WRIGHT.
TM

1056 5 OCT 31 A7:29

Jeffrey G. Roberts
Sr. Vice President & Chief Technical Officer
Direct Dial – 901-867-4645
Facsimile – 901-867-8249
Email – jroberts@wmt.com

October 29, 2005

VIA FEDERAL EXPRESS

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, MD 20852

Dear Sir or Madam:

On behalf of Wright Medical Technology, Inc., please find enclosed an original and four copies of a Citizen Petition submitted under 21 C.F.R. § 10.30.

This petition urges that the Food and Drug Administration, pursuant to 21 U.S.C. § 360e(d) of the Federal Food, Drug, and Cosmetic Act, deny approval of Smith & Nephew's premarket approval application ("PMA") for the Birmingham Hip Resurfacing System (P040033) based on the data currently submitted in support of the PMA.

If you have any questions concerning this petition, please call me at (901) 867-9971.

Thank you for your attention to this matter.

Sincerely,

Jeffrey G. Roberts

Enclosure

2005P-0440

CP 1

October 29, 2005
Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, MD 20852

Docket No. 2005P-0440

CITIZEN PETITION

The undersigned submits this petition under 21 C.F.R. § 10.30 to request the Commissioner of Food and Drugs (the "Commissioner"), pursuant to 21 U.S.C. § 360e(d), deny approval of Smith & Nephew's premarket approval ("PMA") application for the Birmingham Hip Resurfacing System ("BHR") (P040033) based on the data currently submitted in support of the PMA.

A. Action Requested

The Food and Drug Administration ("FDA") has described the BHR PMA as a device that is "first of a kind in the United States . . . supported by clinical data essentially from one source."[1] FDA has further stated that the data relied upon for the BHR PMA are from a "single investigator."[2] This petition requests that the Commissioner determine that Smith & Nephew has not met its statutory burden of providing a reasonable assurance that the BHR is safe and effective, and therefore, that the Commissioner not approve Smith & Nephew's PMA. This decision would be consistent with the applicable statutory and regulatory requirements that FDA has applied to previous Class III orthopedic device submissions, including the petitioner's, the need

---

1 Food and Drug Administration ("FDA"), Briefing Information: Executive Summary for the Orthopedic and Rehabilitation Devices Panel: PMA P040033—Birmingham Hip Resurfacing (BHR) System, Gaithersburg, MD, at 0 (Sept. 8, 2005) [hereinafter Executive Summary], available at http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4181b1_01_PMA%20P040033.pdf. See also Transcript, Orthopedic and Rehabilitation Devices Panel: PMA P040033—Birmingham Hip Resurfacing (BHR) System, Gaithersburg, MD, at 118 (Sept. 8, 2005) [hereinafter Panel Transcript] (testimony of John S. Goode, M.S., Orthopedic Devices Branch).

2 See Executive Summary, supra note 1, at 0 ("FDA requests expert clinical opinion regarding the safety and effectiveness data collection methods, [and] the applicability of the foreign data from a single investigator").

to maintain the integrity of the clinical research process, and the need to ensure the safety and effectiveness of the BHR and other new types of medical devices.

B. Statement of Grounds

a. Introduction

The BHR is a total hip system comprised of two pieces: a resurfacing femoral component and an acetabular component. These two components are characterized as having metal-on-metal articulating surfaces. It is a Class III, single use device with a proposed intended use for patients who require primary hip resurfacing arthroplasty due to non-inflammatory arthritis (degenerative joint disease), including osteoarthritis, traumatic arthritis, avascular necrosis, or dysplasia/DDH, or inflammatory arthritis, including rheumatoid arthritis, and who are at risk of requiring future, ipsilateral hip joint revision.[3]

The PMA submitted by Smith & Nephew for approval of the BHR relies upon, according to the sponsor, a combination of retrospective data and data that were collected prospectively but reviewed retrospectively. These clinical data are from one source: Derek J.W. McMinn, FRCS, of the Birmingham Nuffield Hospital, Birmingham, United Kingdom.[4] According to Smith & Nephew, 3,374 additional BHR implantations have been performed by 140 other surgeons in twenty-three countries.[5] Though the Oswestry Outcomes Center has provided Smith & Nephew with the data from these other cases, Smith & Nephew cannot verify any of the data from these procedures, and has no ability to request additional follow-up or clarifications from the surgeons who performed these other procedures.[6] Consequently, FDA concluded in its Executive Summary of Smith & Nephew's data in support of the BHR PMA that the database containing these other cases "has some limitations, and is not considered a primary data source for this PMA."[7]

---

3 Id. at 3. This indication, however, was not created from a study protocol. Rather, Smith & Nephew has stated that they "believe that the data supports" this indication. Panel Transcript, supra note 1, at 87 (testimony of Neal Defibaugh, Director, Clinical Affairs, Smith & Nephew).

4 Executive Summary, supra note 1, at 0.

5 See Executive Summary, supra note 1, at 23, 58. See also Panel Transcript, supra note 1, at 67 (testimony of Marcos Valez-Duran, Vice President, Clinical/Regulatory Affairs and Quality (Trauma)).

6 Executive Summary, supra note 1, at 23. See also Panel Transcript, supra note 1, at 67 (testimony of Marcos Valez-Duran), 130 (testimony of John S. Goode).

7 Executive Summary, supra note 1, at 23.

The procedures performed worldwide by 140 additional surgeons were not performed under a well-controlled investigation, or under any form of clinical trial. Moreover, there was not any monitoring of the patients who received the BHR through these physicians. Therefore, as FDA concluded in its Executive Summary, any "data" from these additional procedures cannot be considered a primary data source for Smith & Nephew's PMA. Smith & Nephew itself has acknowledged that the PMA's approval can be based only on Dr. McMinn's data.[8] Smith & Nephew's own Vice President of Clinical and Regulatory Affairs and Quality (Trauma) testified before the Orthopedic and Rehabilitation Device Panel (the "Panel") on September 8, 2005 that "[t]here have been more than 33,000 implants implanted worldwide at the time of the PMA submission. The evidence presented in this PMA is based on a consecutive series of 2,385 cases."[9] This consecutive series were from Dr. McMinn's practice, not from the practice of the other physicians that have used the BHR. Thus, the data on which Smith & Nephew's PMA rests, by Smith & Nephew's own admission, are the implantations of the BHR by Dr. McMinn.

Dr. McMinn performed 2,385 procedures, primarily at this single site, from July 1997 through May 2004. The safety and effectiveness data are therefore the result of an uncontrolled case study of consecutive surgeries performed by a single physician. These data were not generated through a study protocol, and there were no predefined follow-up time windows, standardized clinical evaluations, case report forms, inclusion/exclusion criteria, safety endpoints, efficacy endpoints, standardized adverse event report forms, or standardized radiographic evaluations.[10] As the experience of other physicians does not constitute data that can support the PMA, Smith & Nephew cannot validly point to data that replicate Dr. McMinn's results. The results of the other physicians are merely anecdotal evidence.

As explained in detail below, the PMA data are not sufficient to demonstrate the safety and effectiveness of a high-risk, Class III device that will be new to the U.S. market. If approved, the BHR will be the first device of its kind in the United States. Moreover, the type of surgery required to implant the BHR will be new to U.S. surgeons. A determination by FDA that the retrospectively-reviewed clinical experience of a single foreign physician serves as valid scientific evidence sufficient to approve a new Class III device would be unprecedented, unwarranted, and inconsistent with governing law.[11]

---

8 See Panel Transcript, supra note 1, at 67 (testimony of Marcos Valez-Duran).

9 Id.

10 Executive Summary, supra note 1, at 24; Panel Transcript, supra note 1, at 131 (testimony of John S. Goode).

11 The petitioner is not asserting that the data show the BHR to be unsafe or not effective. Rather, as demonstrated in this petition, Smith & Nephew's data was

b. Legal Background

i. PMAs Must Contain Valid Scientific Evidence

New Class III medical devices, such as the BHR, must receive premarket approval from FDA before they may be marketed. The content of PMA applications is governed by both the Federal Food, Drug, and Cosmetic Act ("FDC Act") and FDA regulations. The FDC Act requires that PMA applications contain "full reports of all information . . . concerning investigations which have been made to show whether or not [a] device is safe and effective."[12] FDA's regulations further require applicants to present a summary of the studies conducted, including a summary of clinical investigations involving human subjects.[13] Thus, the burden to prove that a device should be approved through the PMA process rests with the sponsor. As will be described below, the statute and regulations governing PMA approvals generally require sponsors to present data from more than one investigator in support of the PMA application. Other physicians who merely use a device do not constitute investigators whose data can be used in support of a PMA application. If a PMA is based on data from a single investigator, the sponsor bears an additional burden: to present FDA with "a justification showing that data and other information from a single investigator are sufficient to demonstrate the safety and effectiveness of the device and to ensure reproducibility of the test results."[14]

The FDC Act requires FDA to deny any PMA application that lacks a showing of reasonable assurance that the device is safe and effective.[15] The safety and effectiveness of Class III medical devices are to be determined from "valid scientific evidence."[16] FDA's regulations further explain that there is "reasonable assurance that a device is safe when it can be determined, based on valid scientific evidence, that the probable benefits to health for its intended uses and conditions of use . . . outweigh any probable risks."[17] Similarly, the agency's regulations state that there is "reasonable assurance that a device

---

not collected in accordance with the statutory standards for PMAs, FDA's regulations, or the scientific method, and therefore a safety and effectiveness decision cannot be made.

