documents/1992_and_1994_fda_response_to_petition_on_wingspan_stent_system.pdf. Accessed January 14, 2013.

[2] The Food and Drug Administration. FDA news release: FDA revises safety information and limits use of Stryker Wingspan brain stent system. August 8, 2012. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm314845.htm. Accessed January 14, 2013.

We immediately expressed our concern with the FDA's decision in a press release issued on August 8, 2012.[3] This letter outlines more fully our concerns with the FDA's reasoning and application of the relevant legal standard. Despite the FDA's acknowledgment that the Wingspan Stent System will not provide a benefit for most patients compared with the best available medical treatment alternatives, the agency has approved a new, narrowed indication for the device without identifying any evidence that the device confers any additional benefits to the intended patient population specified in the new labeling. Valid scientific evidence must always be the basis for the FDA's regulatory decision-making, and in this case, the available scientific evidence overwhelmingly fails to support the FDA's regulatory decision to allow the Wingspan Stent System to remain on the market ─ even for patients specified in the new labeling. The only way the FDA can address the serious, ongoing safety risk posed to patients by the Wingspan Stent System is by withdrawing approval of the HDE for this device.

I. Background

The Wingspan Stent System is a class III medical device marketed under an HDE originally granted by the FDA on August 3, 2005.[4] The device is a stent system with a balloon catheter that was initially indicated to improve cerebral artery lumen diameter in patients with intracranial atherosclerotic disease, refractory to medical therapy, in intracranial vessels with greater than or equal to 50% stenosis (narrowing).[5] In other words, the device uses a tiny, self-expanding mesh tube inserted into a partially blocked artery in the brain with the goal of increasing blood flow and preventing strokes in patients who have experienced repeat strokes, even after taking medication to prevent blood clotting. The stent is placed in the brain through a highly technical procedure known as percutaneous transluminal angioplasty (PTA), in which a catheter is inserted through a large artery, usually in the groin, to maneuver the deflated stent into small arteries in the brain. Once deployed, the stent expands to prop open the target artery. The procedure is risky and can result in damage to delicate blood vessels in the brain, in some cases causing stroke and even death during the procedure or over the following days.[6] Following the procedure, the stent remains in place permanently, with the goal of preventing future blockages that would result in stroke and possibly death.

The efficacy of the Wingspan Stent System in preventing strokes was not tested in controlled clinical trials prior to the original HDE approval. Instead, the original HDE was supported solely

[3] Public Citizen. FDA ignores evidence linking Wingspan Stent System to stroke and death, keeps dangerous device on the market. August 8, 2012. http://www.citizen.org/pressroom/pressroomredirect.cfm?ID=3690. Accessed January 14, 2013.
[4] The Food and Drug Administration. Approval order: H050001 Wingspan Stent System with Gateway PTA Balloon Catheter. August 3, 2005. http://www.accessdata.fda.gov/cdrh_docs/pdf5/H050001a.pdf. Accessed January 14, 2013.
[5] *Ibid.*
[6] Boston Scientific. Professional labeling: Gateway PTA Balloon Catheter. August 3, 2005. http://www.accessdata.fda.gov/cdrh_docs/pdf5/H050001c.pdf. Accessed January 14, 2013.

by a single, small, uncontrolled safety study, "the HDE study."[7] The HDE study enrolled subjects with a history of stroke who had experienced a second neurological event while on antithrombotic therapy (medication to prevent blood clotting) and had 50% to 99% intracranial artery stenosis. Subjects had to have experienced their qualifying neurological event more than seven days prior to stent insertion. Only 45 subjects were enrolled in the HDE study, and 44 subjects were treated with the stent, two of whom (4.5%) experienced an ipsilateral stroke within 30 days of the procedure. By six months after the procedure, three of the 44 subjects (6.8%) had experienced ipsilateral stroke, and one of these three had died.[8] The study did not include a control group and therefore offered no evidence that the device conferred any benefits when compared to continued medical therapy, the best alternative treatment option. Nevertheless, the FDA granted the HDE approval, reasoning that "[t]he type and frequency of observed adverse events including stroke are consistent with or lower than similar neurovascular procedures," and therefore that the probable benefit to patients outweighed the risks of illness or injury.[9]

