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

March 10, 2006

VIA FEDERAL EXPRESS

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

RE: Docket No. 2005P-0440/CP1

Dear Sir or Madam:

On behalf of Wright Medical Technology, Inc., please find enclosed an original and four copies of a Reply to Smith & Nephew's Response to Wright Medical Technology, Inc.'s Citizen's Petition to deny PMA P040033 (Docket No. 2005P-0440/CP1). This Reply demonstrates that Smith & Nephew's PMA does not meet the applicable requirements and therefore should not be approved.

If you have any questions concerning this Reply, please call me at (901) 867-9971. Thank you for your attention to this matter.

Sincerely,

Jeffrey G. Roberts

Enclosure

2005P-0440

RC 2

March 10, 2006

Division of Dockets Management
Food and Drug Administration
5600 Fishers Lane, Room 1061 (HFA-305)
Rockville, MD 20852

Docket No. 2005P-0440/CP1

Wright Medical Technology, Inc.'s Reply to Smith & Nephew's Response to Wright Medical Technology, Inc.'s Citizen Petition to Deny PMA P040033 Based on the Data Currently Submitted in Support of the PMA

Wright Medical Technology ("Wright") is replying to Smith & Nephew's February 8, 2006 response ("the Response")[1] to the citizen petition filed by Wright ("Wright's Petition")[2] requesting that the Food and Drug Administration ("FDA") deny approval of the Birmingham Hip Resurfacing ("BHR") System (PMA P040033). Smith & Nephew's Response fails to demonstrate why FDA should not deny approval of the PMA. Moreover, Smith & Nephew failed to respond to many of the flaws in the PMA identified in Wright's Petition, as we show below.

As the U.S. Senate Committee on Finance recently emphasized, FDA has the "important mission" of protecting public health.[3] The Committee's February 2006 report underscored that "FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of . . . medical devices . . ." and that the "approval process requires a comprehensive scientific evaluation of the product's benefits and risks, including scientifically sound data supporting an application for approval."[4] As Wright showed in its citizen petition, the PMA for the BHR lacks the "scientifically sound data" needed to meet the applicable legal standards.

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1 Response filed by Smith & Nephew with the Food and Drug Administration ("FDA") (Docket No. 2005P-0440/C1) (Feb. 8, 2006) [hereinafter Response].

2 Citizen Petition filed by Wright Medical Technology, Inc. ("Wright") with FDA (Oct. 29, 2005) (Docket No. 2005P-0440/CP1) [hereinafter Wright's Petition].

3 S. REP. NO. 109-45, at 2 (2006).

4 Id.

A. Wright's Petition is Not Procedurally Flawed

Smith & Nephew's Response asserts that Wright's Petition is "an improper invocation of the citizen petition procedure."[5] According to Smith & Nephew, Wright's Petition is improper because the PMA process is not public and because FDA's regulations governing the PMA process are more specific than those governing citizen petitions.[6] Neither argument precludes a member of the public from filing a citizen petition prior to the approval of a PMA. Wright's submission of a citizen petition to request that FDA deny Smith & Nephew's PMA for the BHR was, in fact, a proper invocation of the citizen petition procedure.

Smith & Nephew asserts that because a PMA application itself is not public, a party cannot file a citizen petition requesting that a PMA application be denied. This argument ignores that during its review of Smith & Nephew's PMA for the BHR, FDA convened a public advisory panel meeting at which interested members of the public could comment.[7] While FDA could not disclose the submission of a PMA, Smith & Nephew was free to do so. And, in fact, Smith & Nephew did just that – it actively declared to the medical and financial community that it had submitted a PMA. It is disingenuous in the extreme for Smith & Nephew to argue that a citizen petition could not be filed because its PMA was confidential when Smith & Nephew itself repeatedly and publicly touted that it had filed a PMA.

In preparation for the public advisory panel meeting, held on September 8, 2005, FDA compiled briefing information (the "Executive Summary") for the Orthopedic and Rehabilitation Devices Panel (the "Panel").[8] This information was available to any member of the interested public. The Executive Summary extensively discussed the contents of the PMA. At the Panel meeting, the Panel members, representatives from FDA, and representatives from Smith & Nephew openly referred to and discussed statements, data, and information from the PMA.