12 21 U.S.C. § 360e(c)(1)(A).

13 21 C.F.R. § 814.20(3)(iii)(v)(B).

14 Id. § 814.20(b)(7).

15 21 U.S.C. §§ 360e(d)(2)(A), (B).

16 Id. § 360c(a)(3)(B).

17 21 C.F.R. § 860.7(d)(1).

is effective when it can be determined, based on valid scientific evidence, that in a significant portion of the population, the use of the device for its intended uses and conditions of use . . . will provide clinically significant results."[18] Therefore, pursuant to the FDC Act and FDA's own regulations, FDA cannot approve a PMA unless the sponsor presents "valid scientific evidence," by which the agency can determine that there is reasonable assurance that the device is safe and effective.

FDA's regulations define "valid scientific evidence" as

> evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use.[19]

This definition presents a hierarchy of types of evidence that constitute valid scientific evidence. The top of the hierarchy—well-controlled investigations—are the most rigorous form of valid scientific evidence. As one descends down the hierarchy, the evidence becomes less rigorous. Well-documented case histories and significant human experience with a marketed device are at the bottom of the hierarchy. Therefore, the use of a device by other physicians—even a large number of physicians—outside the context of a well-controlled investigation is not equivalent to a well-controlled investigation and, therefore, carries minimal weight.

The definition of "valid scientific evidence" further states that "[i]solated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness."[20] Thus, a key element of valid scientific evidence is that results are reproducible. Reproducibility is typically demonstrated by multiple investigators. The FDC Act states that the effectiveness of a Class III device is

> to be determined . . . on the basis of well-controlled investigations, including 1 or more clinical investigations where appropriate, by experts qualified by training and experience to evaluate the effectiveness of the device, from

---

18 Id. § 860.7(e)(1).

19 Id. § 860.7(c)(2).

20 Id.

> which investigations it can fairly and responsibly be concluded by qualified experts that the device will have the effect it purports or is represented to have.[21]

This language reflects that the effectiveness of a device is to be determined in the context of a well-controlled investigation. Additionally, FDA's regulation defining "valid scientific evidence" uses the words "investigations," "studies," "trials," "case histories conducted by qualified experts" and "reports."[22] The use of the plural in the regulation reflects a determination that PMAs supported by a single investigator do not fulfill the requisite standards.

The data submitted in Smith & Nephew's PMA are not the result of a multi-center investigation by multiple investigators. Moreover, the data do not come from investigations, studies, or trials; rather they constitute at best only "well-documented case histories." These types of data are sufficient only when "conducted by qualified experts."[23] Though Smith & Nephew has reported that physicians around the world have used the BHR, the case histories on which Smith & Nephew has relied in support of its PMA are – by Smith & Nephew's own admission – from the work of a single physician.[24]

FDA's regulations emphasize the strong preference for well-controlled investigations: "[t]he valid scientific evidence used to determine the effectiveness of a device shall consist primarily of well-controlled investigations."[25] Only if "the Commissioner authorizes reliance upon other valid scientific evidence which the Commissioner has determined is sufficient evidence from which to determine the effectiveness of a device, even in the absence of well-controlled investigations"[26] can the agency accept less rigorous forms of valid scientific evidence. This determination may only be made, however, "where the requirement of well-controlled investigations . . . is not reasonably applicable to the device."[27] This is not the case for total resurfacing devices, as other manufacturers of metal-on-metal resurfacing arthroplasty devices are

---

21 21 U.S.C. § 360c(a)(3)(A) (emphasis added).

22 21 C.F.R. § 860.7(c)(2) (emphases added).

23 Id. (emphasis added).

24 See Panel Transcript, supra note 1, at 67 (testimony of Marcos Valez-Duran).

25 21 C.F.R. § 860.7(e)(2).

26 Id.

27 Id.

conducting well-controlled investigations.[28] Therefore, well-controlled investigations are "reasonably applicable" to metal-on-metal resurfacing arthroplasty devices like the BHR.

Even if FDA decides to accept forms of valid scientific evidence other than well-controlled investigations, the principles governing, and elements of, well-controlled investigations "are useful in assessing the weight to be given to other valid scientific evidence."[29] These principles, which are discussed below, require that the PMA for the BHR be rejected.

FDA's regulations governing valid scientific evidence and PMA approvals place the same standards and requirements on all PMA applications, regardless of the source of data. The regulations do not distinguish between PMA applications supported by retrospective data and PMA applications supported by prospective data. Therefore, there cannot be a lower standard for establishing safety and effectiveness if data are retrospective. Sponsors who submit retrospective data based on the clinical history of a device at a single site must prove safety and effectiveness of the device to the same degree as sponsors who conduct well-controlled investigations.

1. Elements and Types of Well-Controlled Investigations

Generally, well-controlled investigations are prospective studies that are, among other factors: designed pursuant to a specific protocol; conducted with a control group; reproducible; subject to strict oversight and monitoring; and conducted with enough independence to minimize bias. Moreover, within a well-controlled investigation, investigators apply a consistent method of observing study subjects and recording results. Comparing test groups to a control group permits quantitative evaluation.[30] The data relied upon for the BHR PMA lack every one of these elements.

Protocols for well-controlled investigations include a clear statement of the objectives of the study, define the inclusion and exclusion criteria for subjects, and identify the method of selecting subjects. The agency states that, generally, prospective clinical investigations that predefine a study population with specific inclusion and exclusion criteria allow the study results to be generalized to a particular diagnostic

---

28 See Panel Transcript, supra note 1, at 42 (testimony of William Maloney, M.D., Stanford University School of Medicine).

29 FDA, Center for Devices and Radiological Health, Device Advice—Premarket Approval (PMA), available at http://www.fda.gov/cdrh/devadvice/pma/.

30 See, e.g., Panel Transcript, supra note 1, at 29-30 (testimony of Dr. Susan Krasny, Vice President, Orthopedic Surgical Manufacturers Association).

group.[31] According to FDA, case series studies present tremendous difficulty in generalizing the results to a predefined population because patients were not originally enrolled for predefined conditions.[32]

FDA has stated in the past that a clinical study performed by only one investigator may render the study non-reproducible, may indicate potential bias in the study, and may not provide a reasonable assurance of safety and effectiveness of a device.[33] "[T]o demonstrate the reproducibility of results, clinical investigations of a device should normally involve more than one investigator."[34] Physicians using a device do not constitute investigators, however, and reproducibility cannot be demonstrated by mere use of a device by more than one physician. Any sponsor that submits a study from a single investigator must also show how the single-investigator study has minimized potential bias.[35] Since the only data that can be used to support the PMA for the BHR are derived from one investigator, Smith & Nephew bears these burdens of demonstrating that it has met these requirements. Smith & Nephew, however, has not met these burdens.

Further, federal case law indicates that lack of protocols, including insufficient patient follow-up, may indicate a potentially biased study. In General Medical Co. v. FDA, the United States Court of Appeals for the District of Columbia Circuit evaluated FDA's denial of the reclassification of a Class III medical device to Class I.[36] The sponsors had performed a clinical study of 225 cases, but after six weeks, only sixty cases were still under evaluation. The sponsor offered no explanation of how these sixty cases were chosen for follow-up.[37] This was of serious concern to FDA and the agency determined that the sponsor had not proven the effectiveness of the device, and that the device presented a potential unreasonable risk of injury.[38] The court agreed and further

---

31 Executive Summary, supra note 1, at 19. See also Panel Transcript, supra note 1, at 120 (testimony of John S. Goode).

32 Executive Summary, supra note 1, at 19. See also Panel Transcript, supra note 1, at 120-21 (testimony of John S. Goode).

33 See 51 Fed. Reg. 26,342, 26,349 (July 22, 1986).

34 Id.

35 Id.

36 770 F.2d 214 (D.C. Cir. 1985).