We petitioned the FDA to withdrawal approval of the Wingspan Stent System on December 21, 2011, and submitted a supplement to the petition on January 12, 2012.[10,11] In our petition and supplement, we asked the FDA to withdraw the Wingspan Stent System based on the results of the *Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis* (SAMMPRIS) study, a large, randomized, controlled clinical trial comparing Wingspan Stent System stenting with medical therapy, which was published on September 15, 2012, in the *New England Journal of Medicine.*[12]

The 451 subjects enrolled in the SAMMPRIS study had each experienced a recent stroke or transient ischemic attack (TIA) attributed to stenosis of 70% to 99% in a major intracranial artery. These subjects were randomly assigned to receive PTA and stenting with the Wingspan Stent System plus aggressive medical management (antithrombotic therapy plus management of stroke risk factors) or aggressive medical management alone, without stenting.[13]

Enrollment in the SAMMPRIS study was stopped early because an interim analysis revealed a much higher 30-day rate of stroke or death in the group that had received PTA with stenting plus

[7] The Food and Drug Administration. Wingspan Stent System: summary of safety and probable benefit. August 3, 2005. http://www.accessdata.fda.gov/cdrh_docs/pdf5/H050001b.pdf. Accessed January 14, 2013.
[8] *Ibid.* A fourth subject experienced a contralateral stroke (i.e., on the opposite side of the brain from the site of the procedure).
[9] *Ibid.*
[10] Public Citizen. Petition to the FDA. December 21, 2011. http://www.citizen.org/documents/petition-to-fda-to-withdraw-approval-of-wingspan-stent-system-122111.pdf. Accessed January 22, 2013.
[11] Public Citizen. Supplement to December 21, 2011, petition to the FDA. January 12, 2012. http://www.citizen.org/documents/supplement-to-petition-to-fda-to-withdraw-approval-for-wingspan-stent-system-011212.pdf. Accessed January 22, 2013.
[12] Chimowitz MI, Lynn MJ, Derdeyn CP, et al. Stenting versus aggressive medical therapy for intracranial arterial stenosis. *N Engl J Med* 2011;365(11):993-1003.
[13] *Ibid.*

aggressive medical management (the Wingspan Stent group) compared to the group receiving aggressive medical management alone (the medical management group), and because futility analyses revealed that "there was virtually no chance that a benefit from [treatment with the Wingspan Stent System] would be shown by the end of the follow-up period if enrollment continued."[14] The rate of stroke or death over the first 30 days following randomization was 14.7% in the Wingspan Stent group versus 5.8% in the medical management group, p=0.002. The rates of new stroke occurring beyond 30 days were the same in both groups. As a result, the overall post-procedure rate of stroke or death remained significantly elevated in the Wingspan Stent group, even at one year (20.0% in the Wingspan Stent group versus 12.2% in the medical management group, p=0.009).[15]

We argued in our petition that the Wingspan Stent System should be withdrawn based on the SAMMPRIS study results. More than twice as many SAMMPRIS study subjects died or had a repeat stroke in the 30 days following stent surgery compared with those who did not undergo surgery. This meant that for every 11 subjects treated with the Wingspan Stent System versus aggressive medical therapy alone, one additional patient died or suffered a stroke within 30 days of the procedure. Moreover, the stent did not provide any subsequent benefit in terms of stroke reduction or increased survival in subjects who survived the 30-day period. In other words, the Wingspan Stent System does not prevent stroke and death in the long term, and the procedure to insert the device causes stroke and death in the short term, meaning the device cannot be found safe or effective, and the hypothesized benefits of the device do not outweigh its risks when compared to alternative treatment options.

The FDA responded to our petition by convening a meeting of the Neurological Device Panel of the Medical Devices Advisory Committee on March 23, 2012. The Panel reviewed Public Citizen's petition, the results of the SAMMPRIS study, and other evidence. On August 8, 2012, the FDA issued its letter and press release denying our petition to withdraw the Wingspan Stent System, instead adopting a new indication for the Wingspan Stent System. That indication is described in an FDA Safety Communication posted on the FDA's website on August 8, 2012.[16] Specifically, the new indication restricted use of the Wingspan Stent System to patients:

- who are between 22 and 80 years old;
- who have had two or more strokes despite aggressive medical management;
- whose most recent stroke occurred more than seven days prior to planned treatment with Wingspan;

[14] *Ibid.*
[15] *Ibid.*
[16] The Food and Drug Administration. FDA safety communication: narrowed indications for use for the Stryker Wingspan Stent System. August 8, 2012. http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm314600.htm. Accessed January 15, 2013.