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5 Response, supra note 1, at 11.

6 See id.

7 See 21 C.F.R. § 814.44(a) (allowing FDA to refer a PMA to a panel on its own initiative).

8 FDA, Briefing Information: Executive Summary for the Orthopedic and Rehabilitation Devices Panel: PMA P040033 – Birmingham Hip Resurfacing (BHR) System, Gaithersburg, MD (Sept. 8, 2005) [hereinafter Executive Summary].

The arguments presented in Wright's Petition opposing FDA's approval of Smith & Nephew's PMA are based on the publicly-available transcript of the Panel meeting[9] and on the publicly-available Executive Summary. Wright's submission of its citizen petition was based not on Smith & Nephew's filing of a PMA, but rather on the public advisory panel requested and convened by FDA. Thus, Smith & Nephew's argument that Wright's Petition attacks a confidential process – which Smith & Nephew had itself publicized – is baseless.

Smith & Nephew relies upon 21 C.F.R. § 814.44(d)(1) to argue that FDA's specific regulation governing the PMA process precludes Wright from filing a citizen petition.[10] Under section 814.44(d)(1), after FDA approves a PMA application, the agency will provide "public notice" of the approval as well as "notice of and opportunity for any interested persons to request review" of the PMA approval.[11] The existence of this separate post-approval procedure for review of PMA approvals does not prevent any party from filing a citizen petition before the approval of a Class III medical device.

Wright filed its citizen petition under 21 C.F.R. § 10.30, which provides members of the interested public broad latitude in submitting citizen petitions. This regulation "applies to any petition submitted by a person . . . "[12] and says that citizen petitions can request that the Commissioner of Food and Drugs refrain from taking any administrative action.[13] FDA's decision to approve or deny a PMA application is included in the broad category of "any" administrative action.

Even when read with section 814.44(d)(1), the agency's regulation governing citizen petitions (section 10.30) still permits a request to deny approval of a PMA application. Section 10.30 encompasses "any administrative action." Section 814.44(d)(1) does not purport to narrow that scope.

FDA has recently advanced the same rules of statutory construction in court. The plaintiffs in Med. Ctr. Pharmacy v. Ashcroft, No. 7: 04-cv-130, filed in the U.S. District Court for the Western District of Texas, Midland-Odessa Division, asked the district

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9 Transcript, Orthopedic and Rehabilitation Devices Panel: PMA P040033 – Birmingham Hip Resurfacing (BHR) System, Gaithersburg, MD (Sept. 8, 2005) [hereinafter Panel Transcript].

10 Response, supra note 1, at 11.

11 21 C.F.R. § 814.44(d)(1).

12 Id. § 10.30(a) (emphasis added). "Person" is defined as including "an individual, partnership, corporation, association, or other legal entity." Id. § 10.3(a).

13 See id. § 10.30(b)(A) (emphasis added); see also id. § 10.3(a) (emphasis added).

court inter alia to enjoin FDA from prohibiting the use of bulk ingredients to compound drugs for use in animals. In its motion to dismiss the case, the government cited the definition of "new animal drug": "[a]ny drug intended for use for animals other than man . . . [that is] not generally recognized, among experts . . . as safe and effective for use under the conditions prescribed."[14] The government asserted that "[t]he use of the modifier 'any' eliminates the exception for compounded drugs that plaintiffs seek to read into the statutory definition."[15] Consistent with the government's position, section 814.44 does not narrow the word "any" in section 10.30.