37 Id. at 218, 219.

38 Id. at 221.

noted that the study and follow-up were "potentially biased" which indicated that "the risks of the device may be significantly underestimated by the study's results."[39]

Clinical studies conducted in support of approval of significant risk devices are subject to the Investigational Device Exemption ("IDE") regulations.[40] These studies must adhere to a predetermined investigational plan, which includes a "written protocol describing the methodology to be used and an analysis of the protocol demonstrating that the investigation is scientifically sound."[41] Historically, FDA has expected these protocols to include, among other elements: a control group and a treatment group; safety and efficacy endpoints; inclusion and exclusion criteria; and a valid statistical plan on which to base the conclusions. Sponsors of IDE studies must design written procedures for monitoring the study and must select qualified monitors to monitor the study.[42] All investigators also bear the responsibility to ensure that they conduct the IDE study in accordance with the investigational plan and with FDA's regulations.[43] The agency expects the monitoring to include direct patient evaluation at predefined follow-up intervals. The investigators and the sponsor are also bound to strict recordkeeping and reporting requirements.[44] Further, all sites and records associated with IDE studies are subject to FDA inspection.[45] IDE studies must receive approval from an Institutional Review Board ("IRB"), and all participants in IDE studies must provide informed consent.[46] Each investigator in an IDE study must disclose all financial interests to the sponsor and the sponsor must, in turn, provide FDA with a complete and accurate certification or disclosure statement.[47] The data that Smith & Nephew submitted complied with virtually none of these elements.[48]

---

39 Id.

40 See 21 C.F.R. § 812.1.

41 Id. § 812.25(b).

42 See id. §§ 812.25(e), 812.43(d).

43 See id. §§ 812.43(c)(4)(i), 812.100.

44 See 21 C.F.R. §§ 812.140, 812.150.

45 See id. § 812.145.

46 Id. §§ 812.2(b)(1)(ii), 812.42, 812.20(b)(11).

47 Id. § 812.43(c)(5). See also id. Part 54.

48 There is no reference in either FDA's Executive Summary or the Panel Transcript to an FDA investigation of Dr. McMinn's clinical site.

Foreign studies are not exempt from the need to meet the "valid scientific evidence" standard. Not only must these studies meet that requirement, but PMA applications based on such data must satisfy an additional element: proving that the data are applicable to the U.S. population and to U.S. medical practice.[49] As will be described below, the applicability of Smith & Nephew's data to the U.S. population is, at best, unclear.

ii. Least Burdensome Approach does not Lower the Applicable Data Standards

In determining whether a medical device, including a Class III medical device, is safe and effective, FDA has been charged by Congress to "consider, in consultation with the applicant, the least burdensome appropriate means of evaluating device effectiveness that would have a reasonable likelihood of resulting in approval."[50] FDA defines "least burdensome" as "a successful means of addressing a premarket issue that involves the most appropriate investment of time, effort, and resources on the part of industry and FDA," and has applied the concept to all devices and device components that it regulates.[51] Device manufacturers, however, must meet all statutory and regulatory obligations, "including preparation of appropriate, scientifically sound data to support applications."[52] The least burdensome approach does "not lower the criteria for demonstrating substantial equivalence or reasonable assurance of safety and effectiveness,"[53] and it "is not intended as a way for either FDA or Industry to 'cut corners' regarding the generation of data to support a marketing application."[54] In

---

49 21 C.F.R. § 814.15(d).

50 21 U.S.C. § 360c(a)(3)(D)(ii).

51 FDA, The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles; Final Guidance for FDA and Industry, at 2 (Sept. 30, 2002), available at http://www.fda.gov/cdrh/ode/guidance/1332.pdf [hereinafter Least Burdensome Guidance].

52 Id.

53 Id. at 1 (emphasis added).

54 Medical Officer, FDA, Office of Device Evaluation, Division of General and Restorative Devices, Orthopedic Divisions Branch, Review Memorandum, Hip Guidance Document Submission: Clinical Trial Design for Hip Replacement Systems, at 2 (Apr. 19, 2004), available at http://www.fda.gov/ohrms/dockets/ac/04/briefing/4049b2_01_Hip%20Guidance%20Review.htm [hereinafter Medical Officer Review Memorandum], (citing FDA, Least Burdensome Guidance, supra note 51 (emphasis added)).

enacting the least burdensome approach, Congress did not change the statutory requirements for medical device approvals.

The "least burdensome" provision notwithstanding, a Class III medical device can be approved through the PMA process only if the sponsor demonstrates, through valid scientific evidence, the safety and effectiveness of the device. The application of the least burdensome approach must take into account: the characteristics of a device; the risk presented by a device; a device's conditions of use, warnings, and other restrictions; and experience with a device.[55] Devices with novel designs, those that present significant risk to patients, and those for which there is little experience may require well-controlled clinical trials to demonstrate a reasonable assurance of safety and effectiveness.[56] Additional points identified by FDA as crucial in determining whether well-controlled clinical trials constitute the least burdensome approach include the target population for the device; the appropriate patient inclusion and exclusion criteria for the use of the device; and what is already known about this patient population and indication.[57] In cases where these points can be addressed properly only through a well-controlled clinical trial, these studies are the least burdensome approach. Given that the BHR presents unique approval challenges, such as being a first-of-a-kind device with a new indication, surgical risks associated with a new technique, and lack of evidence of applicability of the device to the U.S. population, the "least burdensome" approach in this case can only be a well-controlled clinical trial.

c. The Data Presented by Smith & Nephew do not meet Legal Requirements

As stated above, Smith & Nephew's PMA for the BHR relied primarily on the retrospective review of the clinical experience of a single surgeon. Data from other physicians do not constitute a data source on which Smith & Nephew can, or did, rely. Data from Dr. McMinn's 2,385 BHR procedures were divided by Smith & Nephew into three main cohorts: the "X-ray cohort" with the first 124 BHR implantations performed by Dr. McMinn in 1997 (however, as discussed later in this petition, Smith & Nephew has stated that the x-rays were of poor quality and not suitable for measurements[58]); "the

---

55 FDA, Center for Devices and Radiological Health, Guidance for Industry and FDA Reviewers on Evidence Models for the Least Burdensome Means to Market: Draft Guidance, at 3 (Sept. 2, 1999), available at http://www.fda.gov/ohrms/dockets/98fr/992873gd.pdf [hereinafter Models Draft Guidance].

56 See, e.g., Medical Officer Review Memorandum, supra note 54, at 2.

57 Models Draft Guidance, supra note 55, at 5.

58 Executive Summary, supra note 1, at 26.

Oswestry cohort" with the next 1,502 BHR implantations performed by Dr. McMinn between 1998 and 2002; and the "McMinn cohort" with the next 759 BHR implantations performed by Dr. McMinn between 2002 and 2004.[59] The McMinn cohort contributed to the data assessing the safety of the BHR, including adverse events and revisions. The X-ray cohort contributed to the assessment of the BHR's effectiveness through radiographic data.[60] The combined X-ray and Oswestry cohort contributed to the assessment of survivorship and patient satisfaction with the BHR.[61] Smith & Nephew's safety and effectiveness data have many limitations and do not demonstrate reasonable assurance and effectiveness of the BHR.

i. Smith & Nephew's Safety Data

1. Patient Self-Assessments

According to an FDA summary of Smith & Nephew's data, annual patient-completed, mail-in questionnaires serve as the sole source of pain and function information for the PMA.[62] The PMA data do not include the results of any post-surgical physician evaluations. That is, the entire efficacy data set is based solely on annual patient self-reports without any medical assessments.

The Oswestry Outcome Center sent the self-assessment questionnaires to the 1,626 patients in the combined X-ray and Oswestry cohorts.[63] These patients had a mean age of fifty-three, with an age range of thirteen to eighty-six.[64] Smith & Nephew's proposed indication for the BHR, however, is for patients who are at risk for requiring future, ipsilateral hip joint revision.[65] Smith & Nephew has asserted that one factor that can increase risk of revision surgery is age less than fifty-five years at index surgery.[66]

---

59 Panel Transcript, supra note 1, at 127 (testimony of John S. Goode).

60 Radiographic evaluations were not provided to FDA for the 1,502 BHR implantations in the Oswestry cohort or for the 759 BHR implantations in the McMinn cohort. Executive Summary, supra note 1, at 50.

61 Panel Transcript, supra note 1, at 128 (testimony of John S. Goode).

62 Executive Summary, supra note 1, at 27.

63 See id. at 24.

64 FDA, Summary Minutes, Meeting of the Orthopedic and Rehabilitation Devices Advisory Panel, Open Session, Hilton Washington D.C. North, Gaithersburg, MD, at 12 (Sept. 8, 2005) [Attachment A].

65 Executive Summary, supra note 1, at 3.

66 Id.

Smith & Nephew reported that eight patients did not consent to the follow-up. Further, more than eleven percent of the patients did not complete all of the questionnaires: 180 individuals failed to return their "last theoretical expected mail-in questionnaire"; eighty-four individuals failed to return "at least 2 yearly evaluations"; and ninety-six failed to return "their last evaluation."[67] In a well-controlled clinical study conducted pursuant to a protocol, these would all be considered protocol deviations and potential exclusions from the data set.

These questionnaires asked patients about their pain, function, movement, revisions, and any adverse events.[68] According to FDA, "[n]o other sources of pain and function were used to support [Smith & Nephew's] PMA."[69] Patients' responses were retrospectively reviewed by an auditing company that recorded every patient comment without interpretation.[70] From the patients' self-assessments, the Oswestry Outcome Center generated the Oswestry-modified Harris Hip ("OSHIP") Score, a novel scale.

