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BY HAND DELIVERY

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

**RE: Docket No. 07D-0290
Draft Guidance for Industry, Cell Selection Devices for Point of Care
Production of Minimally Manipulated Autologous Peripheral Blood
Stem Cells (PBSCs)**

Dear Sir or Madam:

Among Hyman, Phelps & McNamara, P.C.'s ("HPM") clients are development-stage therapeutics companies pursuing autologous stem cell products pursuant to Investigational New Drug Applications ("INDs") for the treatment of various non-hematologic indications, including cardiac indications.

HPM welcomes the opportunity to submit comments in response to the above-captioned draft guidance document (the "Draft Guidance"). We agree that the Food and Drug Administration ("FDA") should address, in a clear and principled way, the use and regulatory status of stem cells sorted and collected by cell selection devices. If finalized, however, the Draft Guidance would represent a significant deviation from FDA regulations and a large shift in FDA's historical treatment of human cells, tissues or cellular or tissue-based products ("HCT/Ps"). A change of this magnitude cannot be implemented in accordance with the Administrative Procedure Act ("APA") absent the administrative safeguards provided by notice and comment rulemaking. Moreover, if implemented, the Draft Guidance would treat similarly situated parties disparately and would abdicate FDA's responsibility to protect US citizens from unsafe and ineffective cellular drug products. Mere publication of the Draft Guidance threatens to violate the APA if FDA fails to

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promptly withdraw the document with a clear statement that the proposal is inconsistent with FDA's current regulatory framework.

I. Current Regulatory Framework for Human Cellular Products

A. The General Rule

FDA defines HCT/Ps as "articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient. Examples of HCT/Ps include, but are not limited to, . . . hematopoietic stem progenitor cells derived from peripheral and cord blood."¹ FDA regulates HCT/Ps as either: (1) tissue under section 361 of the Public Health Service Act ("PHS Act") and 21 C.F.R. Part 1271, i.e., subject to certain general requirements² but not subject to FDA premarket review or approval (hereinafter referred to as "361 Products"),³ or (2) biologic drugs or devices under the Federal Food, Drug, and Cosmetic Act ("FDC Act") and/or section 351 of the PHS Act which are subject to FDA premarket review and approval in addition to the other controls mentioned above ("351 Products").⁴

FDA regulations distinguishing between treatment of HCT/Ps as 361 Products or 351 Products recognize that additional risks are presented by HCT/Ps that are more than minimally manipulated or are intended for a nonhomologous use.⁵ Accordingly, additional

¹ 21 C.F.R. § 1271.3(d). The Draft Guidance addresses only peripheral blood stem cells ("PBSCs") and does not speak to stem cells derived from bone marrow. Accordingly, it is our understanding that FDA would not approve premarket approval applications ("PMAs") for cell selection devices intended for stem cells derived from bone marrow even if the Draft Guidance were finalized and the cells otherwise meet the requirements of the Draft Guidance.

² These requirements include establishment registration and listing, donor screening and testing, and good tissue practices.

³ Id. § 1271.10.

⁴ Id. § 1271.20.

⁵ FDA's regulations set forth the criteria that must be met for an autologous use HCT/P to be a 361 Product. According to those regulations, the autologous HCT/P must:

- Be minimally manipulated;
- Be intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's intent; and

regulatory burdens are applied to such products to ensure patient safety. Among the most important, and most burdensome, of these additional safeguards are the requirements for a filed IND for clinical study and an approved biologics license application (“BLA”) for marketing. Details of preclinical and clinical studies, typically including two adequate and well-controlled clinical trials, as well as the HCT/P manufacturing process, including safety-related release specifications, are reviewed as part of both an IND and a BLA.