Smith & Nephew further relies upon the Supreme Court's decision in Edmond v. United States, 520 U.S. 651 (1997). Smith & Nephew cites Edmond as stating that "'[o]rdinarily, where a specific provision conflicts with a general one, the specific governs.'"[16] The petitioners in Edmond argued that a specific statute (10 U.S.C. § 866(a)), and not a general statute (49 U.S.C. § 323(a)), governed appointments to the Coast Guard Court of Criminal Appeals. The Supreme Court, however, ultimately determined that the general statute – and not the specific one – allowed the Secretary of Transportation the appointment authority at issue.[17]

Moreover, Smith & Nephew's Response asserts that there is no precedent for filing a citizen petition to request that FDA deny approval of PMA applications.[18] This is incorrect. Such petitions have, in fact, been filed with FDA. In both November 2003[19] and May 2005,[20] for example, interested parties filed citizen petitions requesting that FDA deny approval of PMA applications for silicone-gel filled breast implants. The May 2005 petition was filed under 21 C.F.R. § 10.30 on behalf of several organizations and

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14 Defendant's Motion to Dismiss at 18, Med. Ctr. Pharmacy v. Ashcroft, No. 7: 04-cv-130 (W.D. Tex. 2004) (citing 21 U.S.C. § 321(v)(1)) (emphasis added).

15 Id. at 18-19 (citation omitted).

16 Response, supra note 1, at 11 (citing Edmond v. United States, 520 U.S. 651, 657 (1997) (citations omitted)).

17 520 U.S. at 658.

18 Response, supra note 1, at 11-12.

19 Citizen Petition filed by the National Organization for Women, Public Citizen's Health Research Group, and the National Women's Health Network with FDA (Nov. 3, 2003) (Docket No. 2003P-0511/CP1).

20 Citizen Petition filed by William B. Shultz and Carlos T. Angelo on behalf of Public Citizen et al. with FDA (May 23, 2005) (Docket No. 2005P-0204/CP1).

individuals, including Public Citizen, The National Women's Health Network, and The National Organization of Women. This citizen petition is still pending.

Therefore, Wright's submission of a citizen petition requesting that FDA deny approval of a PMA application is permitted under FDA's broad authorizing regulations. In addition, Wright's Petition is based not on confidential information in Smith & Nephew's PMA application but on the public advisory panel meeting.[21] Accordingly, Wright's Petition should not be summarily denied.

B. Device Iterations

In its Response, Smith & Nephew describes the BHR as "a metal on metal bearing produced from high carbon as-cast cobalt chrome alloy" that "consists of a femoral head component (with a central stem) and an acetubular cup."[22] This description overlooks the twenty-three iterations in which the BHR is available. The Response does not justify the failure to provide any information on performance of the multiple device iterations.[23]

At the Panel meeting, Mr. Derek J.W. McMinn (inventor of the BHR) testified that the BHR system is available in twenty-three different iterations across three categories of cups: standard, dysplasia, and bridging.[24] The data presented to the Panel did not look for differences in performance, but assumed that these differences have no effect on patient outcomes. The resulting amalgamated dataset, as presented to the Panel, makes it impossible to discover any differential device effects due to design differences.[25] As Wright stated in its citizen petition, FDA has required "'a detailed justification for the poolability' of data resulting from different iterations of a device."[26] Yet data and

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21 FDA regularly reviews and considers citizen petitions requesting that generic drug applications not be approved, even though that process is entirely confidential, e.g., there is not even a public advisory meeting.

22 Response, supra note 1, at 2.

23 See Wright's Petition, supra note 2, at 21-22.

24 Id. at 21 (citing Panel Transcript, supra note 9, at 55 (testimony of Derek J.W. McMinn, FRCS, Orthopedic Surgeon, Birmingham Nuffield Hospital)).

25 The failure to evaluate this variable may be explainable by the lack of a protocol. Given that all data were gathered on a post-hoc basis, there was no opportunity to prospectively devise a protocol to detect the impact of design difference, or the impact of design differences on patient subpopulations.

26 Wright's Petition, supra note 2, at 21-22.

information about each iteration of the BHR were missing from the data discussed by the Panel.[27] Accordingly, there is a lack of adequate data to support the approval of the multiple versions of the BHR.