---

67 Id. at 24; Panel Transcript, supra note 1, at 132 (testimony of John S. Goode).

68 Executive Summary, supra note 1, at 27. Smith & Nephew stated to FDA that all 2,385 procedures performed by Dr. McMinn were audited. Panel Transcript, supra note 1, at 68 (testimony of Marcus Valez-Duran). A consultant for Smith & Nephew has stated that because the audit was a "retrospective review, . . . every single incident had to be recorded" as an adverse event. Id. at 114 (testimony of Marie Marlowe, Consultant to Smith & Nephew). According to FDA's evaluation of Smith & Nephew's PMA submission, Smith & Nephew "believe[s] that all reported adverse event information has been captured." Id. at 133 (testimony of John S. Goode). Given the loss to follow-up and the non-standardized patient observations, it is difficult to accept that all adverse events have been captured. This is especially the case in light of the fact that patients were assessing themselves rather than an investigator. For example, patients may not associate adverse events with the implant or recall events that occurred ten months before they completed the questionnaire.

Moreover, FDA has expected sponsors of other PMA applications to report information about adverse events in a clinical context that reflects timing of events since surgery. Smith & Nephew's data were not collected at defined follow-up intervals by an investigator, which leaves any reported adverse events devoid of clinical context. FDA has also required other sponsors of PMAs for metal-on-metal resurfacing arthroplasty devices to present the agency with complete analyses and reports for retrieved devices. The agency does not appear to have required this information from Smith & Nephew.

69 Panel Transcript, supra note 1, at 135-36 (testimony of John S. Goode).

70 Id. at 114-15 (testimony of Marie Marlowe).

FDA has never before evaluated the OSHIP Score as a legitimate measure of patient function in support of a PMA application.[71] Historically, FDA has relied on the well-established Harris Hip Score to assess the success of hip arthroplasty. According to Smith & Nephew's PMA application, the OSHIP score is an overall index score that is similar to that of the Harris Hip Score. The Harris Hip Score includes information obtained through a physician or examiner evaluation. The OSHIP Score, on the other hand, is determined completely by patients' own self-assessments. Because there is no physician or examiner evaluation, the OSHIP score does not include three questions used to determine the Harris Hip Score: physician assessment of range of motion; physician assessment of absence of deformity; and physician assessment of a patient's ability to put on socks and tie their shoes.[72] Instead, the OSHIP score merely asks patients to estimate their own ability to flex their hip.[73]

FDA should be concerned about the use of patient self-assessments in place of physician assessments for pain and function. A study in Biomedical Sciences Instrumentation revealed that self-administered patient outcome measures have limitations and the validity of self-administered patient outcome questionnaires can be severely impacted by the patients' understanding of the questions asked, as even the most seemingly simple questions are subject to misinterpretation.[74] Additionally, Chang S. Lao, Ph.D., a statistician with FDA, raised concerns about the true correlation of the OSHIP score to the Harris Hip Score. According to Dr. Lao, the correlation is "unclear" and "subject to potential bias" because of masking and problems with randomization.[75] Moreover, the correlation presents statistical difficulties because there was no sample size justification between the patients in whom the BHR was implanted, and because there is missing OSHIP data from patients who did not complete first, second, and fifth year responses.[76] Thus, the secondary efficacy measure relied upon in the PMA comes from a

---

71 Id. at 135 (testimony of John S. Goode).

72 Executive Summary, supra note 1, at 28.

73 Id.

74 Ragab AA., Validity of Self-Assessment Outcome Questionnaires: Patient-Physician Discrepancy in Outcome Interpretation, 39 Biomed. Sci. Instrum. 579-84 (2003) (abstract [Attachment B] available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12724955&dopt=Abstract).

75 Panel Transcript, supra note 1, at 155, 163 (testimony of Chang S. Lao, Ph.D., Division of Biostatistics, Office of Surveillance and Biometrics, FDA).

76 Id. at 155, 165 (testimony of Dr. Chang S. Lao).

new scale lacking general acceptance, with no valid correlation to accepted scoring instruments, and is based exclusively on patient self-assessments.

2. Dr. McMinn's and Referring Physicians' Evaluations

Smith & Nephew reported that Dr. McMinn performed evaluations of his patients according to standard medical practice and with a retrospective review of patient charts. Dr. McMinn did not conduct his post-operative patient visits pursuant to a standard protocol, however. Thus, the times at which patients were evaluated, and the content of the evaluations, were not pursuant to a standard, predetermined protocol. There were no predefined follow-up time windows, standard clinical evaluations, standard adverse report forms, or standard radiographic evaluations.[77]

In addition, Dr. McMinn was the operating surgeon, not the primary care physician for the patients who received the BHR. There apparently were no instructions issued to the referring physicians as to what reports to submit to Dr. McMinn or when to submit them. Neither FDA's Executive Summary of the data submitted by Smith & Nephew in support of its PMA, nor testimony about Dr. McMinn's data presented before the Panel indicate whether the referring physicians followed a consistent format or protocol in the patient evaluations that they submitted to Dr. McMinn. It is unlikely that, in absence of a protocol and predefined forms, records collected by different physicians were recorded and presented in a consistent format or with identical types of information included.

FDA has repeatedly made known the value that the agency places on protocols and adherence to them. For example, the agency has issued multiple Warning Letters to sponsors of device clinical investigations and to investigators for deviating from protocols. These letters frequently cite the failure to conduct follow-up visits at the time intervals predetermined by the protocol.[78] One representative Warning Letter specifically

---

77 Executive Summary, supra note 1, at 24.

78 See, e.g., Letter from Timothy A. Ulatowski, Director, Office of Compliance, Center for Devices and Radiological Health, FDA to John Brannon Smoot, M.D., 2-3 (July 13, 2004), available at http://www.fda.gov/foi/warning_letters/g4838d.pdf; Letter from Timothy A. Ulatowski, Director, Office of Compliance, Center for Devices and Radiological Health, FDA to Peter A. Engelhard, D.O., President, Apex International Health, 2 (June 14, 2004), available at http://www.fda.gov/foi/warning_letters/g4776d.pdf; Letter from Timothy A. Ulatowski, Director, Office of Compliance, Center for Devices and Radiological Health, FDA to James G. Howe, M.D., University of Vermont College of Medicine, 2 (Jan. 16, 2004), available at http://www.fda.gov/foi/warning_letters/g4498d.pdf; Letter from Larry Spears,

cites the failure of an investigator to take x-rays at the time intervals designated in the study protocol. According to the agency, this failure violated its regulations.[79] In addition to these Warning Letters, FDA employees have stated publicly that the most common deficiency found among clinical investigators is failure to follow investigational plans or regulations.[80]

ii. Smith & Nephew's Effectiveness Data

1. Survivorship Data

Smith & Nephew's primary effectiveness data for the BHR was survivorship, i.e., whether the BHR was still in place, and a review of radiographs in a small percentage of patients in whom Dr. McMinn implanted the BHR. The survivorship study was conducted through the patient self-assessment questionnaires sent to the 1,626 patients grouped into the X-ray and Oswestry cohorts. Of these 1,626 cases, 601 were eligible for five-year follow-up. For reasons not explained in FDA's Executive Summary of Smith & Nephew's data, the company submitted survivorship data on only 546 of these 601 individuals, without accountability for the remaining fifty-five patients.[81] More importantly, the use of survivorship to measure effectiveness is questionable. Survivorship is a measure of freedom from re-operation, but does not measure the effect of the treatment. The primary effectiveness measure in the PMA for the BHR, therefore, cannot even measure what it is trying to prove (i.e., effectiveness).

2. Radiographic Data

As stated above, Smith & Nephew provided radiographic data only in the first 124 implantations. The sponsor asserted that Dr. McMinn, pursuant to standard medical practice, performed radiographic evaluations on all of the patients in whom he implanted

---

Acting Director, Office of Compliance, Center for Devices and Radiological Health to Donald R. Johnson, M.D., Carolina Spine Institute 2-3 (Apr. 27, 2001), available at http://www.fda.gov/foi/warning_letters/g1213d.pdf.

79 Letter from Timothy A. Ulatowski, Director, Office of Compliance, Center for Devices and Radiological Health, FDA to John Brannon Smoot, M.D., supra note 71, at 2-4.

80 See, e.g., Michael E. Marcarelli, PharmD, Director, Division of Bioresearch Monitoring, Office of Compliance, Center for Devices and Radiological Health, Device Bioresearch Monitoring: Perspectives, available at http://www.fda.gov/cdrh/present/advamed-052505-marcarelli/.

81 Executive Summary, supra note 1, at 26.

the BHR.[82] The radiographs for the other 2,261 patients were not, however, included in the PMA. Of the first 124 patients who received the BHR from Dr. McMinn, only 108 presented five-year radiographs for review.[83] Of the 108 sets of radiographs presented to support the effectiveness of the BHR, only eighty-nine included immediate post-operative films. Smith & Nephew stated that, for the other nineteen cases, the immediate post-operative films were too poor in quality to make precise post-operative measurement comparisons.[84] Therefore, in each of the 108 cases, later post-operative films were used as baselines. In a prospective IDE study, each instance of an unusable immediate post-operative radiograph would be a protocol violation and could be potentially excluded. If there had been a protocol (which there was not), and if the protocol had called for the use of the immediate post-operative film (which is generally the case), then Smith & Nephew's X-ray cohort would contain zero protocol-compliant patients.