- who have 70 to 99% stenosis due to atherosclerosis of the intracranial artery related to the recurrent strokes; AND
- who have made good recovery from previous strokes and have a modified Rankin score of 3 or less prior to Wingspan Stent System treatment. The Rankin scale is used to measure the degree of disability in stroke patients; lower scores indicate less disability.

This new indication, proposed by Stryker and approved by the FDA, copies and regresses to some of the enrollment criteria from the HDE study but differs in key respects. Notably, while the HDE study admitted subjects with between 50 and 99% stenosis, the new indication is limited to patients with 70 to 99% stenosis.

The FDA Safety Communication did not further define any of the terms in the new indication. Astonishingly, it also failed to summarize the key safety findings of the SAMMPRIS study, instead stating that the Wingspan Stent System "may present unacceptable risks, such as stroke and death, to many patients previously considered appropriate for treatment with Wingspan."[17]

The FDA acknowledged in its letter to Public Citizen that:

> The SAMMPRIS study results provide clear, scientifically valid evidence that stenting does not provide a benefit over aggressive medical management for most patients with symptomatic intracranial stenosis.[18]

The FDA reiterated this position in its Safety Communication, stating that:

> While [the Wingspan Stent System] is not beneficial for the broad population of stroke patients studied in SAMMPRIS, there is evidence from the original HDE study to show there are probable benefits of using Wingspan to treat the specific population of patients outlined in the new indications for use.[19]

The FDA further explained in its letter to Public Citizen that withdrawal of approval of the HDE for the Wingspan Stent System was not appropriate because the data from SAMMPRIS study and from the HDE study "cannot be easily compared to draw reliable conclusions about the HDE study population."[20]

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[17] *Ibid.*
[18] The Food and Drug Administration. FDA response to Public Citizen's petition on Wingspan Stent System. August 8, 2012. http://www.citizen.org/documents/1992_and_1994_fda_response_to_petition_on_wingspan_stent_system.pdf. Accessed January 14, 2013.
[19] The Food and Drug Administration. FDA safety communication: narrowed indications for use for the Stryker Wingspan Stent System. August 8, 2012. http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm314600.htm. Accessed January 15, 2013.
[20] The Food and Drug Administration. Response to Public Citizen's petition on Wingspan Stent System. August 8, 2012.

Specifically, the FDA looked at the subgroup of 33 subjects enrolled in the SAMMPRIS study who would have qualified for treatment under the new indication and found that although "[t]he comparison between the medical [17-subject] and stenting [16-subject] arms for this subgroup suggests that the outcomes were similar, i.e., that there was no added benefit of implanting the stent," the results "[we]re not statistically confirmatory."[21] Essentially, the number of subjects who fit the new indication was so small, the differences between groups were rendered statistically insignificant, and the FDA "c[ould] not conclude that the result in the 16-subject group [wa]s worse than the results seen in the HDE study."[22]

The FDA argued that because the HDE study supported its original approval, and the patient population in the SAMMPRIS study was not identical to the population in the HDE study, the HDE continued to justify approval under a new indication which copied some, but not all, of the enrollment criteria specific to the HDE study.

In other words, the FDA concluded that approval of the HDE for the device should not be withdrawn because the SAMMPRIS study said very little about the safety, efficacy, or risk/benefit profile of the device under the newly narrowed indication. As the agency stated in its letter to Public Citizen:

> [Public Citizen's] petition does not contain information for FDA to determine that there is a lack of a showing of reasonable assurance that the device is safe under the conditions of use in the revised labeling, that the device is ineffective under the conditions of use in the revised labeling, or that there is no reasonable basis from which to conclude that the probable benefit to health from the use of the Wingspan Stent System [for the population covered by the narrowed indication] outweighs the risk of injury or illness.[23]

Dr. Shuren elaborated on the agency's reasoning in a press release accompanying the decision, stating that "[p]atient benefit is an important factor in agency decision-making," and that the device should remain available to patients "who have exhausted other options."[24]

II. Applicable Legal Standards

A manufacturer wishing to market a class III medical device in the United States must first seek premarket approval (PMA) from the FDA through a PMA application showing, among other

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http://www.citizen.org/documents/1992_and_1994_fda_response_to_petition_on_wingspan_stent_system.pdf. Accessed January 14, 2013.

