Introduction:

The Orthopaedic and Rehabilitation Devices Panel of the Medical Devices Advisory Committee to the Food and Drug Administration met on February 20, 2015 to make recommendations and vote on information related to the Premarket Approval Application (PMA) for the Superion® InterSpinous Spacer (the Superion® ISS) sponsored by Vertiflex® Incorporated.

The sponsor has proposed the following indications for use:

“The Superion® InterSpinous Spacer is intended to treat skeletally mature patients suffering from pain, numbness, and/or cramping in the legs (neurogenic intermittent claudication) secondary to a diagnosis of lumbar spinal stenosis, with or without Grade 1 spondylolisthesis, confirmed by X-ray, MRI and/or CT evidence of thickened ligamentum flavum, narrowed lateral recess, and/or central canal or foraminal narrowing. The Superion® ISS is indicated for those patients with impaired physical function who experience relief in flexion from symptoms of leg/buttock/groin pain, numbness, and/or cramping, with or without back pain. The Superion® ISS may be implanted at one or two adjacent lumbar levels in patients in whom treatment is indicated at no more than two levels, from L1 to L5.”

Panel Deliberations/FDA Questions:

Panel Question 1:

Two radiographic success elements were included in the “absence of major implant or procedure related complications” subcomponent of the primary composite endpoint defined in the IDE protocol. Both the Superion® (88.9%) and X-STOP® (86.1%) cohorts had similar results at 24 months for this subcomponent; in other words, 11.1% of Superion® subjects and 13.9% of X-STOP® subjects experienced a major implant or procedure related complication. However, the majority of failures in the Superion® cohort were due to spinous process fractures (n=31 at any time), while the failures in the X-STOP® cohort were primarily due to migrations (n=16) and dislodgements (n=20). Spinous process fractures (n=17 at any time) also occurred in the X-STOP® group. Please discuss the potential clinical impact of the different types of radiographic failure modes (i.e., spinous process fracture, migration, dislodgement), as well as the appropriateness of comparing them in determining radiographic success, and consequently, overall success.

Panel Response:
The panel generally believed that spinous process fractures in and of themselves may have limited clinical consequences. The panel noted, however, that the presence of spinous process fractures in conjunction with an interspinous spacer may suggest that the device is not achieving distraction of the intradiscal space, and the clinical effects of this loss in posterior disc height is not clear at this time. The panel generally concluded that migration and dislodgement of the device were a more significant concern than the spinous process fractures.

**Panel Question 2:**

During the course of the clinical study, the patient incidence of spinous process fractures observed in the Superion® and X-STOP® cohorts were 16.3% (31/190) and 8.5% (17/201), respectively. At 24 months, 32.3% (10/31) of the Superion® fractures and 41.2% (7/17) of the X-STOP® fractures exhibited signs of healing as described by the sponsor. In addition, the sponsor provided an analysis of Zurich Claudication Questionnaire (ZCQ), Oswestry Disability Index (ODI), Visual Analog Scale (VAS) Leg, and VAS Back scores to support their conclusion that most of the spinous process fractures in both groups were asymptomatic.

- Please discuss the clinical significance of the observed spinous process fractures, particularly given that interspinous process devices rely upon intact spinous processes to exert their treatment effect.

- Please discuss the analysis presented to assess the correlation between spinous process fractures and effectiveness (i.e., ZCQ, ODI, VAS Leg, and VAS Back scores) outcomes at 24 months with particular focus on whether the analysis is adequate to determine the clinical significance of the observed spinous process fractures.

- The diagnosis of spinous process fractures in this clinical trial were made by plain radiographs, and when comparing the treatment groups there was a disproportionate discrepancy between the investigators (Investigational Arm = 13, Control Arm = 10) and core lab (Investigational Arm = 31, Control Arm = 17) in identifying the number of spinous process fractures. Recent literature suggests that spinous process fractures related to interspinous process devices are under-recognized, and recommends the use of CT scans for a more accurate diagnosis (Kim et al., The Spine Journal, 2012). Please discuss the utility of CT scans as compared to plain radiographs in the diagnosis and classification of spinous process fractures after treatment with an interspinous process device, as well as in the assessment of bony healing of fractures that are identified. In addition, please discuss the most appropriate time point(s) for conducting these imaging studies.

**Panel Response**

The panel generally agreed that the spinous process fractures themselves may not be a clinically important short-term issue but remained unsure of the long-term clinical effects of unhealed fractures.

The panel generally believed that the instruments used in this study and discussed (ZCQ, ODI, VAS, etc.) may be useful for comparing performance metrics across studies, but noted that they lack sensitivity and enough patient focus to provide information on whether spinous process fractures have clinical consequences to the patient long-term.

