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February 8, 2006

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061 (HFA-305)
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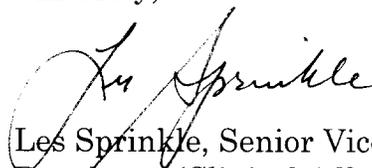
Re: Docket No. 2005P-0440/CP1

Dear Sir or Madam:

On behalf of Smith & Nephew, Inc., please find enclosed an original and four copies of the company's response to Wright Medical Technology, Inc.'s citizen's petition, filed on October 31, 2005 (Docket No. 2005P-0440/CP1). The enclosed response urges that the Food and Drug Administration deny the petition as procedurally improper and substantively lacking merit.

Please contact me if you have any questions concerning this response.

Sincerely,



Les Sprinkle, Senior Vice President
Regulatory/Clinical Affairs & Quality

05P-0440

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Docket No. 2005P-0440/CP1

February 8, 2006

**Smith & Nephew's Response to Wright Medical Technology's Citizen's
Petition to Deny PMA P040033**

Smith & Nephew, Inc. is responding to Wright Medical Technology's (WMT) citizen's petition requesting that the Food and Drug Administration (FDA) deny approval of PMA P040033 for the Birmingham Hip Resurfacing (BHR) System, despite years of data collection and agency review. The WMT petition is procedurally flawed because FDA's well-defined premarket application (PMA) review process does not permit third parties to interject themselves by filing a citizen's petition. Although interested third parties may request review of an approval order, such requests are permitted only *after* an approval order has issued, and must be filed as a *petition for reconsideration*. Flouting this procedure, WMT has jumped in with a citizen's petition while the administrative record is incomplete and before FDA has even made a final decision.

WMT citizen's petition also lacks merit. It simply rehashes issues concerning the BHR System PMA application that were fully vetted before the expert independent advisory panel. WMT asserts that an FDA approval would contravene the governing statutes and regulations, but as will be discussed below, this claim is without merit. As to the scientific issues that WMT raises, the advisory panel was fully justified in finding that the BHR System data provide a reasonable assurance of safety and effectiveness, and FDA would likewise be justified in doing so. As discussed below, WMT does not present any basis for concluding that an FDA approval should be withheld or that it would be outside the bounds of expert scientific judgment. WMT's petition should be summarily denied.

I. FACTUAL BACKGROUND

A. Device Description

The Birmingham Hip Resurfacing (BHR System) Hip arthroplasty device is intended as a primary joint replacement for patients who are at risk of requiring more than one hip joint replacement over their lifetimes (*e.g.*, patients who are relatively young at the time of initial surgery and/or have a high activity level). The device is specifically indicated for relieving hip pain and improving hip function in hips damaged by non-inflammatory degenerative joint diseases (such as

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osteoarthritis), avascular necrosis, dysplasia/DDH, or inflammatory degenerative joint disease (such as rheumatoid arthritis).

The BHR System is a metal on metal bearing produced from high carbon as-cast cobalt chrome alloy. It consists of a femoral head component (with a central stem) and an acetabular cup. Stable fixation of the femoral head is achieved with the use of bone cement. The femoral head has six equally spaced internal recesses to provide stability. The acetabular cup is a cementless, hydroxyapatite (HA) coated interference fit, cast-in porous surface. The beads are integrated with the substrate metal. The geometry of the BHR System produces a polar bearing. It is offered in a range of component sizes appropriate for resurfacing the anatomical hip.

B. Preclinical Studies

The BHR System was subjected to extensive preclinical testing in accordance with FDA's well developed guidance documents in this area. To test and characterize the device component, the following tests were performed: wear testing; friction testing; femoral stem fatigue testing; kinematics - range of motion; metallographic examination; microstructure; and metrology.

To test and characterize the beaded surface, the device was tested according to FDA's guidance, "Guidance Document for Testing Orthopedic Implants with Modified Metallic Surfaces Apposing Bone or Bone Cement" (April 28, 1994). The testing included: static shear strength, shear fatigue strength, and static tensile strength. To test the substrate, the following tests were performed: yield, UTS, % elongation, and abrasion testing.