Notwithstanding the FDA-recognized increased risk presented by more than minimal manipulation or nonhomologous use of HCT/Ps, FDA regulations recognize two relevant exceptions (one stated and one implied) under which products that would otherwise be 351 Products can avoid certain regulatory burdens. First, to the extent that the HCT/Ps are used in the same individual and in the same surgical procedure, no IND or BLA is required. Thus, HCT/Ps for nonhomologous use or HCT/Ps that have undergone more than minimal manipulation can nonetheless avoid the burdens and safeguards applied to 351 Products (and even 361 Products) if they are used “in the same individual in the same surgical procedure” (the “Same Surgery Exception”). This exception is apparently based on an FDA’s belief that the major risks associated with greater than minimal manipulation or with nonhomologous use are mitigated by autologous use and by the proximity in time or distance from cell retrieval to cell implantation.⁶

The second exception is implied by the language of 1271.10(a).⁷ That is, HCT/Ps that are used in a nonhomologous manner are not considered 351 Products subject to IND and BLA requirements absent their being labeled or advertised for such use. Thus, to the extent that a physician treats his patients with nonhomologous HCT/Ps but does not advertise use of such cells, he need not submit an IND or BLA. Unlike the exception above, this one is not risk-based. That is, there is no ameliorating factor to offset the FDA-recognized risks associated with nonhomologous use. Instead, this exception appears to be aimed at more efficient use of FDA enforcement resources perhaps due to the logistical

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- Not be combined with a drug or device.

Id. § 1271.10(a). Thus, any human cellular product intended for a nonhomologous use is a 351 Product.

⁶ In promulgating this exception, FDA merely noted that this activity does “not raise issues the agency currently believes warrant regulation.” 63 Fed. Reg. 26,744, 26,748 (May 14, 1998).

⁷ In setting forth homologous use as a factor in the 351 Product/361 Product determination, the regulation states “(2) [t]he HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer’s objective intent.” 21 C.F.R. § 1271.10(a). See 66 Fed. Reg. 5,447, 5,459 (Jan. 19, 2001).

issues associated with identifying such unadvertised physician use.⁸ It is also consistent with the long-recognized view that FDA does not regulate the practice of medicine, and accepts that a physician may treat his patients with nonhomologous HCT/Ps without FDA interference.⁹

B. FDA's Historic Application of the HCT/P Regulations

FDA's history of product-specific HCT/P regulation has been consistent with the general rule and its two exceptions discussed above. For instance, FDA has required INDs or BLAs for HCT/Ps that are more than minimally manipulated, as evidenced by Dendreon Corporation's Provenge (sipuleucel-T),¹⁰ and for HCT/Ps that are intended for nonhomologous use.¹¹ FDA has also honored the two exceptions to the general rule discussed above and has not taken enforcement action against doctors or hospitals using products that would otherwise be 351 Products in the same surgical procedure, or for an unadvertised nonhomologous use.

FDA has separately approved PMAs for devices intended to minimally manipulate (e.g., sort) cells that are to be used in a homologous application.¹² Cells processed by such devices are 361 Products that avoid the risk-triggers of 351 Products and can be implanted in patients without submission or approval of an IND or BLA. Thus, FDA's approval of PMAs for these devices without a companion IND or BLA for the HCT/P product is

⁸ In proposing the exception, FDA noted that "the actual use of [an HCT/P] for a nonhomologous function would not trigger premarket review requirements if the product was not labeled or promoted for nonhomologous use" and that this exception "is expected to lead to the more efficient use of the agency's resources." 63 Fed. Reg. at 26,749.

⁹ See 37 Fed. Reg. 16,503 (Aug. 15, 1972).

¹⁰ Provenge is an HCT/P in which autologous cells are antigen-loaded and are thus more than minimally manipulated. See also Warning Letter from Mary A. Malarkey, Director, Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research, to Dino Prato, Office Administrator, Envita Natural Medical Centers of America (June 14, 2006) (finding treated cell cultures to be HCT/Ps that require an IND and BLA due to more than minimal manipulation).

¹¹ HPM is aware of several such products that are subject to confidential INDs. The Fred Hutchison Cancer Research Center ("FHRC") has publicly discussed FDA's classification of its CD34+ HCT/P for use in treatment of autoimmune diseases as a 351 Product, subject to an IND and BLA, because of its non-homologous nature. Comments of Shelly Heimfeld, Ph.D., Director, Cellular Therapy Laboratory and cGMP Cell Processing Facility, FHRC, at 1st Biannual Cell Therapy Liason Meeting (Nov. 5, 2004).

¹² See, e.g., Nexell Therapeutics, Inc., Isolex 300 and 300i Magnetic Cell Selection System, PMA No. BP970001 (July 2, 1999).

consistent with the regulatory framework discussed above. We are not aware of any instance in which FDA has approved a PMA for a device that would produce either more than minimally manipulated cells or cells intended for nonhomologous use.