C. Clinical Studies

Smith & Nephew's Response discusses at some length its preclinical studies. This is a red herring. Wright's Petition addressed the substance of the clinical data. Preclinical data is necessary but not sufficient for approval of the PMA for the BHR. No matter how good Smith & Nephew's preclinical data, it cannot compensate for the lack of scientifically valid clinical data.

a. Additional Data

Smith & Nephew's Response relies heavily on arguments that were not presented to or relied upon by the Panel, and misrepresents the way in which FDA's Executive Summary and the Panel described the PMA data. Throughout its Response, Smith & Nephew refers to data from physicians other than Mr. McMinn as corroborative data. The Response states that, "[t]he clinical data utilized to provide reasonable assurance of safety and effectiveness for the [BHR] PMA application were primarily based on a consecutive series of 2,385 BHR System hips implanted by Mr. McMinn."[28] The Response references 3,374 hips implanted by 140 other surgeons worldwide as "additional evidence of safety and effectiveness."[29] In its Response, Smith & Nephew now places great stock on these uncontrolled clinical experiences.

Yet Smith & Nephew is giving these reports more weight than it did when presenting to the Panel. Smith & Nephew told the Panel: "[t]he evidence of safety and effectiveness presented in this PMA is based on a consecutive series of 2,385 cases, surgeries that occur from July of 1997 to 2004."[30] At no time during the Panel meeting did

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27 Id. at 22. Wright's Petition also stated that, according to FDA's review of Smith & Nephew's PMA submission, "'almost all patients received either the standard cup or the dysplasia cup styles.'" Id. (citing Panel Transcript, supra note 9, at 144 (testimony of John S. Goode, M.S., Orthopedic Devices Branch)). Therefore, Smith & Nephew's data apparently provide no evidence of the safety and effectiveness of the bridging version.

28 Response, supra note 1, at 2 (emphasis added).

29 Id. at 3 (emphasis added).

30 Panel Transcript, supra note 9, at 67 (testimony of Marcos Valez-Duran, Vice

Smith & Nephew present the data from the additional 140 surgeons as additional evidence of safety and effectiveness. Rather, at the Panel meeting, Smith & Nephew disclaimed reliance on this information, saying that the company could not verify the data from other physicians and that the PMA was not based on these data.[31] The data from other physicians were used only by Smith & Nephew in an attempt to try to bolster the reproducibility of Mr. McMinn's case series, not as evidence of safety and effectiveness.[32]

The statements in Smith & Nephew's Response are also refuted by FDA's Executive Summary, as well as the testimony of FDA representatives. At the Panel meeting, an FDA representative stated that,

> [a]lthough the sponsor considers the data from [additional physicians] to be of some value, Smith & Nephew has no ability to independently verify any of the data provided . . . by sites other than the McMinn Center and Dr. McMinn has no ability to request additional follow-up or clarifications of any kind from non-McMinn patients or physicians.[33]

Smith & Nephew tries to create the impression that this was a multi-center trial. Yet, at the Panel meeting, the Acting Panel Chairperson stated that the data was "an unusual PMA based on a retrospective study designed by a single surgeon based on a British data set."[34] Deputized Voting Member Brent A. Blumenstein, Ph.D. stated that Smith & Nephew's data collection was "substandard" and that a "single clinical site in another

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President, Clinical/Regulatory Affairs and Quality (Trauma)) (emphasis added).

31 See id. at 67 (testimony of Marcos Valez-Duran); 130 (testimony of John S. Goode). It goes without saying that FDA cannot utilize unverifiable data when reviewing a PMA.

32 Although, as will be seen below, the attempt to use it as a reproducibility measure for Mr. McMinn's series is also invalid.

33 Panel Transcript, supra note 9, at 130 (testimony of John S. Goode).

34 Id. at 182 (statement by Acting Panel Chair Sanjiv H. Naidu, M.D., Ph.D., Pennsylvania State College of Medicine). Smith & Nephew's Response concedes that Mr. McMinn's data "has been described as a retrospective, single-center, uncontrolled clinical study." Response, supra note 1, at 5. Adding uncontrolled reports from other physicians does not increase the number of centers or increase the level of control.

country and a single surgeon . . . means that you cannot assess the homogeneity of results across surgeons or sites."[35] Dr. Blumenstein rightly concluded that "the phrase 'well controlled study' doesn't apply" to Smith & Nephew's data.[36] Other Panel members agreed with Dr. Blumenstein.[37]

Based on FDA's Executive Summary, testimony by FDA representatives at the Panel meeting, and Smith & Nephew's own testimony at the Panel meeting, the reports from the other physicians do not constitute data on which Smith & Nephew – or FDA – can rely.

b. Survivorship as a Primary Effectiveness Measure

As Smith & Nephew states in its Response, the primary effectiveness measure in the McMinn series was survivorship.[38] Wright's Petition points out, however, that "[s]urvivorship 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)."[39] Despite Smith & Nephew's reliance on survivorship as a primary effectiveness measure, survivorship is an inappropriate primary measure of effectiveness.[40]

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35 Panel Transcript, supra note 9, at 235-36 (statement by Panel Deputized Voting Member Brent A. Blumenstein, Ph.D., TriArc Consulting).