Finally, studies of the HA followed FDA's guidance, "510(K) Information Needed for Hydroxyapatite Coated Orthopedic Implants," (Mar. 10, 1995, revised 2/2/97). The studies addressed environmental stability, coating thickness, static shear and tensile strength, and chemical and crystallographic analysis.

C. Clinical Studies

The BHR System was developed in the 1990s by D.J.W. McMinn, an orthopedic surgeon. It is commercially available in 23 countries, including Australia, Canada, the European Union (U.K., Germany, Italy, Spain), and Japan. As of the submission of the PMA application to FDA in July 2004, the device had been used in approximately 33,000 implantations.

The clinical data utilized to provide reasonable assurance of safety and effectiveness for the PMA application were primarily based on a consecutive series of 2,385 BHR System hips implanted by Mr. McMinn. The primary effectiveness measurement was implant survivorship, which is an objective endpoint. Secondary

effectiveness measurements were an Oswestry Modified Harris Hip Score (OSHIP) assessing pain and function, patient satisfaction, and radiographic assessment at five years. The primary safety measurement was the incidence of surgical revision. The secondary safety measurement was the incidence of adverse events.

At the initial introduction of the BHR System in 1997, the Oswestry Centre was commissioned to prospectively follow a total of 5,000 BHR System procedures. The effectiveness data for this PMA application is based on the Oswestry Modified Harris Hip Score and Patient Satisfaction Questionnaire conducted independently by the Oswestry Outcome Centre on the first consecutive 1,626 BHR System hips out of the 2,385 hips implanted by Mr. McMinn. The questionnaire is a modified version of the Harris Hip Score system, which measures differences in pain and function in the patient's preoperative versus postoperative experience. The balance of the 5,000 BHR System cases followed by the Oswestry Centre (3,374) were performed by 140 surgeons worldwide. The survivorship estimate for these cases was presented as additional evidence of safety and effectiveness. At FDA's request, an independent five-year radiographic study was conducted on the first consecutive 124 ($n=124$) of the 2,385 BHR System hips in the McMinn Series. A radiographic study protocol was developed *prior* to evaluation of radiographs and included a *prospectively adopted* definition for radiographic success/failure.

For the assessment of safety, the data were collected via an independent review of all patients' charts for the 2,385 consecutive implantations and abstraction of all records of complications and adverse events. All abstracted records of complications were reported in the PMA.

The patient population can be described as follows:

Men	70.6%
Women	29.4%
Mean Age	53.1 years
Age \leq 65	91.9%
Diagnosis	
• Osteoarthritis	75%
• DDH	15.8%
• AVN	4.1%
• Inflammatory	2.4%
• Other	2.7%

The five year follow-up rate for the consecutive series of 1,626 hips followed by the Oswestry Centre was 90.8%. The results were as follows:

- In the primary effectiveness outcome, the 5-Year Survivorship was 98.4% (95% C.I. 97.3 - 99.5%).

- The OSHIP average was 95.0 at five years.
- Patient Satisfaction was 99.5% Extremely Pleased/Pleased with Operation at 5 years.
- The Radiographic Evaluation showed 97.2% success at five years.

These are extremely good efficacy results, derived over a lengthy follow up period (five years) Furthermore, the consistency among these various measures helps reinforce their validity. In the primary safety outcome, the rate of revisions was only 1.13% (27/2,385). There was a very low incidence of device-related adverse events (all categories at $\leq 1\%$).

These safety and efficacy outcomes, moreover, were comparable to those in case series performed by surgeons other than Mr. McMinn, and in a variety of published studies, fully demonstrating the reproducibility of the results and further validating the data. The following table shows how the survivorship results of other series are comparable to Mr. McMinn's results:

Author	Site	<i>n</i>	Survivorship	Follow Up (months)
Back et al ¹	Melbourne	231	99.14%	33 (25-52)
Ebied et al ²	Liverpool	100	99.00%	17 (mean)
De Smet et al ³	Ghent	200	99.50%	6-42
Treacy et al ⁴	Birmingham	144	98.00%	60 (minimum)
Oswestry Worldwide ⁵	140 surgeons	3,374	96.30%	60 (maximum)