II. The Draft Guidance

The Draft Guidance purports to be consistent with FDA's regulations and history, claiming merely to provide advice on FDA's application of the Same Surgery Exception set forth in 21 C.F.R. § 1271.15(b).¹³ In reality, however, the Draft Guidance announces a significant shift in the FDA's risk-based approach set forth in 21 C.F.R. Part 1271, and opens a new regulatory pathway for approval of certain medical devices. First, the Draft Guidance demonstrates FDA's reassessment of safety risks posed by the various factors set forth in 21 C.F.R. § 1271.10(a) and used in the 351 Product/361 Product determination. The Same Surgery Exception, as promulgated in FDA regulations, applies equally to both more than minimally manipulated HCT/Ps and nonhomologous HCT/Ps. The Draft Guidance attempts to narrow the exemption to only nonhomologous cells by listing

¹³ The Draft Guidance describes the circumstances under which FDA would consider PBSCs to fall within the Same Surgery Exception. Specifically, the Draft Guidance states that:

FDA believes that, for autologous PBSCs processed at the clinical site, the presence of all of the following five factors supports the conclusion that the cells are removed and subsequently implanted in the 'same surgical procedure' and are therefore subject to the exception:

- 1) The cells are autologous and are intended for use for a specific clinical indication;
- 2) The cells are minimally manipulated;
- 3) The device is solely responsible for the production of the autologous cells (i.e., no other manufacturing steps take place outside of the device other than the recovery of the source cells);
- 4) The cells are used within a short period of time (i.e., they are not stored or shipped);
and
- 5) The device and selected cells are only used at the point of care (i.e., cell processing is performed at and by the clinical site where cells are directly administered).

Draft Guidance, at 2-3. The Draft Guidance also describes the data to be included in PMAs for devices used to select PBSCs. Such data are focused on safety and effectiveness of the cell sorter and include device design, manufacturing, and performance characteristics. The Draft Guidance further provides that PBSCs selected through an approved cell sorting device and meeting the Same Surgery Exception would not require submission of an IND or BLA for the cellular product.

minimal manipulation as one of five factors considered by FDA in evaluating the exception. The Draft Guidance states that “[m]ore than minimal manipulation of cells may alter them extensively, changing their essential character. Moreover, such manipulation introduces significant risks into the manufacturing process ... [and] warrants regulation of the manufacturing process and the resulting cells as” 351 Products¹⁴ thereby implying that the exemption may no longer automatically apply to such cells.¹⁵ Thus the Draft Guidance, for the first time, sets forth a dichotomy of relative risks posed by more than minimal manipulation versus nonhomologous use.

Second the Draft Guidance publicly evidences, for the first time, FDA’s willingness to review and approve PMAs for cell sorters intended to produce 351 Products even absent an IND or BLA for such products – essentially opening a regulatory pathway for devices whose output cannot be lawfully marketed.

The ultimate effect of the Draft Guidance, if implemented, goes well beyond the Same Surgery Exception and expands beyond recognition the use of nonhomologous HCT/Ps without FDA oversight and the ability of commercial manufacturing firms to profit from nonhomologous HCT/P use without complying with the IND and BLA safeguards. The vast majority of, if not all, nonhomologous HCT/Ps would be regulated under the Same Surgery Exception rather than through the BLA process. This expansion would come at great cost to patients who, in large numbers, would no longer be protected by FDA’s risk-based regulatory burdens and to HCT/P manufacturers who for years have spent tremendous resources attempting to navigate those requirements.

Perhaps in recognition of its own over-reaching, the Draft Guidance does not overtly state that nonhomologous HCT/Ps are no longer considered 351 Products and can therefore be implanted without an IND or BLA. Instead it sets up an arbitrary distinction such that a company that manufactures and honestly labels HCT/Ps for nonhomologous use must comply with the IND and BLA regulations, while a company that manufactures HCT/P sorters for nonhomologous use and its customers, while performing the very same steps entailing the very same risks, need not comply.

¹⁴ Id. at 3-4.

