Regulatory Insights

Biologics Scientific Affairs

Platelet-Rich Plasma vs. Concentrated Bone Marrow: A Regulatory Perspective

FDA-cleared is FDA-cleared, right? If only the US regulatory environment were that simple…but it is not. This is particularly true for autologous point-of-care products, such as the GPS® III and BioCUE® systems manufactured and distributed by Zimmer Biomet. The regulatory history of these products is complex, and it can be incredibly difficult for a sales representative or physician to understand the nuances of the clearance, the indications for use, and how it compares to our competitors. The purpose of this communication is to simplify the regulatory vernacular so it is easy to understand how we stack up against our competitors from a regulatory perspective. An "FDA Clearance Comparison Table" is provided at the end of this document as well.

To get started, there are a few important definitions and acronyms:

FDA (Food and Drug Administration) – The government agency which reviews and clears/approves medical devices for interstate commerce

CDRH (the FDA Center for Devices and Radiological Health) – The branch of FDA which reviews and clears/approves most medical devices

CBER (the FDA Center for Biologics Evaluation and Research) – The branch of FDA which reviews and clears/approves biologics and blood products

IFU (Indications for Use) – The intended use of the device which has been agreed upon by FDA

Blood processing devices, such as the GPS III and BioCUE, are medical devices, but they also process blood. So which branch of FDA should review and grant marketing clearance for these devices? There is a lengthy and detailed agreement in place between the two branches of FDA which determines this[1], but the simple answer is that it depends on the IFU (i.e. what the device is intended to be used for). The following history of regulatory clearances of our devices provides a clear understanding of where FDA draws the line.

In 2003, an early version of the GPS device received a 510(k) clearance from CDRH, and the IFU was for diagnostic tests. When they granted the clearance, FDA said we were required to include the following warning in the labeling: "The safety and effectiveness of this device for in vivo indications for use has not been established." This warning is required because, according to their letter,

> *"The Office of In Vitro Diagnostic Evaluation and Safety has determined that there is reasonable likelihood that this device will be used for an intended use not identified in the proposed labeling and that such use could cause harm."*

In short, the device was cleared for the intended use of processing blood *for diagnostic use*, and FDA thinks that it *might be used clinically* (i.e. applied back to the patient), and such use has not been evaluated by FDA and *could cause harm*.

In 2004, we submitted a new 510(k) for another early version of the GPS device, and the proposed IFU was

1. "Intercenter Agreement Between the Center for Biologics Evaluation and Research and the Center for Devices and Radiological Health", Effective Date: 31OCT1991.

for "mixing with autograft and allograft bone prior to application to an orthopedic surgical site". Because this new IFU intended for the output of the device to be *delivered back to the patient* (i.e. clinical use), CDRH moved the submission over to CBER for review. From CBER, we achieved clearance for the clinical use of mixing the platelet-rich plasma (PRP) with autograft and allograft bone, and we were not required to include the above warning in our labeling.

As we've made continuous improvements to our devices and have submitted additional 510(k)s to FDA, they have continued to follow the same pattern. For example, the MarrowStim™ device (no longer available on the market in the US) was cleared through CDRH to concentrate bone marrow *for diagnostic use*. Then, a few years later, we achieved clearance of the BioCUE System through CBER, for mixing with autograft and allograft bone *to be used clinically*. **Importantly, CBER required that the BioCUE System be processed using a mixture of blood and bone marrow and that the output of the device be referred to as PRP.**

Since the BioCUE System was launched, a number of competitors have entered the market with similar products. **Many of these competitors market their products for concentration of bone marrow.** How are they doing this when we are unable to? The answer is that they have the same clearance we have, and they should be using a mixture of bone marrow AND blood. There are two ways that bone marrow processing devices have received FDA clearance:

1) Same as MarrowStim device – Process bone marrow to produce concentrated bone marrow *for diagnostic use only*
    - Cleared through CDRH, Office of In Vitro Diagnostic Evaluation and Safety
    - Required to have this warning on the labeling: "The safety and effectiveness of this device for in vivo indications for use has not been established"
    - **Cannot legally be marketed by the manufacturer for clinical use**
2) Same as the BioCUE device – Process a *mixture* of blood and bone marrow for diagnostic use or for mixture with autograft and allograft bone *for clinical applications*
    - Cleared through CBER – Office of Cellular Tissue and Gene Therapy
    - **Not** required to have the following warning: "The safety and effectiveness of this device for in vivo indications for use has not been established"
    - Instead, a different warning is required: "The platelet-rich plasma prepared by this device has not been evaluated for any clinical indications."
        i. This is to say that CBER did not evaluate any *specific* clinical indications, because the BioCUE device was evaluated for the *general use* of mixing with bone graft material for application to an orthopedic site[2]
    - Another requirement is that all the labeling and promotional material **must refer to the output as Platelet-Rich Plasma or PRP**
        i. The purpose of this is to prevent manufacturers from misbranding their devices by referring to the output as concentrated Bone Marrow Aspirate (cBMA)

In conclusion, there is no point-of-care concentrated bone marrow aspirate product on the market that has been cleared by FDA for clinical use. There are simple ways to tell which clearance our competitor has:

- If their labeling includes the following warning: "The safety and effectiveness of this device for in vivo indications for use has not been established", the clearance is from CDRH, and the product cannot be legally marketed for clinical use
- If their labeling includes the following warning: "The platelet-rich plasma prepared by this device has not been evaluated for any clinical indications", the clearance is from CBER, the input should be a mixture of blood and bone marrow, and the output is required to be referred to as PRP in the labeling and promotional material

2. FDA has an entire Guidance Document dedicated to the nuances between general versus specific use. http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM073945.pdf

- If you know their 510(k) clearance number:
  - o If it begins with a K, it was cleared through CDRH
  - o If it begins with a B, it was cleared through CBER

A reference table of common products is included below.

FDA Clearance Comparison Table[3]

Product	Manufacturer	FDA Branch	Use Type
MarrowStim[4]	Zimmer Biomet	CDRH	cBMA for diagnostic use
BioCUE	Zimmer Biomet	CBER	PRP (blood + BMA) for clinical use
GPS III	Zimmer Biomet	CBER	PRP (blood only) for clinical use
Pure PRP II (Genesis CS)	EmCyte Co.	CBER	PRP (blood only) for clinical use
PureBMC (Genesis CS)	EmCyte Co.	CDHR	cBMA for diagnostic use
BMC System 544E (Genesis CS)	EmCyte Co.	CDHR	cBMA for diagnostic use
Cyclone BMC, Alliance Spine	EmCyte Co.	CDHR	cBMA for diagnostic use
Arthrex ACP System	Arthrex	CBER	PRP (blood only) for clinical use
Arthrex Angel System for BMC	Arthex	CBER	PRP (blood + BMA) for clinical use
SmartPrep2 BMAC System	Harvest Technologies, Corp.	CDHR	cBMA for diagnostic use
Magellan Autologous Platelet Separator System	Medtronic Sofamor Danek	CBER	PRP (blood + BMA) for clinical use
AutoXpress, MarrowXpress	Thermogenesis	CDHR	cBMA for diagnostic use
Res-Q 60 BMC	Thermogenesis	CBER	PRP (blood only) for clinical use

3. Regulatory Clearance information garnished from 510(k) Premarket Notification database and "Cleared 510(k) Submissions with Supporting Documents" page on the FDA website

4. The MarrowStim device, which was cleared through CDRH in 2007, is no longer availabe in the United States. We have replaced it with the BioCUE device, since we are able to market the BioCUE product for clinical use.

For complete product information, including indications, contraindications, warnings, precautions, and potential adverse effects, see the package insert and www.biomet.com

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Legal Manufacturer
Biomet Biologics
P.O. Box 587
56 E. Bell Drive
Warsaw, Indiana 46581-0587
USA

www.biomet.com