1. Back DL Dalziel R Young D Shimmin A. Early results of primary Birmingham hip resurfacings. An independent prospective study of the first 230 hips. *J. Bone Joint Surg. Br.* (2005 Mar) 87(3):324-9.
2. Ebied A Journeaux SF Pope JA. Hip Resurfacing Arthroplasty: The Liverpool Experience. International Conference Engineers & Surgeons – Joined at the Hip. (June 2002).
3. de Smet KA Pattyn C Verdonk R. Early results of primary Birmingham hip resurfacing using a hybrid metal-on-metal couple. *Hip Int'l* (2002) 12:2:158-62.
4. Treacy RB McBryde CW Pynsent PB. Birmingham hip resurfacing arthroplasty. A minimum follow-up of five years. *J. Bone Joint Surg. Br.* (2005 Feb) 87(2):167-70.
5. FDA Review Memo, page 59.

Likewise, the low rate of revision in Mr. McMinn's series compares favorably to the published revision rates for comparable products. The following table sets forth the revision rates for two of the study cohorts compared to published

literature reporting results for comparable Metal/Poly and Ceramic/Ceramic products in patients with similar demographics. The table shows equivalent or better results for the BHR System as compared to these comparable marketed products:

System/Source	Total# Hips	Percent Revisions	Maximum f/u years
All Cohorts ¹ (X-Ray+Oswestry+McMinn)	2,385	1.1	5 (mean 2.9)
X-Ray+Oswestry Cohort ¹	1,626	1.4	5 (means 3.7)
Ceramic/Ceramic THR ²	338	1.2	3
Metal/Poly THR ²	151	5.2	3
Ceramic/Ceramic THR ³	333	1.2	1-3

1. FDA Review Memo, page 38.
2. D'Antonio J, Capella W, Manley M, Bierbaum B. New experience with Alumina-on-Alumina Bearings for Total Hip Arthroplasty. *J. of Arthroplasty* (June 2002) 17(4):390-97.
3. Garino J. Modern Ceramic-on-Ceramic Total Hip Systems in the United States. *Clinical Orthopaedics and Related Research* (Oct 2000) (379):41-47.

As Smith & Nephew demonstrated, the target patient population, surgical technique, practice of medicine, and in-hospital procedures are comparable in the United Kingdom and the United States. To further ensure that Mr. McMinn's results can be replicated, Smith & Nephew will provide robust training to all surgeons using the BHR System to ensure standardized procedures. Mr. McMinn and other BHR System-experienced surgeons will train a group of core surgeons on the device and surgical technique by allowing them to view live surgery, attend lectures, and participate in appropriate workshops. This group of core surgeons will provide training to other U.S. surgeons interested in the BHR System device. Each core surgeon will be supported by S&N representatives at their first 10 surgeries, at a minimum. A core surgeon is not eligible to train other surgeons until after completing 10 (or more) surgeries.

The study has been described as a retrospective, single-center, uncontrolled clinical study. Nevertheless, there are characteristics of this study that make the data very powerful as an assessment of the safety and effectiveness of the BHR System. Essentially, the study consists of extensive 5-year follow up of a very large consecutive series. This robust data set is supported still further by an independent review of x-rays based upon a prospectively adopted protocol, clinical assessment managed independently of the operating clinician, and use of patient

self-assessment of pain, function, and satisfaction. The combined data set provides a strong basis for establishing that there is reasonable assurance that the BHR System is safe and effective for its intended use. Finally, there have been no design or surgical technique changes for the BHR System since market introduction in 1997, which means that the data collected are fully applicable to the device as it will be sold in the U.S.

D. FDA's Review of the PMA Application

Smith & Nephew filed a PMA application for the BHR System in July 2004. After more than a year of FDA review, the agency sought the advice of an expert advisory panel. Such panel review is expressly authorized under the PMA regulation and is a typical FDA practice in reviewing PMA applications.¹

Six weeks prior to the meeting, the Panel received a voluminous written package of information and analysis concerning the PMA from both FDA and Smith & Nephew. The panel meeting took place on September 8, 2005. At that meeting, the Panel responded to written questions that FDA previously provided. These questions called for a detailed, broad-ranging, and comprehensive review of the clinical data supporting the BHR System PMA application. Specifically, FDA asked the Panel:

1. Please discuss the evaluation methods used to collect safety data (i.e., data on revisions, adverse events, deaths, metal ion literature analysis) and whether or not these methods are reliable to assess the safety of the device;
2. Please discuss the evaluation methods used to collect effectiveness data (i.e., data on survivorship, OSHIP score, radiographic, and patient satisfaction) and whether or not these methods are reliable to assess the effectiveness of the device;
3. Please discuss whether the foreign data from a single investigator and the U.K. practice of medicine is applicable to target U.S. population and U.S. practice of medicine;
4. Based on the safety data in 2,385 patients in the Overall McMinn Cohort (i.e., data on revisions, adverse events, deaths) and the analysis of the metal ion literature, please discuss whether or not you believe that the data contained in this PMA provide reasonable assurance of safety;

¹ 21 C.F.R. § 814.44(a).

5. Based on the:

- 5-year survivorship analysis of the 1,626 procedures in the X-Ray/Oswestry combined effort;
- 5-year radiographic data of the 124 procedures in the X-Ray cohort;
- 5-year pain and function (OSHIP) data of the 1,111 unilateral procedures in the X-Ray/Oswestry combined cohort; and
- 5-year patient satisfaction analysis of the 1,626 procedures in the X-Ray/Oswestry combined cohort;

Please discuss whether or not you believe that the data contained in this PMA provide a reasonable assurance of effectiveness;

6. Do the patient selection methods and data presented on the BHR System device support the proposed labeling indication? Please comment on any other aspects of the product labeling, such as:

- Contraindications,
- Warnings,
- Precautions, and
- Potential Adverse Effects on Health;

7. A reasonable assurance of safety and effectiveness as defined in questions #4 and #5 above must be demonstrated for device approval. If you believe the data in the PMA demonstrate a reasonable assurance of safety and effectiveness but think there are remaining specific questions regarding this device that should be addressed in a post-approval study, please identify those questions.²

At the meeting, the Panel heard from speakers representing Smith & Nephew, FDA, and interested members of the public (including a representative of Wright Medical Technology). Then, the Panel deliberated among themselves and discussed each of these questions, sometimes obtaining factual clarification from representatives of FDA or the company. Based upon this extensive deliberation, the

² Panel Transcript ("Tr.") at 246-79.

Panel voted 3-2 for approval with specific limited conditions.³ The acting chairman did not vote but indicated he agreed with those voting for approval, "because there is enough valid scientific data."⁴ After the meeting, FDA has continued to review the PMA application. From filing, FDA's exhaustive review of the BHR System PMA application has consumed more than eighteen months thus far.

II. THE PMA APPLICATION FOR THE BHR MEETS THE LEGAL REQUIREMENTS FOR FDA APPROVAL

A. FDA Must be Provided with a Reasonable Assurance of Safety and Effectiveness

Under the Federal Food, Drug, and Cosmetic Act (FDCA), an applicant for premarket approval must provide reasonable assurance of the safety and effectiveness of the device proposed for commercial distribution.⁵ Such assurance must be based, *inter alia*, upon full reports of all investigations made to show whether the device is safe and effective.⁶ Although effectiveness often will be shown from a well-controlled investigation, FDA is permitted to base its finding on other types of data if a qualified expert could fairly and responsibly do so.⁷

FDA has promulgated regulations to implement this statutory scheme. In 1978, FDA issued a regulation addressing the classification of medical devices, which requires that the evidence "taken as a whole" must be "adequate to support a determination that there is reasonable assurance that the device is safe and effective for its conditions of use."⁸ In particular, data supporting a PMA application must be "valid scientific evidence from well-controlled studies, 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."⁹ In contrast, "[i]solated case reports, random experience, reports lacking sufficient details to

³ Tr. at 316-17.

⁴ The Grey Sheet (Sept. 12, 2005).

⁵ FDCA § 515(d)(2)(A) & (B).

⁶ *Id.* § 515(c)(1)(A).

⁷ *Id.* § 513(a)(1)(C)(3).

⁸ 21 C.F.R. § 860.7(c)(1).