Moreover, the majority of the patients included in the X-ray cohort were men with osteoarthritis.[85] Yet the proposed indication is much broader: "for use in patients

---

82 See id. at 24.

83 Id. at 26. FDA's Executive Summary of Smith & Nephew's data did not reveal why so few radiographs were presented for review. Of the original 124 patients, one died from a disease unrelated to the BHR and four patients required revision surgery. Smith & Nephew reported that three of these revisions were required due to infection, while one was due to femoral neck fracture. Ten other individuals, however, were missing due to lost to follow-up or incomplete film records. Id. Out of the 2,385 BHR devices implanted across the three cohorts, there were twenty-seven reported revisions – the majority of which were required because of femoral neck fracture. Panel Transcript, supra note 1, at 74 (testimony of Marcos Valez-Duran).

84 Executive Summary, supra note 1, at 26.

85 Panel Transcript, supra note 1, at 70 (testimony of Marcos Valez-Duran). See also Executive Summary, supra note 1, at 33. The majority of patients in each of the three cohorts were men with osteoarthritis. Of the 124 patients in the X-ray cohort, eighty-one were men and forty-three were women. Ninety-two (74.2%) of the 124 patients had osteoarthritis, twenty-two (17.7%) had DDH, seven (5.6%) had avascular necrosis, two (1.6%) had inflammatory arthritis, and one (0.8%) had "other." Of the 1,502 patients in the Oswestry cohort, 1,082 were men and 420 were women. Of these, 1,171 (78.0%) had osteoarthritis, 197 (13.1%) had DDH, fifty-nine (3.9%) had avascular necrosis, thirty-nine (2.6%) had inflammatory arthritis, and thirty-six (2.4%) had "other." Of the 759 patients in the McMinn cohort, 520 were men and 239 were women. Of these, 526 (69.3%) had osteoarthritis, 158 (20.8%) had DDH, thirty-one (4.1%) had avascular necrosis, sixteen (2.1%) had inflammatory arthritis, and twenty-eight (3.7%) had "other."

requiring primary hip resurfacing arthroplasty due to: [n]on-inflammatory arthritis (degenerative joint disease) such as osteoarthritis, traumatic arthritis, avascular necrosis, or dysplasia/DDH, or [i]nflammatory arthritis such as rheumatoid arthritis," and who are at risk of requiring future, ipsilateral hip joint revision.[86] The radiographic data presented do not include evidence of the effectiveness of the BHR in patients with other forms of non-inflammatory arthritis (degenerative joint disease), including traumatic arthritis, avascular necrosis, or dysplasia/DDH, or with inflammatory arthritis, such as rheumatoid arthritis. However, Smith & Nephew's proposed indications for use include these diagnoses, despite this lack of patients in the X-ray cohort with these indications.

Smith & Nephew presented arguments that the five-year radiographic success result was 97.2%. Since the patients included in the X-ray cohort were mostly men with osteoarthritis, there were few patients with other forms of arthritis who received the BHR. Further, Smith & Nephew has asserted that there were predefined failure and success criteria for the radiographic data.[87] This is difficult to accept, given that the radiographs were not collected pursuant to a specific protocol or within the context of a well-controlled investigation. Though a prospective protocol may have been used to assess the radiographs, the radiographs were not collected pursuant to a prospective protocol. Thus, the radiographic data are from a review of X-rays of questionable quality taken at non-standardized intervals and evaluated according to post-hoc criteria.

iii. The PMA Does Not Contain Data from Well-Controlled Investigations

FDA stated in its Executive Summary of Smith & Nephew's data that Smith & Nephew's BHR PMA rests upon "clinical data essentially from one source."[88] John S. Goode, a biomedical engineer and reviewer in FDA's Orthopedic Devices Branch who serves as the lead investigator for Smith & Nephew's PMA used these exact words when he testified before the Panel.[89] Well-controlled investigations are at a minimum: prospective studies designed pursuant to a specific protocol with data captured in a reproducible way; conducted with a control group; subject to strict oversight and

---

Id. From these numbers, it does not appear that any of the patients had traumatic arthritis, and it is unclear how many of the patients with "inflammatory arthritis" had rheumatoid arthritis. See id.

86 Executive Summary, supra note 1, at 3.

87 Panel Transcript, supra note 1, at 73 (testimony of Marcos Valez-Duran).

88 Executive Summary, supra note 1, at 0.

89 Panel Transcript, supra note 1, at 118 (testimony of John S. Goode) (stating that "[t]he PMA is supported by clinical data essentially from one source").

monitoring; and conducted with enough independence to minimize bias. The primary data presented by Smith & Nephew in support of their PMA for the BHR—the retrospective review of Dr. McMinn's clinical experiences—do not satisfy any of these elements.

Failure to maintain accurate, complete, and current case histories has been cited by FDA as a protocol violation and as a violation of federal regulations.[90] Well-controlled investigations rely upon the use of case report forms ("CRFs") to ensure that the relevant data are reproducibly captured at each critical, predefined endpoint. FDA can use CRFs to identify protocol violations. The agency cited a violation of a protocol requiring in-person follow-up when the CRF indicated that a study subject was only followed-up over the telephone. The agency determined that the "results documented on that CRF could not be performed by phone contact."[91] CRFs also are essential for ensuring that the data are homogeneous, rather than varying patient by patient. Dr. McMinn, who was not conducting a study at the time he performed his surgeries, did not use CRFs. Rather, data were obtained based on a retrospective review of his notes.[92] It is common during the monitoring of well-controlled studies to examine surgeon notes for consistency with CRFs and the protocol; however, that is completely different than reviewing the non-standardized notes years later as a key basis of the supportive data.

The protocols for well-controlled investigations define inclusion and exclusion criteria which can then be generalized to a predefined population. Dr. McMinn did not perform well-controlled investigations and did not design an investigational protocol, and the patients in whom Dr. McMinn implanted the BHR were not selected based on predefined inclusion and exclusion criteria. Dr. McMinn "did not predefine a set of diagnostic indications for the device, but instead provided a list of the diagnostic indications for the patients implanted with the device."[93] The patient pool from which Dr. McMinn selected patients to receive the BHR were referred to him by other physicians; Dr. McMinn estimates that eighteen out of every twenty patients were

---

90 See Letter from Timothy A. Ulatowski , Director, Office of Compliance, Center for Devices and Radiological Health, FDA to Reynaldo F. Mulingtapang, M.D., 2-3 (Oct. 7, 2005), available at http://www.fda.gov/foi/warning_letters/g5506d.pdf (citing the failure to maintain accurate, complete, and current case histories as a violation of 21 C.F.R. § 812.140(a)(3)).

91 Id. at 3.

92 See Panel Transcript, supra note 1, at 112-13 (testimony of Derek J.W. McMinn, FRCS, Orthopedic Surgeon, Birmingham Nuffield Hospital).

93 Id. at 121 (testimony of John S. Goode).

referred to him because they were young and had good bone stock—factors that favor resurfacing arthroplasty over total hip arthroplasty.[94]

Though Dr. McMinn appears to have been successful in implanting the BHR, the factors that he says he used to decide whether to implant the BHR were not developed as inclusion/exclusion factors from a standard protocol. Rather, "[a]s an alternative and in order to retrospectively develop the indications for use in physician labeling, [Smith & Nephew] provided a list of the factors that contributed to Dr. McMinn's decision to perform a total hip replacement . . . in certain patients rather than the BHR hip resurfacing procedure."[95] Smith & Nephew has not presented actual clinical data to support any factors as selection criteria for patients.[96] During the same period in which Dr. McMinn implanted BHR devices, he also implanted conventional hip prostheses in other patients.[97] Without having conducted well-controlled investigations, however, these groups were not compared; there is no control group against which to compare data from patients who received the BHR.[98] Consequently, labeling that establishes the appropriate patient population for the BHR cannot be written. Other manufacturers of hip systems, including the petitioner, have been directed by FDA to use a control group and inclusion/exclusion criteria to ensure that proposed labeling corresponds to the population studied.