[21] *Ibid.*

[22] *Ibid.*

[23] *Ibid.*

[24] The Food and Drug Administration. FDA news release: FDA revises safety information and limits use of Stryker Wingspan brain stent system. August 8, 2012. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm314845.htm. Accessed January 14, 2013.

things, reasonable assurance of safety and effectiveness.[25] A manufacturer may obtain an exemption from the PMA efficacy requirements by applying for a Humanitarian Device Exemption (HDE).[26]

Prior to granting an application for an HDE, the FDA must find, among other things, that:

> the device will not expose patients to an unreasonable or significant risk of illness or injury and 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.[27]

In addition, FDA regulations state that the FDA will deny or withdraw approval of an HDE if it finds that:

> (1) There is a lack of a showing of reasonable assurance that the device is safe under the conditions of use prescribed, recommended, or suggested in the labeling thereof;
>
> (2) The device is ineffective under the conditions of use prescribed, recommended, or suggested in the labeling thereof;
>
> (3) The applicant has not demonstrated that there is a reasonable basis from which to conclude that the probable benefit to health from the use of the device outweighs the risk of injury or illness, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment. . .[28]

Even after an HDE is granted, the HDE only exempts a device manufacturer from the PMA efficacy requirements, not the PMA safety requirements. Thus, even devices granted an HDE cannot be approved if the FDA finds that:

> there is a lack of a showing of reasonable assurance that such device is safe under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof.[29]

III. Discussion

A. The FDA has inappropriately granted approval for a new indication for the Wingspan Stent System without finding reasonable assurance that the device is safe or effective, or that the probable benefits outweigh the risks under the new indication.

[25] 21 U.S.C. § 360e(d)(2) (Section 515 of the Food, Drug, and Cosmetics Act).
[26] 21 U.S.C. § 360j(m)(2) (Section 520 of the Food, Drug, and Cosmetics Act). *See also* 21 C.F.R. §§ 814.3, 814.100 et seq.
[27] 21 U.S.C. § 360j(m)(2)(C).
[28] 21 C.F.R. § 814.118(a).
[29] 21 U.S.C. § 360e(d)(2)(A).

The FDA has approved a new indication for the Wingspan Stent System without finding reasonable assurance that the device is safe or effective under the new indication or that the probable benefits outweigh the risks when compared to alternative forms of treatment. The agency has done so by inappropriately shifting the legal burden onto Public Citizen, which seeks withdrawal of the HDE approval, and demanding "statistically confirmatory" evidence that the Wingspan Stent System is unsafe or ineffective, or that the risks outweigh the benefits under the new proposed indication prior to withdrawing approval of the device.

The FDA acknowledges that "stenting does not provide a benefit over aggressive medical management for most patients with symptomatic intracranial stenosis" based on "clear, scientifically valid evidence" from the SAMMPRIS study. Given this acknowledgement, the FDA could not approve the Wingspan Stent System under a narrowed indication unless it found that a procedure that is manifestly harmful to most patients with stenosis is nevertheless of some probable benefit to a subset of patients with stenosis on whom data are not yet available, and that such probable benefit outweighs the clearly identified risks to this subgroup.

The FDA has no evidence upon which to base such a finding. In its Safety Communication, the FDA cites "evidence from the original HDE study" for its assertion that "there are probable benefits of using Wingspan to treat the specific population of patients outlined in the new indications for use."[30] However, it is clear that the HDE study provides no such evidence. We have not disputed whether the FDA was right to grant its initial HDE approval of the Wingspan Stent System based on this highly questionable study. Yet regardless of whether the HDE study adequately supported the original approval, it is amply clear that the HDE study provides no evidence that a narrowed subpopulation of patients might find probable benefit under the new indication where clear harm has been demonstrated in a broader population. This is because the HDE study did not contain a medically managed control group, so it offers no insights as to whether stenting is effective, safe, or likely beneficial to patients under the new indication in terms of stroke prevention when compared to aggressive medical management, the best available alternative to stent surgery.