⁹ *Id.* § 860.7(c)(2).

permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness.”¹⁰

In 1986, FDA issued a regulation directly governing the review of PMA applications. The regulation expressly provided that an applicant for PMA approval may rely *exclusively* upon foreign data, provided that the data are shown to be applicable to the U.S. population and U.S. medical practice, the studies are performed by clinical investigators of recognized competence, and the data can be considered valid without an on-site inspection or, if FDA believes that an inspection is needed, FDA can validate the data through inspection or other appropriate means.¹¹ FDA stated in the preamble that the purpose of this provision “is to facilitate the availability of devices as soon as scientifically valid data are available that show the devices to be safe and effective.”¹² The PMA regulation also expressly permits an applicant to rely upon data from a single investigator, if there are data and information to ensure the reproducibility of the test results. The applicant must provide a “justification showing that the data and other information from a single investigator are sufficient to demonstrate the safety and effectiveness of the device and to ensure reproducibility of test results.”¹³

B. The BHR System PMA Application Has Provided FDA With a Reasonable Assurance of Safety and Effectiveness

The BHR System PMA application meets the above-described legal requirements. It is supported by an extensive body of preclinical and clinical data providing FDA with a reasonable assurance of safety and effectiveness. The consecutive series of 2,385 BHR System hips implanted by Mr. McMinn is one of the largest cohorts supporting a PMA application in the orthopedics area, with unusually long follow up. The rich data from this cohort and from a variety of other data sources provide information about the safety and efficacy of the BHR System that is robust, internally consistent and consistent with results from 140 other surgeons. These data demonstrate a reasonable assurance that the BHR System is safe and effective.

As noted, the primary data come from a single investigator in the United Kingdom and do not involve a prospective randomized, controlled trial. Under FDA’s regulation, studies without matched controls and case histories may legally support a PMA approval, if they are scientifically valid. The McMinn cohort clearly meets this standard of scientific validity. The BHR System PMA does not

¹⁰ *Id.*

¹¹ 21 C.F.R. § 814.15(d).

¹² 51 Fed. Reg. 26,342, 26,346 (July 22, 1986).

¹³ 21 C.F.R. § 814.20(b)(7).

consist of isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, or unsubstantiated opinions. On the contrary, the data consisted of a large and well-documented consecutive series generated by a qualified professional in a scientifically valid manner. The primary endpoint of survivorship can be measured objectively. The evaluation of radiographs, done at FDA's request, was conducted by independent reviewers pursuant to a prospectively adopted protocol. The collection of OSHIP data was pursuant to a prospectively adopted protocol, using a slightly modified but still validated version of the Harris Hip score, a validated instrument commonly used to evaluate total hip replacement devices. Thus, FDA has an ample legal and scientific basis for accepting this data as adequate to support the BHR System PMA application.

FDA also may grant approval based upon data from a single investigator if the data and information are sufficient to ensure reproducibility. In this case, the BHR System PMA application contains ample information to make this showing, including supporting data from 140 other surgeons achieving similar results to Mr. McMinn in 3,374 patients. Finally, FDA permits approval based upon foreign data if the applicability to the U.S. population is shown. In this case, the BHR System PMA application meets this requirement.

FDA's questions to the Panel provided a public demonstration that the clinical data supporting the BHR System PMA application are receiving a full and careful vetting. In these questions, FDA carefully delineated the data supporting safety and effectiveness and asked the Panel not just whether the study results supported a finding of safety and effectiveness, but also whether the data collection methods themselves were sufficiently reliable to allow an assessment of safety and effectiveness. FDA specifically asked the Panel to consider the foreign origin of the data and its generation by a single investigator. FDA also asked whether the patient population studied was appropriate to support the proposed labeling. FDA presented these questions to its independent and expert Panel for advice because the agency also is focused on these issues in its review of the BHR System PMA application.

As with any PMA study, one could suggest ways in which the data collection might have been done differently.¹¹ FDA's regulations, however, require the agency to make a judgment as to whether the "evidence, when taken as a whole, is adequate to support a determination that there is reasonable assurance that the device is safe and effective for its conditions of use."¹⁵ As the court noted in Ethicon, Inc. v. FDA, 762 F. Supp. 382, 386 (D.D.C. 1991): "Congress gave FDA sweeping

¹¹ Indeed, as always happens during panel meetings, some of the Panel members in fact did raise questions about the data collection methods.