Smith & Nephew's data contain yet other significant flaws as a result of not being generated from well-controlled investigations. For example, there is no reproducibility. As Smith & Nephew cannot request additional follow-up or clarifications with respect to the 3,374 BHR cases performed by 140 other surgeons, the limited information that is available from these other experiences with the BHR does not constitute reproducibility.[99] Thus, as Smith & Nephew and FDA have admitted, the primary data on which the PMA for the BHR rests are the results obtained from Dr. McMinn. Dr. McMinn developed the BHR; there is no valid scientific evidence in the PMA that other surgeons can use it safely and effectively. The mere anecdotal report of other physicians' use does not scientifically demonstrate reproducibility of Dr. McMinn's results. Dr. McMinn had been using the BHR for years before the data set used in the PMA was

---

94 Id. at 111 (testimony of Dr. Derek J.W. McMinn).

95 Id. at 121-22 (testimony of John S. Goode).

96 See id. at 195 (testimony of Cecil Rorabeck, M.D., Consultant for Smith & Nephew).

97 Id. at 121 (testimony of John S. Goode).

98 See id.

99 See Executive Summary, supra note 1, at 23.

generated. Thus, all that the PMA can show are the results obtained by the surgeon-inventor after several years of experience with the BHR. Although Dr. McMinn treated numerous patients, this does not support reproducibility either. At most, Dr. McMinn's own experience could show he could reproduce his own results.[100]

There was also no concurrent monitoring of Dr. McMinn's implantations. The monitoring of studies is a key element of ensuring the validity and completeness of the data. Monitoring by qualified monitors is required for IDE studies under FDA's regulations.[101] A review of a surgeon's notes years after the fact is not a substitute for concurrent monitoring.

iv. Additional Safety and Effectiveness Issues not Demonstrated by Smith & Nephew

In addition to the problems inherent in Smith & Nephew's data because they were not generated from well-controlled investigations, significant additional issues related to the safety and effectiveness of the BHR remain unresolved. These issues include: the safety and effectiveness of the different types of available iterations of the BHR; the ability of U.S. surgeons to implant the device; and the applicability of the data to the U.S. population. These issues are discussed below.

1. Proper Assessment of Different Device Iterations

Smith & Nephew's BHR system is available in twenty-three different cups across the three categories of cups—standard, dysplasia, and bridging.[102] There are design and operative technique differences between these three categories. The data presented to FDA do not assess these three categories individually. For example, Smith & Nephew did not present separate inclusion and exclusion criteria for each of these iterations. A well-designed investigation would have included a separate arm for each iteration in order to accrue enough data to evaluate the differences between the BHR system and control devices. FDA has historically required such data and information in PMA applications and has asked for that data from the petitioner. According to the agency, "a detailed justification for the poolability" of data resulting from different iterations of a

---

100 As set forth here, there are many reasons to question the internal reproducibility of Dr. McMinn's data.

101 See 21 C.F.R. §§ 812.25(e), 812.43(d).

102 See Panel Transcript, supra note 1, at 55 (testimony of Dr. Derek J.W. McMinn), 119-20 (testimony of John S. Goode).

device must be presented if the data from the different iterations are pooled.[103] Such data and information, however, are missing from Smith & Nephew's application.[104]

2. Training U.S. Surgeons and the Applicability of Smith & Nephew's Data to the U.S. Population

Dr. McMinn is an expert surgeon with extensive experience in resurfacing. He designed the BHR, has done thousands of surgeries with it, and is therefore more familiar with the BHR than any other surgeon in the world. No data were presented to the Panel that show that Dr. McMinn's reported results would be replicated by U.S. surgeons.

The type of surgery required to implant the BHR—femoral head resurfacing arthroplasty—is especially challenging and is not a standard procedure taught in U.S. orthopedic residency programs.[105] Smith & Nephew did not present data analyzing the expected learning curve for U.S. surgeons, and has not specified how many BHR implantations a U.S. surgeon would have to perform before being able to perform the surgery reliably.[106] In fact, Smith & Nephew has acknowledged that "[t]here is no data" on the learning curve for U.S. surgeons.[107] Consequently, FDA should look closely at "whether widespread implementation of this technique would or would not reflect the results seen in countries where the procedure is more commonplace and may be part of their usual training program."[108] Given that the only data on which the PMA rests come from the single U.K. surgeon-inventor, it is difficult to discern a valid basis for extrapolating from Dr. McMinn's experiences to the U.S. orthopedic surgeon community. Moreover, the use of the BHR by other physicians cannot, by itself, demonstrate that Dr. McMinn's experience can be extrapolated to the United States. Smith & Nephew has not presented any data that define the learning curve experienced by these other 140 surgeons.

---

103 Id.

104 Moreover, according to FDA's review of Smith & Nephew's PMA submission, "almost all patients received either the standard cup or the dysplasia cup styles." Panel Transcript, supra note 1, at 144 (testimony of John S. Goode). Therefore, Smith & Nephew's data do not fully evaluate all of the iterations of the BHR.

105 Panel Transcript, supra note 1, at 37 (testimony of Dr. William Maloney).

106 See id. at 222 (question by Panel Voting Member Choll W. Kim, M.D., Ph.D., University of California, San Diego).

107 Id. at 223 (testimony of Dr. Cecil Rorabeck).

108 Id. at 182 (statement by Panel Deputized Voting Member Jay D. Mabrey, M.D., Baylor University Medical Center).

Though Smith & Nephew has not identified a learning curve for U.S. surgeons, the company has presented its plan to train U.S. surgeons to implant the BHR if the device is approved by FDA. Smith & Nephew plans to bring a group of "core surgeons" to Birmingham, United Kingdom, to observe an implantation of a BHR and to receive lectures and "hands-on experience." This hands-on experience will be on sawbones only. The company then plans to provide the core surgeons with follow-up lectures and additional hands-on components, including sawbones and cadavers. These surgeons would return to the United States, begin implanting the BHR in live patients, and train other surgeons in the procedure.[109] Neither sawbones nor cadaver surgery can adequately replace the learning curve accomplished by a surgeon participating in a well-controlled IDE clinical study. In other words, the first time these surgeons will implant the BHR will be on patients in the United States, without being supervised by surgeons who have had experience. Our concern with Smith & Nephew's training plan is that the core surgeons will not have progressed sufficiently up the learning curve prior to their first experience implanting the BHR in a live patient in the United States. (As stated above, the learning curve for U.S. surgeons has not even been established.) In contrast, surgeons participating in a prospective, multi-center IDE clinical trial, such as the one sponsored by the petitioner, master the learning curve in a more controlled manner.

This petition does not assert that Smith & Nephew is unable to train surgeons, that the company's training program could not work, or that U.S. surgeons cannot learn how to implant the BHR. However, the utter lack of data in the United States combined with the limitations in the training program raise significant questions as to whether Dr. McMinn's results will apply to U.S. surgeons.

Smith & Nephew has asserted that orthopedic surgeries are performed in the same manner in both the United States and the United Kingdom.[110] At the Panel meeting held to consider the PMA for the BHR, the sponsor provided no specific data to support this claim. The surgical technique required to implant the BHR is not taught in the United States.[111] Moreover, given that the pivotal data are generated by a single surgeon in the U.K., it is extremely difficult to see any scientific basis for saying that these experiences can be readily extrapolated to multiple surgeons treating a heterogeneous population of U.S. patients.

Indeed, Dr. Chang S. Lao, one of FDA's own statisticians, specifically indicated three reasons why the data presented in the PMA application are statistically difficult to generalize to the U.S. population. The first reason identified by Dr. Lao is that Smith &

---

109 Id. at 88-90 (testimony of Neal Defibaugh), 92-93 (testimony of Dr. Marc Thomas, Employee, Smith & Nephew).

110 Id. at 69 (testimony of Marcos Valez-Duran).

111 Id. at 37 (testimony of Dr. William Maloney).

Nephew's data source was a single physician with no multi-center trial. According to Dr. Lao, there was a "unique investigator, Dr. McMinn."[112] Thus, Dr. Lao, one of FDA's own statisticians, did not recognize the use of the BHR by other physicians as a data source. The other reasons why Smith & Nephew's data are statistically difficult to generalize to the U.S. population identified by Dr. Lao are that there was no control group and the data were not randomized, and that the data resulted from combined retrospective and prospective registry data.[113] Since Smith & Nephew's data did not result from a predefined sample pursuant to a predefined sample size, and since Dr. McMinn did not study his patients based on a prespecified hypothesis, the data cannot be generalized to a group or subgroup of patients in the United States.

Finally, the Smith & Nephew data do not appear to be representative of the target population in the United States. For example, there are higher percentages of minority races in the United States than in the United Kingdom; FDA has stated that there are "noted differences in the higher percentage of people with African descent and other races in the general U.S. population as compared to the general U.K. population."[114] The agency's Executive Summary of Smith & Nephew's data revealed that 75.1% of the U.S. population is white, 12.3 % is of African descent, 3.6% is of Asian descent, 0.9% is Native American, 0.1% is Pacific Islander, 2.4% is of mixed race, and 5.5% is classified as "other race."[115] In contrast, 92.1% of the overall U.K. population is white, 2.0% is of African descent, 4.4% is of Asian descent, 1.2% is of mixed race, and 0.4% is classified as "other race."[116] Further, FDA has stated that "[t]here was no racial or ethnic data, origin data, for the patients in the PMA."[117] This further compounds the difficulty of applying Smith & Nephew's data to the U.S. population.

d. Review of Smith & Nephew's PMA by the Orthopedic and Rehabilitation Devices Panel

---

112 Id. at 154 (testimony of Dr. Chang S. Lao).

113 Id.

114 Id. at 150 (testimony of John S. Goode).

115 Executive Summary, supra note 1, at 57.

116 Id. The 4.4% of the U.K. population that is of Asian descent includes 0.4% specifically listed as Chinese. Id. FDA's Executive Summary did not provide values for Native American and Pacific Islander populations in the United Kingdom. Id.