36 Id. at 239 (statement by Dr. Brent A. Blumenstein).

37 See, e.g., id. at 248 (statements by Panel Deputized Voting Member Jay D. Mabrey, M.D., Baylor University Medical Center; Panel Voting Member Choll W. Kim, M.D., Ph.D., University of California, San Diego).

38 Response, supra note 1, at 2.

39 Wright's Petition, supra note 2, at 16.

40 According to FDA's Executive Summary, Smith & Nephew measured survivorship in the 1,626 patients in the X-ray and Oswestry cohorts. Executive Summary, supra note 8, at 26. Of the 1,626 cases in these two cohorts, 601 were eligible for five-year follow-up, but Smith & Nephew provided five-year survivorship data on only 546 of these patients. Wright's Petition, supra note 2, at 16 (citing Executive Summary, supra note 8, at 26). From FDA's Executive Summary, it appeared that Smith & Nephew had not provided accountability for the remaining fifty-five patients. See id. Smith & Nephew's Response fails to address this point and also fails to reveal why the company has five-year follow-up data for only 546 patients. Nor does Smith & Nephew explain how it

Smith & Nephew cited several articles in its Response which it argues demonstrates the reproducibility of Mr. McMinn's data.[41] However, the data in support of Smith & Nephew's PMA for the BHR – as presented to the Panel by FDA and as discussed by the Panel – were not derived from a multi-center study. One of the many benefits of a multi-center study is that reproducibility can be measured through a treatment outcome under a common protocol.[42] Under such circumstances, the same inclusion/exclusion criteria and definition of device failure is applied. The result is a measure of reproducibility. In contrast, Smith & Nephew relies upon an arbitrary comparison of values from one investigator for one variable (which does not measure safety) to available literature involving heterogeneous data sets. In multi-center trials, the results for each investigator can be analyzed separately and inter-investigator comparisons can be made. None of this is possible here.

The Response contains a table[43] of literature references that report survivorship among patients in whom the BHR has been implanted. Yet, Smith & Nephew failed at both the Panel meeting and in its Response to justify why these survivorship figures are valid indicators of reproducibility of the pivotal dataset. None of the literature references cited in the Response contains critical details of how the respective surgeons defined survivorship, or how those survivorship figures relate to patient demographics, particular operative techniques, or postoperative management regimens. Simply stating that an assortment of literature references yield survivorship values that are similar to those in Mr. McMinn's series falls far short of any definition of statistical or clinical reproducibility.

Moreover, showing that an implant is still in place is not the same as showing that the device remains effective. Durability is not the same as effectiveness. FDA cannot conclude that a device is effective just because it remains in situ.

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statistically analyzes these missing patients.

41 See Response, supra note 1, at 4.

42 FDA has stated in the past that to "demonstrate the reproducibility of results, clinical investigations of a device should normally involve more than one investigator." 51 Fed. Reg. 26,342, 26,349 (July 22, 1986). Wright's Petition stated that "[a]ny sponsor that submits a study from a single investigator must also show how the single-investigator study has minimized potential bias." Wright's Petition, supra note 2, at 8. Smith & Nephew's Response does not address the company's failure to meet this burden.

43 Response, supra note 1, at 4.

The lack of reproducibility of the McMinn dataset remains unresolved; Smith & Nephew has provided no justification as to why the cited literature references are valid comparators. Smith & Nephew restates its intention to provide surgeons with "robust" training "to further ensure that Mr. McMinn's results can be replicated."[44] No matter how "robust," post-approval surgeon training plans are no substitute for properly conducted pre-market studies.[45] Even the most stringent post-approval training plan does not obviate the need for reproducibility data; without it, there is no way to know whether the results will be reproducible beyond the single surgeon.