¹⁵ 21 C.F.R. § 860.7(b)(4).

discretion in determining the classification of devices and therefore in judging the safety and effectiveness of medical devices.” In this case, there is no question that FDA could rationally, within its expert discretion, conclude that the very substantial body of scientifically valid BHR System data met that standard, just as the Panel agreed that the clinical data provide a reasonable assurance of safety and effectiveness.

IV. WRIGHT MEDICAL TECHNOLOGY'S PETITION SHOULD BE DENIED

A. Fatal Procedural Flaws

The WMT citizen's petition is an improper invocation of the citizen's petition procedure. To begin with, the PMA approval process is not public. Under the PMA regulation, FDA may not disclose the *existence* of a PMA file prior to the approval order (unless it has been previously publicly disclosed or acknowledged).¹⁶ The PMA file itself is not available for disclosure prior to approval (with certain exceptions not pertinent here).¹⁷ The regulatory procedure FDA follows for reviewing a PMA application does not provide for public input, with the exception of the advisory panel meeting, which has a portion during which interested members of the public may comment (although without benefit of reviewing the PMA file).¹⁸ Thus, it is fair to say that the PMA approval process is the opposite of FDA rulemaking, in which public comment is solicited and considered. Rather, it is an essentially private proceeding in which a single PMA applicant attempts to satisfy FDA that it has met the statutory burden of demonstrating a reasonable assurance of the safety and effectiveness of the device proposed for commercial distribution.

In light of these considerations, if FDA were to address the petition on the merits, it would seriously undermine the confidential nature of the PMA review and turn it into a public proceeding. It also would be a drastic departure from the PMA review procedures that FDA has consistently followed for the past 30 years. WMT has filed its citizen's petition under a very general regulation that simply permits the public to file petitions on any subject at any time.¹⁹ In the context of a PMA review, this general authorization must yield to FDA's specific regulation governing the PMA review process.²⁰ FDA's PMA regulation does not authorize this use of a citizen's petition to allow public input during a PMA review. We know of no

¹⁶ 21 C.F.R. § 814.9.

¹⁷ *Id.*

¹⁸ *Id.* § 814.44; 21 C.F.R. § 14.25.

¹⁹ *Id.* § 10.30.

²⁰ Edmond v. United States, 520 U.S. 651, 657 (1997) (“[o]rdinarily, where a specific provision conflicts with a general one, the specific governs”) (*citation omitted*).

precedent for doing so, nor did WMT cite any. FDA should deny WMT's ill-founded petition on this ground alone.

B. Lack of Merit

WMT summarizes its attack on the BHR System PMA application as follows: "The petition is not asserting that the data show the BHR System to be unsafe or not effective. Rather, as demonstrated in this petition, Smith & Nephew's data was 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."²¹ The thrust of WMT's complaint is that the BHR System application was not supported by data from a prospective, randomized, controlled trial and that the data come primarily from a single investigator in the U.K.²²

Nonetheless, WMT concedes (as it must) that the FDCA and FDA's regulations permit reliance upon the type of data in the BHR System PMA application. That is, WMT concedes that it is lawful for FDA to approve a PMA supported exclusively by data from sources other than a well-controlled trial and generated by a single investigator outside the U.S., if the regulatory requirements for doing so are met.²³ WMT apparently disagrees with the independent expert Panel that the BHR System data were shown to be scientifically valid and adequate to demonstrate reasonable assurance of safety and effectiveness. Nonetheless, WMT's repeated assertions that the data were not collected in accordance with the FDCA and FDA's regulations should be recognized as mere hyperbole, contradicted by WMT's own necessary concessions as to what the existing law and regulations actually permit.

WMT acknowledges that FDA is required under the FDCA to "consider the least burdensome appropriate means of evaluating device effectiveness that would have a reasonable likelihood of resulting in approval."²⁴ WMT argues that the "least burdensome approach" in this case can only be a well-controlled trial. Obviously, the Panel did not agree. Inasmuch FDA concededly could approve the BHR System PMA in compliance with its regulations, WMT's assertion is not based

²¹ *Id.* at 3-4 n. 11.