In fact, the only evidence of efficacy, relative risk, or probable benefit for the subpopulation covered under the new indication points toward increased risk with no added benefit from stenting.

First, as we explained in detail in our supplemental petition to the FDA, many of the subjects enrolled in the SAMMPRIS study share one or more of the characteristics required under the new, narrowed indication, making the SAMMPRIS study results generalizable to patients

[30] The Food and Drug Administration. FDA safety communication: narrowed indications for use for the Stryker Wingspan Stent System. August 8, 2012. http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm314600.htm. Accessed January 15, 2013.

covered under that indication.[31] To the extent that few SAMMPRIS study subjects fail to possess *all* of the attributes required under the new indication, the same can be said of subjects who enrolled in the uncontrolled HDE study, many of whom did not have 70 to 99% stenosis. (Subjects in the HDE study ranged from 57 to 99% stenosis, with a median stenosis of 75%, average of 74.9%, and standard deviation of 9.8%.)[32] Also, reports conflict as to whether all subjects in the HDE study experienced two strokes prior to enrollment.[33] Clearly, if the SAMMPRIS study failed to support conclusions about the safety, efficacy, or probable benefit of the Wingspan Stent System under the newly narrowed indication, the HDE study likewise failed to support such conclusions because, using the FDA's reasoning, it too did not exclusively enroll subjects who would have qualified for the new indication.

Second, a post hoc subgroup analysis of data from the SAMMPRIS study showed that for each of the proposed criteria of the new indication, the risk of stroke or mortality is higher at 30 days among subjects who received the Wingspan Stent System when compared to those who did not (see table below).

Probability of stroke or death at 30 days for stenting versus medical therapy among subjects enrolled in the SAMMPRIS study and meeting various criteria for the narrowed Wingspan indication

Narrowed Indication	**Medical Management**	**Stent Surgery**	**P-value**
Subjects with 70 to 99% stenosis	5.8% (13/227)	14.7% (33/224)	0.002[34]
Medically refractory* **Taking antithrombotics at the time of their "qualifying event" (i.e., the stroke or transient ischemic attack qualifying them for enrollment in the trial).*	4.4% (6/140)	16.0% (23/144)	0.0276[35]
Medically refractory with two or more strokes	13.9% (4/29)	17.9% (5/28)	0.5918[36]
>7 days since most recent stroke or TIA	4.5% (5/112)	13.6% (15/110)	0.1496[37]
All of the above	12.2% (2/17)	12.5% (2/16)	0.9972[38]

[31] Public Citizen. Supplement to petition to FDA, January 12, 2012. http://www.citizen.org/documents/supplement-to-petition-to-fda-to-withdraw-approval-for-wingspan-stent-system-011212.pdf. Accessed January 22, 2013.
[32] *Ibid.*
[33] *Ibid.*
[34] Chimowitz MI, Lynn MJ, Derdeyn CP, et al. Stenting versus aggressive medical therapy for intracranial arterial stenosis. *N Engl J Med* 2011;365(11):993-1003.
[35] The Food and Drug Administration. FDA executive summary prepared for the March 23, 2012 meeting of the Neurological Devices Panel of the Medical Devices Advisory Committee. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/NeurologicalDevicesPanel/UCM296664.pdf.
[36] *Ibid.*
[37] *Ibid.*
[38] *Ibid.*

The results from this subgroup analysis are not statistically significant in all cases.[39] In spite of this, the results show that for each of the criteria the FDA has chosen to narrow the indication of the Wingspan Stent System, the trend is toward greater risk for the Wingspan Stent group. Moreover, even if the data do not provide "statistically confirmatory" evidence that stenting is harmful for all of the subpopulations identified, the results certainly offer no support for the hypothesis that stenting is safe or effective, or that the probable benefits of the device outweigh its risks for the specific population of patients outlined in the new indications for use.

The FDA has therefore cited no evidence upon which to base a finding of reasonable assurance of safety and probable benefits outweighing the risks for the new, narrowed indication, when the opposite is true for the population as a whole.[40] Instead of working to make such a finding, the FDA has required Public Citizen to demonstrate that the Wingspan Stent System is unsafe or ineffective, or that the risks it presents outweigh the benefits under the newly narrowed labeling. This analysis turns the appropriate legal standard on its head, making approval the default position and requiring further dangerous experiments before pulling the device from the market, rather than requiring a demonstration of safety and efficacy, as well as a favorable risk/benefit ratio, prior to approving the device under a new indication.