¹⁵ While the Draft Guidance lists the five factors as “support[ive of] the conclusion that cells are removed and subsequently implanted in the ‘same surgical procedure,’” it provides no rationale regarding how each factor supports such a conclusion. Id. at 2. While some types of manipulation (e.g., expansion) may require lengthy steps inconsistent with the Same Surgical Procedure, others (e.g., surface marker upregulation) may not. It is telling that FDA’s rationale for inclusion of minimal manipulation as a factor discusses the effects of more than minimal manipulation on cell safety rather than any mention of protracted time periods.

III. The Draft Guidance, if Implemented, Would Violate the APA and Pose Safety Risks

The Draft Guidance presents two fundamental issues under the APA as well as an issue of patient safety. First, the Draft Guidance alters both the intent and the boundaries of the Same Surgery Exception and, more broadly, the general rule regarding 351 Product and 361 Product determinations. Such changes are improper under the APA absent notice-and-comment rulemaking. Second, these changes result in regulatory disparities among various entities seeking to commercialize nonhomologous HCT/Ps, with certain manufacturers subject to the rigorous IND and BLA requirements and others subject only to PMA requirements. Third, these disparities lead to diminished assurances of safety for patients receiving less-regulated HCT/Ps.

Prior to the Draft Guidance's publication, the general rule that nonhomologous use HCT/Ps were regulated as 351 Products under the IND/BLA paradigm was unquestioned. The exceptions to that rule permitted, but did not encourage, limited use of such products in situations where the proximity of processing ameliorated certain safety concerns, and where the lack of commercial advertising rendered the activities not sufficiently pervasive or too difficult to track to warrant FDA enforcement. The Draft Guidance, if implemented, would instead permit a sham in which manufacturers obtain PMA approval for a cell sorter, advertise its approval for manufacture of nonhomologous use HCT/Ps, and install such sorters in various facilities with the intent that they be used to produce cells for nonhomologous use, thereby avoiding the more rigorous and burdensome BLA requirements. Its implementation would functionally remove homologous use as a factor in the 351 Product/361 Product decision under 21 C.F.R. § 1271.10(a) by rendering a BLA for all, or nearly all, nonhomologous HCT/Ps unnecessary. Instead, such products would be manufactured at the point of care via a PMA-approved cell sorter. That is, the Same Surgery Exception would essentially swallow the general rule as to nonhomologous use.

A. The Draft Guidance, if Implemented, Would Violate the APA

1. *Notice-and-Comment Rulemaking*

The APA requires notice-and-comment rulemaking¹⁶ whenever a federal agency acts in a way that materially changes established burdens and benefits,¹⁷ "by which 'rights or

¹⁶ 5 U.S.C. § 553.

¹⁷ APA notice-and-comment requirements achieve three purposes: "to ensure that agency regulations are tested by exposure to diverse public comment, to ensure fairness and an opportunity to be heard, and to enhance judicial review." Bldg. Indus. Ass'n. of Superior Cal. v. Babbitt, 979 F. Supp. 893, 901 (D.D.C. 1997).

obligations have been determined,' or from which 'legal consequences will flow.'"¹⁸ The Draft Guidance significantly and substantively changes the existing HCT/P regulations. In doing so, the Agency is acting to substantively change the "rights and obligations" of companies developing HCT/Ps and companies developing cell sorters. These are the very kinds of fundamental changes that warrant the protections afforded by rulemaking.

The APA requires FDA to explain its new policy, open the new policy to public comment, and respond to these public comments.¹⁹ Any final rule must contain a "concise general statement of basis and purpose" sufficient to permit a reviewing court "to see what major issues of policy were ventilated by the informal proceedings and why the agency reacted to them as it did."²⁰ FDA cannot act as if Draft Guidance is merely a clarification of the regulations and thereby avoid the strictures of rulemaking. The FDA's process of accepting comments on non-binding documents such as the Draft Guidance does not absolve the Agency of its legal obligation to carry out rulemaking when announcing changes of this magnitude.

At least three aspects of the Draft Guidance cannot be addressed appropriately through guidance and raise the need for a rulemaking procedure.