The panel generally concluded that most patients do not warrant a CT scan in a routine fashion due to the potentially greater risk of radiation exposure, but may be warranted if there is a symptomatic patient. The
Panel also concluded that while there is no standardized methodology, it may also be possible to use higher quality radiographs, or potentially a limited CT scan, to achieve similar results. The panel further concluded that the data suggests that imaging studies should be conducted early (< 3 months), instead of later (24 months). The panel also concluded that in this type of analysis, clinical outcomes are more important than imaging studies.

**Panel Question 3:**

Overall success of the Superion® device as compared to the control device (X-STOP®) was evaluated based on a primary composite endpoint consisting of: clinically significant improvement in 2/3 domains of the Zurich Claudication Questionnaire (ZCQ), no additional surgeries at the index level(s), no major implant or procedure related complications, and no confounding treatments (e.g. epidural injections or rhizotomies). This composite endpoint, as suggested by the FDA during review of the original IDE application, includes effectiveness measurements, safety measurements, and takes into account potential risks. Overall success for the Superion® modified Intent-to-Treat (ITT) cohort (52.7%) as compared to the X-STOP® mITT cohort (50.2%) was demonstrated to be non-inferior at 24 months, per the IDE protocol reviewed and approved by FDA.

Considering the patient population defined in P140004, and the intent of the Superion® device, please discuss the adequacy of the primary composite endpoint and the timepoint at which non-inferiority was tested (24 months).

Please discuss the overall clinical success rates (in both the Superion® and X-STOP® groups) in the context of expected clinical success rates for commonly used treatments for the patient population defined in this study.

**Panel Response:**

The panel generally believed that both the primary composite endpoint and evaluation time point were adequate. The panel expressed some concern about the possibility of leaving out patient experience from the ZCQ (i.e., only measuring success as 2/3 components of ZCQ instead of using all 3 elements of the ZCQ). The panel did express some concern that the Superion® device was tested for non-inferiority against the X-STOP® device, which some members of the panel considered exhibited questionable performance.

The panel generally believed the overall success rates were soft and/or weak, and were further compromised by comparison to the X-STOP®, a device that does not have outstanding clinical results. The panel recommended that longer term results are needed to see if the Superion® device is a valuable “tool in the armament” of a spine surgeon.

**Panel Question 4:**

In May of 2008, the Agency approved the Superion® IDE clinical trial using a PMA approved device (X-STOP®) as the control. Subsequently, as described above, overall success for the Superion® as compared to the X-STOP® was demonstrated to be non-inferior at 24 months. The Agency is aware of literature which has been published on interspinous process spacer devices including randomized, controlled, clinical trials (Moojen, BMJ, 2013; Moojen, European Spine Journal, 2015; Strömqvist, Spine, 2013), which suggest that decompression alone (the “gold standard” to treat lumbar spinal stenosis) results in comparable effectiveness outcomes compared to treatment with an interspinous process device alone, although use of an interspinous process device is associated with a higher reoperation rate. In addition, the Agency is aware of recent literature that suggests patients with degenerative spondylolisthesis should be considered as a
distinct sub-population of spinal stenosis patients (Pearson, *Spine*, 2010), and the use of interspinous process devices to treat patients with degenerative spondylolisthesis is controversial (Kabir, *Spine*, 2010). Please comment on whether the literature referenced above is a fair representation of your current understanding of treatments available for this patient population and whether or not the findings are relevant to the device under discussion today. If so, the please discuss the impact, if any, of this literature on the interpretation of the results of the Superion® study (e.g., study design, study endpoints, determination of benefit risk, device labeling, etc.). Please note that your feedback might also be useful to the clinical trial design of future interspinous process spacers.

**Panel Response:**

The panel generally believed that the literature presented was a good representation of the current body of literature but that it was only a small part of a greater body of published data and that there were many other publications which should be taken into consideration. The panel also generally believed that the decision of whether or not patients with degenerative spondylolisthesis would be included as a sub-population for interspinous spacer devices would be dependent upon the intended use of the device. The panel generally felt that if the device were to be used as a permanent treatment then spondylolisthesis patients should not be included together; however, if the technology were intended to be more of a “bridging” treatment to relieve pain and postpone (possibly indefinitely) more aggressive decompression surgery then inclusion of spondylolisthesis, inclusion of this patient subgroup may be appropriate.

The panel generally believed that there is some lack of clarity regarding the duration of efficacy of interspinous process spacer devices. The panel generally believed that 24 months was an insufficient amount of time to measure the long term efficacy of these devices. The panel generally agreed that the appropriate control group for this device type would depend upon the conditions of use (e.g., permanent vs. bridge) and the patient population (e.g., patients with degenerative spondylolisthesis would be more appropriately compared to a decompression control), and that comparison of the Superion® device to a decompression control group in a new post approval study would be appropriate.