Notwithstanding the utter lack of effectiveness data, Smith & Nephew is already promoting the BHR in the United States with claims related to pain relief and activity level. The November 2005 issue of The Journal of Bone & Joint Surgery (JBJS, 87-A) contained full page advertisements by Smith & Nephew promoting the BHR as having "outstanding clinical results" and "deliver[ing] consistent performance."[46] This advertisement also directed readers to the website www.hipresurfacing.com. Though www.hipresurfacing.com is an England-based website, the JBJS is published in the United States and is widely read by U.S. orthopedists. Smith & Nephew's advertisement, therefore, directed U.S. physicians to this website.

Significantly, the website contains anecdotal "Patient Experiences" which imply that the BHR is safe and effective. For example, the story of a "Fell Runner" states that he "was back on [his] feet" the day after his resurfacing operation, and that "[i]n just six months, [he] was back on the Fells running seven miles twice a week."[47] Another story features a "Judo Champion" who says that he has "had absolutely no pain since the

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44 Id. at 5.

45 Moreover, as Wright emphasized in its citizen petition, the type of surgery required to implant the BHR is "especially challenging and is not a standard procedure taught in U.S. orthopedic residency programs." Wright's Petition, supra note 2, at 22 (citing Panel Transcript, supra note 9, at 223 (testimony of Cecil Rorabeck, M.D., Consultant for Smith & Nephew)). Smith & Nephew has also acknowledged that "'[t]here is no data' on the learning curve for U.S. surgeons." Id. at 23 (citing Executive Summary, supra note 8, at 0).

46 See Attachment A. Given the lack of reproducibility data presented at the Panel meeting, it is especially telling that Smith & Nephew would claim "consistent performance."

47 Smith & Nephew, Birmingham Hip Resurfacing, Patient Experiences: George Dobson – Fell Runner, at http://www.hipresurfacing.com/content/content.asp?article=265 (Attachment B).

operation and was up and walking the very next day. Twelve weeks later [he] was back training and was able to do the splits and squat thrusts."[48]

These claims of remarkable effectiveness are unsupported by Smith & Nephew's data. The efficacy data presented by Smith & Nephew at the Panel meeting cannot translate into restored mobility or pain relief.

c. The Validity of the Oswestry Modified Harris Hip ("OSHIP") Score

Smith & Nephew's Response mentions that the OSHIP Score is a secondary measure for effectiveness in the McMinn series.[49] Wright's Petition points out, however, that "FDA has never before evaluated the OSHIP Score as a legitimate measure of patient function in support of a PMA application."[50] Wright also pointed out in its citizen petition that one of FDA's own statisticians, Chang S. Lao, Ph.D., testified before the Panel that the correlation between the OSHIP Score and the well-accepted Harris Hip Score is "'unclear' and 'subject to potential bias.'"[51] Therefore, the OSHIP score should not be considered a valid measure of patient function. In its Response, Smith & Nephew fails to explain why the OSHIP score is a valid measure. FDA cannot rely upon this novel measure.

d. The Insufficiency of Smith & Nephew's Radiographic and Five-Year Data

Smith & Nephew's Response emphasizes that the data in support of the PMA for the BHR "consists of extensive 5-year follow up . . . . This robust data set is supported still further by an independent review of x-rays . . . ."[52] Yet, this data set is anything but

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48 Smith & Nephew, Birmingham Hip Resurfacing, Patient Experiences: David Walker – Judo Champion, at http://www.hipresurfacing.com/content/content.asp?article=264 (Attachment C).

49 See Response, supra note 1, at 2-3.

50 Wright's Petition, supra note 2, at 14 (citing Panel Transcript, supra note 9, at 135 (testimony of John S. Goode)) (emphasis added).

51 Id. at 14 (citing Panel Transcript, supra note 9, at 155, 163 (testimony of Chang S. Lao, Ph.D., Division of Biostatistics, Office of Surveillance and Biometrics)).