²² *Id.* at 4-27.

²³ *E.g.*, Wright Medical Technology Citizen's Petition at 4 (data from a single investigator permitted if reproducibility shown); *id.* at 5 (well-documented case histories and significant human experience with a marketed device may constitute valid scientific evidence to support a PMA); *id.* at 10 (foreign data permitted to support a PMA if shown to be applicable to the U.S. population and medical practice).

²⁴ *Id.* § 515(c)(a)(3)(D)(ii).

upon the legal meaning of “least burdensome approach.”²⁵ Rather, WMT simply disagrees with the Panel’s acceptance of the BHR System effectiveness data as sufficient to support approval.

All of WMT’s questions about the sufficiency of the BHR System safety and effectiveness data are being actively considered by FDA in the review of the BHR System PMA application. Indeed, as already noted, FDA’s questions to the Panel called for comprehensive consideration of the scientific validity, reliability, and sufficiency of the BHR System data to support PMA approval. The questions called not only for the Panel’s general view of the sufficiency of the data, but also discussion of the specific issues that WMT is raising now, such as the sole-investigator and foreign origin of the data. A majority of the Panel nonetheless concluded that the data were sufficiently compelling to provide a reasonable assurance of safety and effectiveness and voted in favor of approval (with limited conditions).

WMT also complains that Mr. McMinn did not follow a standard protocol with patient inclusion-exclusion criteria that would support the labeled indications for the BHR System. Thus, WMT asserts, “labeling that establishes the appropriate patient population for the BHR System cannot be written.”²⁶ However, as was noted during panel discussion, Mr. McMinn did use certain criteria (i.e., advanced age, low activity level, poor bone stock) to screen patients. FDA specifically asked the Panel (Question #6) if the “patient selection methods and data presented on the BHR System device support the proposed labeling indication,” and the Panel answered in the affirmative.²⁷

WMT’s own discussion of General Medical Co. v. FDA, 770 F.2d 214 (D.C. Cir. 1985) actually highlights the strength of the BHR System data. WMT cites that case as a cautionary tale about the need for a protocol, because FDA apparently objected when a sponsor studied 225 cases in a clinical study, but after six weeks, only 60 cases were still under evaluation, and there was no explanation as to how those cases were selected.²⁸ The court and FDA apparently agreed that there was a serious concern about bias in the data and that effectiveness was not proven. The BHR System application is notably different, however, because it is supported by *2,385 consecutive cases* rather than 60 selected cases. Thus, it is

²⁵ It is an inversion of the statutory meaning to argue that the “least burdensome” provision requires FDA to impose *more* burdensome data requirements. Yet, that is the logic of WMT’s argument.

²⁶ Wright Medical Technology Citizen’s Petition at 20.

²⁷ Tr. at 275-78.

²⁸ Wright Medical Technology Citizen’s Petition at 8.

entirely rational for the same agency to conclude that the potential for selection bias is virtually absent here and that the data set is robust.

In sum, WMT paints a picture of an agency that vigilantly monitors the scientific validity of data collected to support marketing applications through detailed regulatory requirements, warning letters, and requirements imposed in other PMA application reviews. At the same time, WMT does not present any evidence or reasons for one to conclude that FDA is not being equally vigilant in this case.²⁹ On the contrary, there can be no question that the BHR System data is receiving careful and thorough scrutiny, if one considers the detailed and broad-ranging questions for which FDA sought answers from the Panel during their meeting and the length of this PMA review (already exceeding 18 months). It is also apparent that WMT has not raised any new issues that call into question FDA's decision-making process. An approval in this case would be well within the bounds of FDA's expert scientific discretion.

V. CONCLUSION

For all of the foregoing reasons, Wright Medical Technology's Citizen's Petition should be summarily denied.



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²⁹ WMT also challenges the BHR System data because of Mr. McMinn's financial interests. However, this has been fully disclosed to FDA during the PMA review. Furthermore, the McMinn data were generated over a lengthy period with the involvement of many other persons, were consistent with the data from 140 other surgeons, were subject to independent retrospective review, and otherwise have indicia of reliability sufficient to demonstrate their validity. There is no issue here.