117 Panel Transcript, supra note 1, at 150 (testimony of John S, Goode).

FDA's Orthopedic Devices Branch of the Division of General, Restorative, and Neurological Devices, Center for Devices and Radiological Health, presented Smith & Nephew's PMA application to the Panel. FDA sought the Panel's expert clinical opinion on various issues, including: "the safety and effectiveness data collection methods, the applicability of the foreign data from a single investigator and United Kingdom practice of medicine to the target United States population and practice of medicine, and the study results with respect to the device's safety and effectiveness."[118] Thus, FDA's questions to the Panel concerning the applicability of Smith & Nephew's data to evaluate the safety and effectiveness of the BHR were based on the recognition that the data were derived from only one physician. The Panel narrowly voted to recommend approval of the BHR with conditions. For the reasons set forth in this petition, FDA should not follow the Panel's recommendation.[119]

The agency specifically asked the Panel to address seven questions before making their recommendation: (1) whether the evaluation methods used to collect safety data were reliable to assess the safety of the device; (2) whether the evaluation methods used to collect effectiveness data were reliable to assess the effectiveness of the device; (3) whether the foreign data from a single investigator and the U.K. practice of medicine are applicable to the target U.S. population and the U.S. practice of medicine; (4) whether the data contained in the PMA application provide reasonable assurance of safety; (5) whether the data contained in the PMA application provide reasonable assurance of effectiveness; (6) whether the patient selection methods and data presented in the PMA application support the proposed labeling indication; and (7) whether the Panel had any remaining questions about the safety and effectiveness of the BHR that should be addressed in post-approval studies.[120]

Although the Panel recommended by a three-to-two vote that the PMA be approved with conditions, Panel members expressed serious reservations throughout the meeting. The split vote in favor of approval should not mask the significant concerns expressed by multiple Panel members. For example, the Panel Chairperson acknowledged that Smith & Nephew's PMA was "unusual" in that it was "based on a retrospective study designed by a single surgeon based on a British data set."[121] Other

---

118 Executive Summary, supra note 1, at 0 (emphasis added).

119 FDA, of course, is free not to accept a panel's recommendation. See 21 C.F.R. § 14.5(b) (stating that "[t]he Commissioner has sole discretion concerning action to be taken and policy to be expressed on any matter considered by an advisory committee.")

120 See Panel Transcript, supra note 1, at 247-89.

121 Id. at 182 (statement by Acting Panel Chair Sanjiv H. Naidu, M.D., Ph.D., Pennsylvania State College of Medicine).

Panel members characterized the data as "far from impeccable," and said it "falls far short of what a study should be."[122] Four of the seven Panel members concluded that Smith & Nephew's safety data collection methods were not adequate.[123] On the issue of whether the methods through which Smith & Nephew collected effectiveness data were adequate, one Panel member questioned the "validity" of how Smith & Nephew described its data collection and asserted that if the data were collected prospectively and analyzed retrospectively, "the data would be collected in a uniform fashion. You wouldn't have three cohorts."[124] This Panel member went on to state that he was not questioning the "actual contents of the data, but the method by which it was collected," and that he did not believe that the method by which it was collected was appropriate.[125]

Four of the seven Panel members concluded that Smith & Nephew's data were not applicable in the United States.[126] One of these Panel members emphasized that the issue of applicability to the United States was not that the data were foreign or that the U.K. population was unique, but that the data were from a single clinician, and that this did not create "reassurance that it's applicable to the U.S. population at risk."[127] Another of these Panel members expressed concern that "we have no estimate whatsoever of the variability across surgeons or clinical sites. All we have is the experience of the inventor."[128] The Panel's discussion focused on Dr. McMinn as the sole source of the safety and effectiveness data for the BHR PMA.

Although the Panel unanimously agreed that the data presented reasonable assurance that the BHR is safe,[129] not all Panel members believed that data presented by

---

122 Id. at 247 (statement by Panel Deputized Voting Member Michael B. Mayor, M.D., Dartmouth Hitchcock Medical Center), 248 (statment by Panel Deputized Voting Member Brent A. Blumenstein, Ph.D., TriArc Consulting).

123 Id. at 247-53 (statements by Dr. Brent A. Blumenstein, Dr. Jay D. Mabrey, Dr. Choll W. Kim, and Panel Consumer Representative Connie Wittington, M.S.N., R.N., O.N.C., Piedmont Hospital).

124 Id. at 256 (statments by Dr. Choll W. Kim).

125 Id.

126 See id. at 263-67 (statements by Dr. Michael B. Mayor, Dr. Brent A. Blumenstein, Dr. Jay D. Mabrey, and Dr. Choll W. Kim).

127 Id. at 263 (statement by Dr. Michael B. Mayor) (emphasis added).

128 Id. (statment by Dr. Brent A. Blumenstein).

129 See id. at 267-69.

Smith & Nephew provided reasonable assurance that the BHR is effective. One Panel member asserted that, due to the fact that "[t]he methodology is significantly flawed," it was not possible to "confidently determine if this device is more or less effective than the existing treatment."[130] Another Panel member emphasized that "in light of the fact that there are predicate interventions," the public is not well-served without well-controlled investigations to compare new devices to predicate devices.[131]

Finally, the Panel's recommendation that FDA approve the PMA for the BHR was conditioned on the unanimous recommendation that "a post-market study be performed . . . plus clinical data and X-ray data from ten years be reported based on sound statistical principles."[132] FDA's regulations allow approval of a medical device conditioned on continuing evaluation and periodic reporting on the safety and effectiveness of the device for its intended use.[133] Post-market studies, however, are not a substitute for valid scientific evidence that provides a reasonable assurance of safety and effectiveness prior to approval. The agency's evaluation of safety and effectiveness must be based on premarket data.[134] The condition of approval of post-market studies would require Smith & Nephew to carefully monitor patients from a well-defined group according to well-defined criteria. This is what should be done before the PMA is approved.[135]

e. Approval of Smith & Nephew's PMA would be Inconsistent with FDA's Precedents for Class III Orthopedic Devices

---

130 Id. at 271 (statement by Dr. Choll W. Kim).

131 Id. at 273 (statment by Dr. Brent A. Blumenstein).

132 Id. at 311-12.

133 See 21 C.F.R. § 814.82 (stating that FDA may impose post-approval requirements in a PMA approval).

134 Susan Gardner, Ph.D., Director, Office of Surveillance and Biometrics, Center for Devices and Radiological Health, FDA, Presentation at the Food and Drug Law Institute Annual Meeting: Postmarket Surveillance: Medical Devices (Apr. 8, 2005), available at http://www.fda.gov/cdrh/present/FDLI-Apr05-gardner.ppt.

135 There was a "general consensus" among the Panel that "a fairly extensive post market surveillance study" would be necessary if the PMA for the BHR is approved. Panel Transcript, supra note 1, at 285-86 (statement by Dr. Sanjiv H. Naidu). It was pointed out, however, that "a post marketing study of any significance, of any size that would be significant to get a randomized clinical trial would simply be another [PMA-type study]." Id. at 283 (statement by Panel Deputized Voting Member Harry B. Skinner, M.D., Ph.D., University of California Irvine).

The use of metal-on-metal hip joint devices predates the Medical Device Amendments of 1976. On July 2, 1982, FDA issued a Proposed Rule classifying seventy-seven orthopedic devices.[136] FDA proposed to classify many implanted orthopedic devices into Class III because important information concerning their safety and effectiveness was not currently available.[137] The Final Rule, issued on September 4, 1987, established twelve separate categories of implantable hip prostheses.[138] Each of the twelve types of hip prostheses were placed in either Class II or Class III.[139]

On April 19, 1994, a memorandum from the Acting Director of the Office of Device Evaluation was released outlining the strategy for implementation of the provision of the Safe Medical Devices Act of 1990 that mandated further activity on these Class III devices. Three groups were created regarding the Class III devices.[140] Group I included devices that had fallen into disuse or limited use and were unlikely to result in viable PMAs or reclassification petitions. Group 2 devices were those which FDA believed to have a high potential for reclassification. Finally, Group 3 devices were those not considered candidates for reclassification and would most likely require a PMA in the near future.[141] Hip joint metal-on-metal and metal-on-polymer semi-constrained total hip prostheses were placed in High Priority Group 3.[142] High Priority Group 3 devices were ones that "present an unreasonably high risk to public health because significant issues of safety and/or effectiveness are not being resolved or, to the best of FDA's knowledge, have little probability of being resolved."[143]

FDA's longstanding policies and practices reflect a continued concern with the safety, especially the long-term safety, of hip joint replacement devices. In 2001, an advisory panel recommended against a petition to reclassify metal-on-metal hip joint prostheses to Class II. FDA accepted the Panel's recommendation and denied the

---

136 47 Fed. Reg. 29,052 (July 2, 1982).

137 Id.

138 52 Fed. Reg. 33,686 (Sept. 4, 1987).

139 21 C.F.R. §§ 888.3300 - 888.3410.