52 Response, supra note 1, at 5.

robust. FDA requested an independent, five-year radiographic study on the first consecutive 124 cases in the McMinn series.[53] However, Smith & Nephew presented FDA with radiographic data from only 108 of these 124 patients, and of the radiographic data for these 108 patients, only eighty-nine radiographic sets included post-operative films.[54] Smith & Nephew has stated that the films were of low quality and unusable for the purposes of postoperative comparisons.[55] William J. Maloney, M.D., Chairman of Orthopedics at Stanford University School of Medicine, stated before the Panel that "baseline films for the purpose of comparisons were made in each of the 108 cases in the postoperative time period, usually within three months, but eight of the 108 procedures had baseline evaluations performed at the time points ranging from 110 to 860 days."[56] Dr. Maloney pointed out that in a prospective IDE study, "these would all be protocol violations and could be potentially excluded. So you could actually end up with a cohort in the X-ray study of zero if you had a strict analysis of the data."[57] Moreover, this subset of eighty-nine is only a small fraction of Mr. McMinn's patients. These patients were not even selected pursuant to a prior clinical plan or pursuant to any clinical criteria. In its Response, Smith & Nephew fails to explain why they have provided such limited radiographic data, or to address Wright's points about the inadequacy of the radiographic data.

e. Smith & Nephew's Clinical Data are Not Scientifically Valid

Smith & Nephew recognizes in its Response that "studies without matched controls and case histories" may support a PMA approval only "if they are scientifically valid."[58] Smith & Nephew argues that Mr. McMinn's data meet this standard of scientific validity.[59] This is incorrect.

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53 Id. at 3.

54 Wright's Petition, supra note 2, at 17 (citing Executive Summary, supra note 8, at 26).

55 See Panel Transcript, supra note 9, at 39 (testimony of William J. Maloney, M.D., Chairman of Orthopedics, Stanford University School of Medicine).

56 Id.

57 Id.

58 Response, supra note 1, at 9.

59 Id.

Wright's Petition emphasized that the consecutive case series from the experience of one physician does not meet FDA's standards of safety and effectiveness. In its Response, Smith & Nephew cites FDA's regulations allowing a PMA applicant to rely exclusively on foreign data to support its application.[60] The cited regulation, 21 C.F.R. § 814.15(d)(2), says, though, that these "studies" must "have been performed by clinical investigators of recognized competence . . . ." This language underscores Wright's point: Smith & Nephew's data is inadequate because it did not include an investigation performed by multiple investigators. Even if Mr. McMinn's clinical series could be considered to be a study (and it lacks all the attributes of a study), it would remain a study with a single surgeon. Additionally, Mr. McMinn's case series lacks virtually every element of Good Clinical Practices ("GCPs"). A study conducted by a single investigator does not meet the regulatory standard of a study with multiple investigators.

D. Smith & Nephew's Response Misrepresents the Panel's Deliberations

Smith & Nephew's Response emphasizes that the Panel recommended by a three-to-two vote that the PMA for the BHR be approved with conditions.[61] This emphasis on the outcome of the vote completely ignores the serious reservations that all Panel members – including those who voted in favor of recommending approval of the PMA with conditions – expressed throughout the meeting. The Response notes that there was "extensive deliberation" among Panel members before the Panel rendered its vote.[62] The Response fails to state, however, that much of this deliberation was critical of Smith & Nephew's data.

As noted above (and as Wright stated in its citizen petition), even the Panel Chairperson, Sanjiv H. Naidu, MD., Ph.D. (who supported the recommendation for approval of the PMA for the BHR with conditions), was critical of the data, since it was "an unusual PMA based on a retrospective study designed by a single surgeon based on a British data set."[63] In concurrence with Panel members who believed that Smith & Nephew's data are not applicable to the U.S. population, Dr. Naidu offered his "opinion": it was "a single surgeon study" that is "not . . . applicable to the general practice of orthopedic surgery in the U.S. population."[64] Panel members who voted in favor of

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60 Id. (citing 21 C.F.R. § 814.15(d)).