Narrowing of 21 C.F.R. § 1271.15(b). The Draft Guidance seeks, in one aspect, to narrow the Same Surgery Exception defined at 21 C.F.R. § 1271.15(b). As codified in FDA's regulations and explained in the preamble to those regulations, the Same Surgery Exception is broadly applicable; the only qualifying requirements are that the establishment removes HCT/Ps from an individual and implants them in the same individual during the same surgical procedure. It applies to HCT/Ps regardless of their level of manipulation or the methods used in their processing. The Draft Guidance seeks to change that. The document's five factors to be considered in applying the Same Surgery Exception amount to a narrowing of the exception such that some HCT/Ps, despite their use in the same individual in the same surgery, might nonetheless have to comply with 351 Product or 361 Product requirements if, for instance, they are more than minimally manipulated or if they are not sorted using a device that is solely responsible for their production. The Draft

Without such open and public discussion of substantive proposed changes in its enforcement policies, FDA thwarts the overarching APA intent that "interested parties" shall be heard.

¹⁸ Bennett v. Spear, 520 U.S. 154, 178 (1997).

¹⁹ See 5 U.S.C. § 553(c); 21 C.F.R. § 10.40(c)(3).

²⁰ Automotive Parts and Accessories Ass'n. v. Boyd, 407 F.2d 330, 338 (D.C. Cir. 1968).

Guidance does list minimal manipulation as a factor that is “support[ive of] the conclusion that cells are removed and subsequently implanted in the ‘same surgical procedure’” but provides no rationale to support this view. Instead FDA’s rationale for inclusion of minimal manipulation as a factor discusses the potential that more than minimal manipulation of cells may change their character and introduce significant risks rather than any mention of protracted time periods that would refute a “same surgical procedure” conclusion. The Draft Guidance therefore inappropriately creates new limitations on facilities whose practices fall under the Same Surgery Exception. Such limitations can only be imposed through rulemaking.

Alteration of the Risk Assessment Underlying 21 C.F.R. 1271.10(a). Prior to promulgating 21 C.F.R. § 1271.10(a), FDA held numerous public meetings and published several draft documents in an effort to determine those factors that would render an HCT/P a 351 Product. Both more than minimal manipulation and nonhomologous use were discussed as factors that could raise safety concerns and, in the end, FDA determined that the existence of either factor would raise sufficient safety concerns to warrant IND and BLA protections. The Draft Guidance effects a change in FDA’s risk assessment for HCT/Ps – apparently concluding that the risks associated with more than minimal manipulation are greater than those associated with nonhomologous use.²¹ Any such change must be evidence-based and must afford the regulated industry the opportunity for an open dialogue. While the Draft Guidance addresses only the Same Surgery Exception rather than the general rule, its attempt to limit that exception to only minimally-manipulated products is inconsistent with FDA’s prior published thinking. The Draft Guidance fails to explain FDA’s rationale or evidence for such a change and also fails to discuss why the change should not also affect the general rule set forth in 21 C.F.R. § 1271.10(a). FDA’s proposed implementation of new or revised burdens must be based on any new risk assessment, be open and consistent, and must undergo notice-and-comment rulemaking.

Creation of a New Regulatory Pathway for HCT/P Approval. The Draft Guidance seeks to fundamentally alter the rights and obligations of HCT/P manufacturers and cell sorter manufacturers by announcing significant and substantive changes to existing approval requirements. It would, in essence, establish a new regulatory pathway for review and approval of some 351 Products via a PMA for a cell sorting device intended to produce

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FDA has noted that homologous use is consistent with 361 Product classification because of the intuitive effectiveness of HCT/Ps in a homologous setting, akin to the intuitive effectiveness of solid organ transplantation. Absent a “clear demonstration” of homologous use, an IND or BLA is required. Comments of Stephen Grant, M.D., Medical Officer, CBER at 1st Biannual Cell Therapy Liason Meeting (Nov. 5, 2004).

HCT/Ps for nonhomologous use. Approval under the medical device authorities of a cell selection device for the production of cells intended for a nonhomologous use is inappropriate and inconsistent with the FDC Act, the PHS Act and their implementing regulations absent an accompanying BLA approval for the HCT/P itself. Otherwise, the PMA approval would result in a medical device that cannot lawfully be used in accordance with its labeling and whose purpose is to produce a product that cannot be lawfully marketed.²²

This pathway represents a fundamental shift in the type and quantity of data needed for product approval, and more importantly, in the section of the law under which such products are regulated.²³ The magnitude of this shift is so significant as to cause an upset in the HCT/P marketplace with cell sorter manufacturers set to significantly expand sales of their devices while nonhomologous HCT/P manufacturers pursuing BLAs consider halting all research and development efforts since, under the Draft Guidance, facilities could purchase a cell sorter labeled to produce the very cells that currently require BLA approval.