**Panel Question 5:**

If the Superion® device is deemed approvable by the FDA, the sponsor has proposed a post approval study to continue following the IDE subjects for up to 5 years, as well as an additional “actual conditions of use” post approval study which would enroll new subjects. Please discuss the adequacy of the sponsor’s proposed post approval study plans for the evaluation of the safety and effectiveness of the Superion® device in the post-market setting. In your discussion, please specifically address the following:

The proposed new cohort post approval study is powered to demonstrate that Superion® performance is not clinically inferior in the new Superion® cohort as compared to the pivotal IDE Superion® cohort based on a comparison of the primary endpoint at 24 months. The proposed secondary objective of the new cohort study is to compare clinical outcomes in subjects implanted with the Superion® device to clinical outcomes in subjects treated with surgical decompression at 24 months post operatively. Please discuss the clinical importance of these two objectives, and discuss the most clinically relevant primary objective of the new cohort post approval study.

Within the current outline for the long term follow-up of the IDE cohort, it is unclear whether CT scans will be done to evaluate spinous process fractures in the Superion® and X-STOP® groups. In addition, the proposed new cohort post approval study states that CT scans will be done at 24 months only in symptomatic Superion® subjects. Please discuss the role of CT scans in evaluating subjects (in both the Superion® and X-STOP® treatment groups) for spinous process fractures in order to assess the long term
safety profile of the Superion® device. Please specifically discuss the most appropriate timepoints for CT evaluation in order to identify all spinous process fractures, as well as whether there should be different algorithms in symptomatic and asymptomatic subjects. If different algorithms are recommended, please discuss the specific criteria that should be used to define “symptomatic” subjects.

Panel Response:

The panel generally believed that a decompression control group comparison should be the primary objective of the “actual conditions of use” study and that the post approval study should be carried out beyond 24 months. The panel took issue with the 24 month timepoint as they said any cut off point would bias the device. The panel further suggested that for the secondary objective of the “actual conditions of use” study that the new enrollment Superion® cohort should be compared to the IDE subjects at 36 months because of the increasing trend of revisions between 24 and 36 months.

The panel believed there may only be limited utility in CT imaging of subjects with significant symptoms (e.g., leg pain or leg and back pain), and the CT imaging would have little to no utility for use in routine monitoring of study patients. The panel once again reiterated that if CT imaging were performed, the best timepoint to use would be very early (< 3 months).

Panel Vote

The panel voted on the safety, effectiveness, and risk benefit ratio of the VertiFlex® Superion® InterSpinous Spacer (ISS).

1) The VertiFlex® Superion® InterSpinous Spacer (ISS) is indicated for those patients with impaired physical function who experience relief in flexion from symptoms of leg/buttock/groin pain, numbness, and/or cramping, with or without back pain. Is there a reasonable assurance that the VertiFlex® Superion® ISS is safe for the indication for use as treatment for pain, numbness, and/or cramping in the legs (neurogenic intermittent claudication) secondary to a diagnosis of moderate lumbar spinal stenosis, with or without Grade 1 spondylolisthesis?

On Question 1, the panel voted 5 (Yes), 2 (Abstain), 1 (No) that the data shows reasonable assurance that the VertiFlex® Superion® InterSpinous Spacer (ISS) is safe for use in patients who meet the criteria specified in the proposed indication.

2) The VertiFlex® Superion® InterSpinous Spacer (ISS) is indicated for those patients with impaired physical function who experience relief in flexion from symptoms of leg/buttock/groin pain, numbness, and/or cramping, with or without back pain. Is there a reasonable assurance that the VertiFlex® Superion® ISS is safe for the indication for use as treatment for pain, numbness, and/or cramping in the legs (neurogenic intermittent claudication) secondary to a diagnosis of moderate lumbar spinal stenosis, with or without Grade 1 spondylolisthesis?

On Question 2, the panel voted 5 (Yes), 2 (Abstain), 1 (No) that there is reasonable assurance that the VertiFlex® Superion® InterSpinous Spacer (ISS) is effective for use in patients who meet the criteria specified in the proposed indication.

3) The VertiFlex® Superion® InterSpinous Spacer (ISS) is indicated for those patients with impaired physical function who experience relief in flexion from symptoms of leg/buttock/groin pain, numbness, and/or cramping, with or without back pain. Is there a reasonable assurance that the VertiFlex® Superion® ISS is safe for the indication for use as treatment for pain, numbness, and/or cramping in the legs
neurogenic intermittent claudication) secondary to a diagnosis of moderate lumbar spinal stenosis, with or without Grade 1 spondylolisthesis?

On Question 3, the panel voted 4 (Yes), 2 (Abstain), 2 (No) that the benefits of the VertiFlex® Superion® InterSpinous Spacer (ISS) outweigh the risks for use in patients who meet the criteria specified in the proposed indication.

Public Speakers

The following Open Public Speakers attended the meeting: 1) Christina Silcox, Senior Fellow at the National Center for Health Research (formerly National Research Center for Women & Families) and Kathryn Simpson, Ph. D., Manager of Clinical Regulatory Affairs, The Orthopedic Surgical Manufacturers Association (OSMA).

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