61 See id., at 8, 13.

62 Id. at 7.

63 Panel Transcript, supra note 9, at 182 (statement by Dr. Sanjiv H. Naidu).

64 Id. at 267 (statement by Dr. Sanjiv H. Naidu).

recommending approval of the PMA for the BHR also questioned the data. For example, Panel Deputized Voting Member Michael B. Mayor, M.D. (who voted in favor of recommending approval with conditions) called Smith & Nephew's data "far from impeccable."[65] Additionally, Panel Deputized Voting Member Jay D. Mabrey, M.D. (who also voted in favor) said that he had to "echo" the statement that Smith & Nephew's data "falls far short of what a study should be" and further concluded that "the data presented [was] a testament to Mr. McMinn's surgical skills," not a broad study across physicians.[66] Both Dr. Mayor and Dr. Mabrey also stated that there was no reassurance that Smith & Nephew's data was applicable to the U.S. population.[67]

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

Smith & Nephew's Response also disregards another key consideration: that approval of the PMA for the BHR would set a dangerous precedent. As Wright's Petition explains,

> [n]ot 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.[68]

Wright's Petition also pointed out that 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.'"[69] FDA, though, could not easily ignore the impact of a PMA approval. The agency is prohibited from approving Smith & Nephew's PMA while saying that this is a one-time abandonment of standards. If FDA approves

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65 Id. at 247 (statement by Panel Deputized Voting Member Michael B. Mayor, M.D., Dartmouth Hitchcock Medical Center).

66 Id. at 248 (statement by Dr. Jay D. Mabrey).

67 See id. at 263 (statements by Dr. Michael B. Mayor and Dr. Jay D. Mabrey).

68 Wright's Petition, supra note 2, at 31.

69 Id. at 31 (citing Panel Transcript, supra note 9, at 321-22 (statement by Dr. Michael B. Mayor)).

Smith & Nephew's PMA based on the current data, then other sponsors are bound to follow Smith & Nephew's lead. The quality of PMAs will inevitably decline, as companies replace well-controlled studies with reports of clinical series of single, foreign surgeons.

Smith & Nephew's complete lack of compliance with U.S. GCPs provides further incentive to sponsors to do "studies" of this type. Avoiding the costs of well-controlled clinical studies conducted pursuant to U.S. GCPs will certainly be tempting. But, if permitted by FDA here, such avoidance will also erode the statutory standards set by Congress.

Furthermore, as noted in Wright's Petition – and ignored by Smith & Nephew – FDA has, in fact, held other companies to higher data standards and the requirement with GCPs. FDA is not free to treat similarly situated companies in such dramatically different ways. Applying entirely different standards to different companies violates the Administrative Procedure Act.[70]

F. Conclusion

Smith & Nephew's Response largely ignores the points raised in Wright's Petition, and fails to demonstrate why FDA should not deny approval of the PMA for the BHR based on the content of Wright's Petition. The data in support of the PMA for the BHR – as summarized by FDA, discussed at the Panel meeting, and explained in Smith & Nephew's own Response – is not scientifically valid as defined by the Federal Food, Drug, and Cosmetic Act. Smith & Nephew has not proven that the BHR is effective.

The U.S. Senate Committee on Finance has recently declared that "surgically implanted devices carry known risks including infection, need for future removal of the device, and injury to structures in and around the operative site . . . . In order to outweigh these risks, a device must demonstrate efficacy."[71] The Committee concluded that "FDA should not be making devices available to the public if those devices have not reached the agency's standard for safety and effectiveness."[72]

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70 See Bracco Diagnostics, Inc. v. Shalala, 963 F.Supp. 20, 27-28 (D.D.C. 1997) ("'If an agency treats similarly situated parties differently, its action is arbitrary and capricious in violation of the [Administrative Procedure Act].'" (citation omitted)).

71 S. REP. NO. 109-45, at 14-15 (citations omitted).

72 Id. at 28.

The PMA for the BHR – which rests on a retrospective, uncontrolled case series at a single center by a single physician without any protocol and with incomplete follow-up – is not scientifically valid and does not satisfy the agency's standards for safety and effectiveness. Wright properly invoked 21 C.F.R. § 10.30 and submitted a citizen petition requesting that FDA deny approval of the PMA for the BHR. This request should be granted.