B. The FDA Safety Communication minimizes safety risks and fails to identify the key findings of the SAMMPRIS study.

Public Citizen also is concerned that the FDA has not taken adequate action to protect patients who may be treated with the Wingspan Stent System by informing physicians of the key safety findings of the SAMMPRIS study. Given the substantial risk the Wingspan Stent System presented to the subjects enrolled in the SAMMPRIS study, the FDA had a responsibility to do more than simply state that the device "may present unacceptable risks, such as stroke or death, to many patients previously considered appropriate for treatment with Wingspan."[41] Rather than give this brief, vague warning, the FDA should have clearly and explicitly stated to physicians that the Wingspan Stent System has been shown to more than double the 30-day risk of mortality

[39] This is because the SAMMPRIS study was not designed to answer whether the device was safe or effective for the subpopulation meeting each of these criteria. At the time the SAMMPRIS study was designed, no researcher had proposed that stent surgery might prove especially beneficial to such a subpopulation: That hypothesis was first proposed by Stryker after the SAMMPRIS study results had been published.

[40] Some commentators, though not the FDA, have speculated that the SAMMPRIS study investigators may have lacked "operator experience and technique," resulting in unusually high complication rates. Siddiq F, Chaudhry SA, Khatri R, et al. Rate of postprocedural stroke and death in SAMMPRIS trial-eligible patients treated with intracranial angioplasty and/or stent placement in practice. *Neurosurgery.* 2012;78(1);68-73. The SAMMPRIS study investigators were selected by a panel of experienced neurointerventionists on the basis of their performance history and patient outcomes. The FDA has not proposed limiting the indication for the Wingspan Stent System so that only those physicians with higher levels of experience can implant the device in patients, and there is no reason to believe that the outcomes in actual practice will be better than the results obtained through the SAMMPRIS study.

[41] The Food and Drug Administration. FDA safety communication: narrowed indications for use for the Stryker Wingspan Stent System. August 8, 2012. http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm314600.htm. Accessed January 15, 2013.

and stroke for subjects enrolled in the SAMMPRIS study, a large, randomized, controlled clinical trial with one-year follow-up, and that the device failed to provide any benefits in terms of stroke prevention beyond 30 days.

The FDA also minimized the safety risks revealed in the SAMMPRIS study by directing physicians toward low-quality evidence designed to cloud the SAMMPRIS study results. The FDA opaquely references the SAMMPRIS study in its Safety Communication by saying that physicians should "[b]ecome familiar with the design and results of the SAMMPRIS trial."[42] Yet if physicians click on the hyperlink embedded in that sentence, they will be led not to the published SAMMPRIS study results but to a small (69-patient), nonrandomized, retrospective study published after the SAMMPRIS study that devotes most of its introduction and discussion sections to criticizing the SAMMPRIS study.[43] That low-quality study, published by Siddiq et al. in the journal *Neurosurgery* in July 2012, did not include a control group that received medical therapy alone.[44] The 30-day postprocedural stroke and death rate was actually three times higher in the stent group than in the angioplasty-only control group (10.2% stent-treated, 3.3% angioplasty), although the difference was not significant because of the size of the sample ($p=0.27$).[45] Nevertheless, the authors asserted — without providing supporting evidence — that stenting should be continued "in selected settings" because some populations of patients may experience a lower rate of stroke or death as a result of the stenting procedure than the population enrolled in the SAMMPRIS study. [46]

By linking to this this low-quality study rather than the SAMMPRIS study results, the FDA minimizes the importance of the SAMMPRIS results and tacitly encourages physicians to continue inserting this dangerous device into patients, provided the physicians feel they are in an appropriate "selected setting." Such communications by the FDA are outrageous and demonstrate the agency's reckless failure to inform the healthcare community of the best available scientific evidence.

C. The FDA has opened the door to substantial off-label use.

The Wingspan Stent System is unsafe, ineffective, and unacceptably high-risk, even for patients meeting the new, narrowed indication. Yet even assuming the FDA was correct in allowing the device to remain on the market under the new indication, we are concerned that the Wingspan Stent System will be used off-label for patients who will undoubtedly be harmed by it.