2. *Disparate Treatment*

In order to successfully withstand judicial scrutiny, the actions of administrative agencies must not be arbitrary, capricious or an abuse of discretion.²⁴ “[A]n agency’s unjustifiably disparate treatment of two similarly situated parties works a violation of the arbitrary-and-capricious standard.”²⁵ For example, in Bracco Diagnostics, Inc. v. Shalala,

²² We acknowledge and agree with FDA’s careful avoidance of regulating HCT/Ps based on actual versus intended nonhomologous use. The regulations and their preambles make clear that FDA looks to whether an HCT/P is intended for homologous use “as reflected by the labeling, advertising, or other indications of the manufacturer’s objective intent,” thereby avoiding regulation of the practice of medicine. 21 C.F.R. § 1271.10(a)(2). See also 63 Fed. Reg. at 26,749; 66 Fed. Reg. at 5,458. We therefore understand that FDA would not seek to impose the IND and BLA requirements on healthcare facilities that use stem cells as the practice of medicine for a nonhomologous use (e.g., cardiac use) without, for instance, that facility advertising availability of this therapy and thereby establishing the objectionable intent. FDA approval of a medical device specifically intended to produce such cells for such nonhomologous use, on the other hand, would take the exemption too far by permitting commercialization, including advertising and promotion, of an FDA-approved product intended to manufacture an HCT/P that would otherwise require an IND or BLA. Such an outcome would completely circumvent the important distinction between homologous and nonhomologous use HCT/Ps.

²³ Absent an amendment to the “device” definition in section 201(h) of the FDC Act or the requirement for a biologics license for interstate shipment of a biological product in section 351 of the PHS Act, FDA does not have the authority to create this new approval pathway.

²⁴ 5 U.S.C. § 706(2)(A).

²⁵ Federal Election Comm’n v. Rose, 806 F.2d 1081, 1089 (D.C. Cir. 1986) (citation omitted).

the United States District Court for the District of Columbia reviewed FDA's application of different premarket review standards to two similar products.²⁶ Bracco and other manufacturers of injectable contrast imaging agents successfully challenged FDA's determination that their products should be regulated as drugs, while a competitor's similar product was classified and regulated as a device. The court enjoined FDA action on these products until the agency decided on a uniform regulatory approach, holding that "[t]he disparate treatment of functionally indistinguishable products is the essence of the meaning of arbitrary and capricious."²⁷

The Parties are Similarly Situated and the Products are Functionally Indistinguishable. If implemented, the policy articulated in the Draft Guidance would result in the disparate treatment of similarly situated parties: (1) entities that manufacture cell sorters and their customers who use such sorters to produce nonhomologous HCT/Ps at the point of care versus (2) entities that use cell sorters to produce nonhomologous HCT/Ps at a distant facility. In the first case, the sorters would be approved under PMAs and the HCT/Ps themselves, despite their status as 351 Products, would be exempt from any premarket review requirements. In the second case, the cell sorters would be manufacturing equipment used to produce HCT/Ps that would require approval of a BLA prior to marketing. This paradigm is akin to permitting manufacturers of cell sorters to establish nonhomologous use HCT/P manufacturing facilities at various hospitals and thereby avoid the BLA requirements.

This paradigm is also not grounded in sound science. The Draft Guidance appears to take the position that validation of a cell sorting device, combined with point of care processing, provides sufficient assurance of the safety and efficacy of nonhomologous HCT/Ps and that, absent more than minimal manipulation, nonhomologous HCT/Ps could be safely administered without the IND and BLA protections imposed upon other 351 Products. To the extent that an HCT/P manufacturer utilizes an approved cell sorter to process autologous minimally-manipulated cells intended for use for a specific clinical indication, it has met three of the five factors in the Draft Guidance. The other two, that the cells be used within a short period of time and at the point of care, recognize that storage and shipment can introduce additional safety risks into use of such cells. In this situation, where the only difference between the two manufacturing processes is storage and

²⁶ 963 F. Supp. 20 (D.D.C. 1997).