140 59 Fed. Reg. 23,731 (May 6, 1994).

141 Id. at 23,731-32.

142 21 C.F.R. §§ 888.3320, 888.3330.

143 Acting Director, Office of Device Evaluation, Memorandum: Preamendments Class III Strategy, (Apr. 19, 1994), available at http://www.fda.gov/cdrh/ode/odeot611.html.

petition for reclassification. In a memorandum concerning the petition, the agency reasoned that advanced novel designs entail "new risks that are not foreseen."[144] Likewise, the uncontrolled retrospective data from Dr. McMinn's medical practice are not adequate either to identify or resolve the risks associated with the BHR.

FDA has consistently placed a heavy burden of proof on applicants to fully address FDA's and the public's need for adequate safety and effectiveness data. Prior PMAs approved by FDA for hip joint replacement prostheses have relied on properly designed clinical studies. For example, in 2003, the agency approved the petitioner's PMA for the Ceramic Transcend Hip Articulation System for use in primary total hip arthroplasty. The approval was based on a prospective, multi-center, historical control, clinical trial. Similarly, in 2004, FDA approved the PMA for the Reflection Ceramic Acetabular System. The approval was based on a multi-center, prospective, open-label concurrently controlled clinical trial of ten sites with fourteen surgeons.

Approval of the PMA for the BHR would be inconsistent with data requirements established for hip joint metal/polymer or ceramic/polymer semi-constrained resurfacing cemented prostheses.[145] While discussing the requirements for these PMAs, FDA stated that devices should be evaluated in "prospective, randomized, clinical trials that use adequate controls or other forms of valid scientific evidence."[146] The agency has stated that such clinical trials should have: a clear study hypothesis statement; objectively measured endpoints; a well-defined patient population that is based on carefully defined inclusion and exclusion criteria; and should be designed to minimize selection bias, disease misclassification bias, comparison bias, or any other potential bias.[147] PMA applications are currently under review by FDA from at least two sponsors who have conducted IDE studies on metal-on-metal resurfacing devices. The Smith & Nephew PMA for the BHR contains none of these elements.

The Panel members who recommended approval of the PMA with conditions relied heavily on the sheer number of patients.[148] Sheer numbers of patients, though, cannot fully compensate for the absence of good science. The scientific reliability of data gathered from a retrospective, uncontrolled "study" from a single physician contain none

---

144 Health News Daily, Metal Hip Downclassification Petition Does Not Address Long-Term Risks-FDA (Aug. 8, 2001) [Attachment C].

145 69 Fed. Reg. 10,390 (Mar. 5, 2004).

146 Id. at 10,394.

147 Id.

148 See, e.g., Panel Transcript, supra note 1, at 270 (statement by Panel Industry Representative Pamela W. Adams, M.S., R.A.F., C.Q.M., Etex Corp., Inc.).

of the elements that FDA has identified as essential in setting standards for other orthopedic PMAs.

Well-controlled investigations should be required for the BHR and for similar devices, given that metal-on-metal resurfacing arthroplasty presents unique risks for complications compared to conventional total hip arthroplasty.[149] The petitioner is unaware of any PMA for an orthopedic device that has ever been approved based on a retrospective, uncontrolled, single site, single physician study.

f. Dr. McMinn has a Financial Conflict of Interest

FDA has recognized that an investigator's financial interests can tend to influence the investigator's findings.[150] Dr. McMinn, the sole investigator here, apparently has a direct financial interest in the approval of the BHR in the United States. Dr. McMinn informed the Panel that he co-invented the BHR, has a financial interest in the BHR, is a "consultant" for Smith & Nephew, and serves as a "non-Executive Director of Smith & Nephew."[151] Dr. McMinn also designed the BHR and founded Midland Medical Technologies ("MMT") through which to sell his new form of resurfacing arthroplasty. Smith & Nephew purchased MMT for £67 million (approximately $119 million), and according to news reports in the United Kingdom, will pay an additional £33 million (approximately $59 million) to MMT—and therefore, at least in part, to Dr. McMinn—if and when FDA approves the BHR for use in the United States.[152] FDA's conflict of interest regulations set the threshold for a "significant equity interest" at $50,000 in a

---

149 For example, FDA has recognized that femoral neck fracture is a risk accompanying metal-on-metal resurfacing arthroplasty devices and has required other manufacturers performing clinical studies with such devices to present the agency with changes to patient selection or surgical technique that help to minimize this risk. Smith & Nephew did not present such data to FDA.

150 See generally 21 C.F.R. Part 54. In the proposed rule that preceded these regulations, FDA asserted that "[t]here is a growing recognition in the academic and scientific communities that certain financial arrangements between clinical investigators and product sponsors, or the personal financial interests of clinical investigators, can potentially bias the outcome of clinical trials." 59 Fed. Reg. 48,708, 48,708 (Sept. 22, 1994).

151 Panel Transcript, supra note 1, at 47-48 (testimony of Dr. Derek J.W. McMinn).

152 Real Business, £100m Sale for Hip Midland Medical: Brummie Surgeons McMinn and Treacy Reap Reward for Pioneering Hip Replacements; Vow to Stay on as Smith & Nephew Plan for U.S. Expansion, (May 2004) available at http://www.realbusiness.co.uk/women/showdetail.asp?ArticleID=2708 [Attachment D].

publicly traded company and at $25,000 for "significant payments of other sorts."[153] Dr. McMinn apparently stands to gain far more than this regulatory threshold if the PMA for the BHR is approved.[154] FDA says that if a disclosable financial interest exists, the agency will assess what steps have been taken to mitigate the risks. These include determining the reproducibility of results by other investigators.[155] As noted above, the lack of reproducibility is a major flaw in the data; Dr. McMinn's financial stake tends to exacerbate this issue. None of the mitigating factors is present here.

g. Conclusion

As shown above, the data presented by Smith & Nephew do not comply with the standards that have been set by Congress and FDA for Class III devices. FDA has recognized that Smith & Nephew's PMA for the BHR is based on the retrospective review of the clinical experience of a single physician outside of the United States under no established protocol, and without predefined inclusion and exclusion criteria, without standardized clinical evaluations, without standardized adverse report forms, and without standardized radiographic evaluations. Approval based on such data would set a dangerous precedent. Not only would it mean approval of this PMA based on inadequate data, it would mean that manufacturers of other new orthopedic medical devices would have no incentive to conduct IDE studies. Rather than conduct expensive prospective, controlled studies, sponsors could obtain approval far more cheaply by using retrospective data generated in other countries. One of the Panel members specifically suggested that "future [PMA] applicants should not assume significant savings can be achieved by following [Smith & Nephew's] example."[156] Yet approval of this PMA would lead sponsors to make precisely that assumption. Basing PMAs on retrospective data held to low standards would also allow applicants to mitigate the risks of FDA bioresearch monitoring, since these applications would not need to meet Good Clinical Practices, e.g., being audited for compliance with a protocol.

Regardless of the skill of the practitioners in treating their patients, Smith & Nephew's data fail to establish reasonable assurance of safety and effectiveness. The burden to prove that a device should be approved through the PMA process rests with the sponsor. Smith & Nephew and FDA have both recognized that the primary data on

---

153 21 C.F.R. §§ 54.2(b), (f).

154 See Real Business, £100m Sale for Hip Midland Medical: Brummie Surgeons McMinn and Treacy Reap Reward for Pioneering Hip Replacements; Vow to Stay on as Smith & Nephew Plan for U.S. Expansion, (stating that Dr. McMinn has signed a five-year contract with Smith & Nephew and "will stay on").

155 21 C.F.R. § 54.5.

156 Panel Transcript, supra note 1, at 321-22 (statement by Dr. Michael B. Mayor).

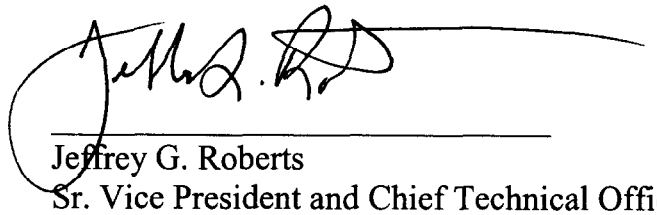
which Smith & Nephew's PMA can rely are the results from Dr. McMinn – a single physician. If a PMA is based on data from a single investigator, the sponsor bears the additional burden of justifying to FDA that the data demonstrate the safety and effectiveness of the device and that the results are reproducible.[157] Smith & Nephew has not met either of these burdens. The anecdotal evidence of use of the device by other physicians does not serve as evidence of safety and effectiveness. Therefore, this petition requests that the Commissioner deny approval of Smith & Nephew's PMA for the BHR, unless and until valid scientific evidence providing adequate assurance of safety and effectiveness is submitted.

C. Environmental Impact Statement

The action requested in this petition will have no impact on the environment.

D. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.



Jeffrey G. Roberts
Sr. Vice President and Chief Technical Officer
Wright Medical Technology, Inc.
5677 Airline Road
Arlington, TN 38002
(901) 867-9971

157 See 21 C.F.R. § 814.20(b)(7).