[42] *Ibid.*
[43] Siddiq F, Chaudhry SA, Khatri R, et al. Rate of postprocedural stroke and death in SAMMPRIS trial-eligible patients treated with intracranial angioplasty and/or stent placement in practice. *Neurosurgery* 2012;71(1):68-73.
[44] *Ibid.*
[45] *Ibid.*
[46] *Ibid.*

We note the new, narrowed indication is subject to substantial room for interpretation, particularly with respect to identifying patients who have had repeated strokes despite "aggressive medical management." The FDA has failed to define "aggressive medical management" in its Safety Communication and has not, to our knowledge, posted or linked to any new labeling offering additional clarification. This is a concern because the FDA appears to have based the "two or more strokes despite aggressive medical management" requirement on fine distinctions in enrollment criteria between the SAMMPRIS study and the HDE study.[47]

The Safety Communication also does not make clear that while the SAMMPRIS study failed to show harm for subjects who were "medically refractory" with *two or more* strokes while on antithrombotic therapy, the study did show statistically significant harm for medically refractory subjects with *one or more* stroke or transient ischemic attack while on antithrombotic therapy. Sixteen percent of such "medically refractory" subjects in the Wingspan Stent group experienced stroke or death at 30 days, compared with 4.4% of subjects in the medical management group, p=0.0276.[48] By failing to state this fact in its Safety Communication, the FDA increases the chances that physicians will stray outside the parameters of the new indication, using the device on patients who have not yet had two or more strokes and would therefore experience demonstrably greater benefits from continuing on aggressive medical management as opposed to undergoing risky, invasive interventions with the Wingspan Stent System.

IV. Conclusion

Public Citizen has grave concerns with the FDA's flawed reasoning and application of the appropriate legal standards in its recent determination not to withdraw the HDE approval of the Wingspan Stent System. We call on the FDA to reverse its decision and immediately withdraw approval of this dangerous device, on the following grounds:

- The FDA presents no valid scientific evidence upon which to base a finding of reasonable assurance that the Wingspan Stent System is safe or effective, or that the probable benefits of the device outweigh the risks for a narrowed subset of patients with stenosis. The FDA has acknowledged that the device does not provide a benefit for most patients with stenosis, but it approved the new indication by default on the ground that Public Citizen failed to prove that the device is unsafe or ineffective, or that its risks outweigh probable benefit.

[47] We questioned this reasoning in our supplemental petition of January 12, 2012, noting that most of the SAMMPRIS study subjects (63.4%) were on antithrombotic therapy at the time of their qualifying stroke or TIA and therefore suffered from two or more strokes while on what might be termed "aggressive medical management." Public Citizen. Supplement to petition to FDA, January 12, 2012. http://www.citizen.org/documents/supplement-to-petition-to-fda-to-withdraw-approval-for-wingspan-stent-system-011212.pdf. Accessed January 22, 2013.

[48] FDA executive summary prepared for the March 23, 2012, meeting of the Neurological Devices Panel. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/NeurologicalDevicesPanel/UCM296664.pdf.

- The FDA's safety announcement minimizes the risks of the Wingspan Stent System by failing to mention the key findings of the SAMMPRIS study and directing physicians to low-quality evidence aimed at undermining the study's findings. Such information is grossly inadequate to inform doctors and patients of the known life-threatening safety risks of this device.
- By failing to withdraw the device and by crafting ambiguous limitations on the device's new, narrowed indication, the FDA has created substantial risk that the Wingspan Stent System will continue to be used outside the new indication.

Public Citizen acknowledges the importance of maintaining patient access to safe and effective treatments for life-threatening conditions, particularly when treatment options are limited. However, we find no "patient benefit" in exposing desperate patients to a dangerous and costly invasive procedure that has been demonstrated to be ineffective and to cause life-threatening injury and death. We believe that the FDA's standards for evaluating evidence should not be lowered where treatment options are limited and a disease is fatal, because patients with such conditions are even more vulnerable to false promises regarding treatments that do more harm than good. In this case, we believe that the FDA has failed in its duty to protect patients by exposing the public to a device that will more than double the chances of stroke or death – the very outcomes that the device has been sold to prevent.

Thank you for your prompt attention to this important public health matter.

Sincerely,

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