²⁷ *Id.* at 28 (citation omitted); see also *United States v. Diapulse Corp. of America*, 748 F.2d 56, 62 (2d Cir. 1984) (holding that FDA must act "evenhandedly" and may "not 'grant to one person the right to do that which it denies to another similarly situated.'"); *Willapoint Oysters, Inc. v. Ewing*, 174 F.2d 676, 697 (9th Cir.), cert. denied, 338 U.S. 860 (1949).

shipment, one would expect that INDs and BLAs from such nonhomologous HCT/P manufacturers should contain nothing more than data related to the effects of any anticipated storage and shipment on the HCT/Ps. In reality, however, these applications are required to contain a tremendous amount of additional data unrelated to storage and shipping such as data on characterization of cell populations and contaminating subpopulations, viability and sterility of cells, potency, sample handling prior to sorting, release specifications, and catheter compatibility. Such data either are or are not necessary to show the safety and effectiveness of HCT/Ps produced by a cell selection device regardless of shipment and storage. They cannot be required of one manufacturer and not another.

That the Same Surgery Exception should, in any way, hinge on the regulatory status of the sorter used to manufacture HCT/Ps – the product at issue in the exception – seems odd at best. So odd, in fact, that some might argue that the Draft Guidance is little more than an economic boon to cell sorter manufacturers disguised as guidance on a previously obscure HCT/P exception. In the end, the Draft Guidance, if implemented would essentially permit commercialization, including advertising and promotion, of nonhomologous use HCT/Ps without a BLA. To say that it merely permits such commercialization of cell sorters is to split a very fine regulatory hair. This would be akin to arguing that FDA could approve, as medical devices, various pieces of equipment used to manufacture drugs, and, to the extent that a drug was manufactured with that equipment, it need not obtain separate premarket approval as a drug.

PMAs and BLAs Present Different Regulatory Burdens. The regulatory burdens for BLAs and PMAs are substantially different. PMAs are required to provide a “reasonable assurance” of the subject device’s safety and effectiveness.²⁸ BLAs, on the other hand must “demonstrate that” the subject biologic is “safe, pure, and potent” and that the facilities involved in its production meet “standards designed to assure” its continued safety, purity and potency.²⁹

These differing laws translate into different regulatory data and submission requirements. In regulating 351 Products, including HCT/Ps intended for nonhomologous use, FDA has required that the related INDs and BLAs include substantial specific manufacturing and controls information.³⁰ While some of this information pertains to the

²⁸ FDC Act § 513(a)(1)(C).

²⁹ PHS Act § 351(a)(2)(C).

³⁰ See FDA Biological Response Modifiers Advisory Committee, Summary Minutes, Meeting #37, at 3-4 (Mar. 18-19, 2004).

actual sorting of the target cells from the larger PBSC or bone marrow preparation (as would be required in a cell sorter PMA), FDA has required as critical to the safety of the final product that is administered to patients, additional information for INDs and BLAs including HCT/P identity (including cell subtypes and differentiation), potency assays (applied as release specifications to each lot of HCT/Ps manufactured), and sterility testing of to-be-infused final product. Preclinical testing in HCT/P applications has included large animal model studies involving the clinical route of administration and data demonstrating compatibility of HCT/Ps with delivery devices (e.g., catheters). In addition, BLAs are typically required to be supported by two adequate and well-controlled clinical trials to establish the safety, purity and potency of the biologic. These trials are often large and are most frequently required to show statistical superiority over placebo or the current standard of care on a clinically meaningful primary endpoint. A mere showing of non-inferiority to an unapproved product would not suffice.

Consider, by contrast, the quality and quantity of data submitted in the PMA for Nexell's cell sorter.³¹ While the PMA discusses twelve preclinical studies, each of those studies tests the reactivity or other characteristics of the device components or peptide. There are no preclinical tests performed with the HCT/Ps produced by the cell sorter despite that this is the product that will be implanted into patients. Moreover, the PMA is supported by a single major efficacy trial designed to evaluate recovery from myeloablative chemotherapy in breast cancer patients. The study sought to establish the non-inferiority of sorted CD34+ cells to unsorted PBSC in time to neutrophil engraftment.

B. Ignoring 351 Product Safeguards Would Compromise Patient Safety

FDA oversight of the output of cell selectors under the IND and BLA pathway is essential. Two important safety concerns arise from FDA's willingness to permit large-scale use of non-homologous HCT/Ps without protections normally afforded to patients receiving 351 Products. First, the administration of drugs with no proven efficacy causes patients to forego other more effective therapy and exposes patients to the risks inherent in the products with no known potential for benefits. Second, lack of IND and BLA controls on cell processing and characterization can lead to serious adverse outcomes for patients.

Autologous HCT/Ps have the potential for wide spread use as the ability to manufacture such products becomes more streamlined. U.S. patients have appropriately come to trust that non-investigational drugs and biologics to which they are exposed have

³¹ Summary of Safety and Effectiveness, PMA BP97-0001 and BP97-0001/01, Hematopoietic Stem Cell Concentration System (July 2, 1999).

been deemed safe and effective by FDA. The Draft Guidance would expose large numbers of such patients to therapeutic products with no real ability to demonstrate safety, purity or potency. The Draft Guidance for instance, would permit use of HCT/Ps for cardiac applications despite a lack of data on the cells' ability to cross the endothelial wall in order to reach their target tissue.

Public health risks involved with implantation of poorly characterized HCT/Ps or HCT/Ps tested under preclinical and clinical studies that were not designed to recognize the cells as the product are magnified in the nonhomologous use setting. Poor characterization of cell populations and contaminating subpopulations, failure to verify viability and sterility of cells prior to administration, and lack of proper potency assays can lead to serious adverse outcomes for patients. The Draft Guidance would create a paradigm under which processing steps that occur after cell sorting, and release testing of each patient's cells, would not be required. Cell sorters produce a cellular suspension which must be pelleted, resuspended in a final formulation, and loaded into a syringe. HCT/P manufacturers subjected to IND and BLA requirements must justify, in a data-driven manner, post-selection processing, as well as the components and composition of the final HCT/P formulation. Under the Draft Guidance, no such controls would be in place. The IND and BLA process further requires that the final formulation undergo release testing using validated assays. Under the Draft Guidance, patients would no longer be assured that the HCT/Ps, as loaded for delivery, are safe, pure or potent.

Poorly characterized or manufactured HCT/Ps for nonhomologous use can lead to aberrant study results, leaving unanswered questions regarding whether failure to see a treatment effect is related to ineffectiveness of the cells or, rather, poor selection of cells or doses. Absent availability of a pharmaceutical grade final formulation subject to FDA review through a BLA for the specific indication, patients may be treated with subpotent product that fails to contain adequate numbers of chemotactic cells expressing correct surface markers or, worse, a non-sterile product. The September 21, 2006 issue of the New England Journal of Medicine reported three studies of bone marrow-derived stem cells injected into cardiac muscle after acute myocardial infarction.³² Although the three studies included many similar design features, two showed improvement in left ventricular ejection fraction while one did not. Absent characterization data similar to that required in an IND

³² Ketil Lunde, Svein Solheim, et al. *Intracoronary injection of mononuclear bone marrow cells in acute myocardial infarction*. 355 NEJM 1199 (Sept. 21, 2006). Volker Schächinger, Sandra Erbs, et al. *Intracoronary bone marrow-derived progenitor cells in acute myocardial infarction*. 355 NEJM 1210 (Sept. 21, 2006). Birgit Assumus, Jörg Honold, et al. *Transcoronary transplantation of progenitor cells after myocardial infarction*. 355 NEJM 1222 (Sept. 21, 2006).

or BLA for late-stage cellular therapeutics, these disparate results may never be fully understood.

IV. Conclusion

The APA requires that FDA regulate all cell selection devices for nonhomologous use in the same manner, regardless of where they are used. The APA also requires that FDA implement a change of the magnitude contemplated by the Draft Guidance through notice-and-comment rulemaking. Accordingly, we request that FDA withdraw the Draft Guidance with a clear statement that the proposal is inconsistent with FDA's current regulatory framework. We also request that FDA initiate notice-and-comment rulemaking prior to making any change like that proposed in the Draft Guidance.

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We look forward to swift FDA action on these comments.

Sincerely,



Josephine M. Torrente



Michelle L. Butler

JMT//MLB/dh