October 22, 2013

Regenerative Cell Therapy

Osiris Grafix: Trick or Treat? Grafix Goes Through the Front Door

Companies mentioned include:

Athersys, Inc. (ATHX) – $1.75 – Buy
Baxter (BAX) – $65.25 – NR
Capricor (private)
Cytori Therapeutics (CYTX) – $2.24 – Buy
Dendreon (DNDN) – $2.40 – Sell
IntelliCell Biosciences (SVFC) – $0.007 – NR
Mesoblast (MBLTY) – $29.25 – Buy
Osiris (OSIR) – $14.51 – NR
Pfizer (PFE) – $30.40 – NR
Pluristem (PSTI) – $3.63 – Buy
RTI Biologics (RTIX) – $3.43 – NR
Teva Pharmaceuticals (TEVA) – $40.21 – Buy
**Closing prices (10/21/2013)*

Jason Kolbert
[redacted]

- Last month, Osiris Therapeutics demonstrated the utility of Grafix—the company's allogeneic product for diabetic foot ulcers (DFU), long a graveyard of failed therapies. Grafix is a 3D cellular matrix comprising endogenous mesenchymal stem cells (MSCs) and growth factors. It has been sold in the U.S. to treat chronic wounds, under FDA regulatory pathway 21 C.F.R. Part 1271. We examined this regulatory pathway (in our 8/16/2013 report), trying to make sense of its implications in the cell therapy space. Yesterday, Osiris clarified the regulatory status.
- The company announced that it has reached an agreement with the FDA regarding the regulatory pathway for its biosurgery products, Grafix and Ovation:
  - After discussions with the FDA, the regulatory status of Grafix is confirmed, and the product will remain on the market as a wound cover for the treatment of acute and chronic wounds. For certain expanded indications for Grafix, Osiris has committed to submit a Biologics License Application (BLA).
  - Osiris will leverage existing clinical data in the preparation of the applications, including data from Protocol 302, its multi-center, randomized controlled trial that demonstrated a 192% relative improvement in closure rates of chronic diabetic foot ulcers as compared to patients receiving conventional therapy ($p < 0.0001$).
- In addition to marketing Grafix under 361, RTI Biologics may also soon be in the market with map3 cellular allogeneic bone graft, which incorporates Athersys' MAPC stem cells, under 361 as well. This opens the question about other cell therapy products that can come to the market under 361.
- Following Osiris' release, [redacted] issued an article that contained material factual misstatements relating to this news, according to Osiris. The article claims that Osiris was issued a "Warning Letter" from the FDA and that Osiris would need to stop marketing Grafix for diabetic foot ulcers. Osiris replied that both statements are wholly false and fundamentally misstate the nature of the agreement with the agency.
- **Our conclusion.** We believe Osiris has taken the high road, and the FDA has spoken. Good, safe products that work won't be removed from the marketplace, but these products do need to be supported with properly designed clinical trials. Osiris is moving forward along exactly that path.

INVESTMENT SUMMARY

Osiris reported breakthrough data in September. Today, it clarified the regulatory path forward to continue to market Grafix. The company has been marketing and selling Grafix without the typical pre-market review process, under PHS sec. 361 and 21 C.F.R. Part 1271. As we understand, under this regulatory framework the company can claim that that a product is "361" compliant, which leaves the FDA to confirm the claim.

While not technically obligated to seek a designation by the FDA, Osiris appears to have done exactly that and will submit a BLA application.

While 361 represents what is in essence a "backdoor pathway" for a company to bring products to market, we note that simply by claiming that they fall under the PHS sec. 361 and 21 C.F.R. Part 1271, is not enough, and still leaves companies "at-risk". Companies can choose to wait and see if the FDA agrees or disagrees. In the meantime, the product can be marketed, but again, not without risk. Osiris has now essentially eliminated this risk.

RTI Biologics may also be in the market shortly with map3 cellular allogeneic bone graft, which incorporates Athersys' MAPC stem cells. We believe that there are several other companies/products positioned ideally in the cell therapy space that may qualify under 21 C.F.R. Part 1271.

These might include products that use MSC-based cells in a combination product, such as Nuvasive's (NUVA - $25.31 - NR) Osteocel and Orthofix's (OFIX - $20.35 - NR) Trinity Evolution. In several years, these companies have developed this into a $100-150 MM market segment.

We look at the regulatory pathway to qualification under PHS sec. 361 and 21 C.F.R. Part 1271 as it may relate to stem cell therapies.

Minimal manipulation

The first criterion has created lot of confusion in the industry. As it relates to cells, they are considered more than minimally processed if there is cell expansion in culture, encapsulation, and activation of the cells and genetic modifications. As we understand, actions generally classified as chemical or biological in nature have a greater likelihood of altering characteristics of the cells.

The cells are considered "minimally processed" if they have been sorted (cell separation), lyophilized, cryopreserved, and separated by density gradient and selective removal of cells (B cells, T cells or platelets).

Our understanding is that Osiris' Grafix does not expand MSCs so they could be considered minimally processed. RTI is using Athersys' technology to isolate MAPC-based cells from a qualified donor, and to combine them with bone material taken from the same organ donor. Since RTI is not expanding the isolated cells, they can be considered minimally processed. So as the regulation is written, they will meet the first criterion. On the other hand, Athersys' MAPC, Mesoblast's mesenchymal precursor cells (MPC), or Pluristem's Placental eXpanded (PLX) cells will not meet this requirement since they are expanded in the culture. On the flipside, IntelliCell Biosciences Stromal vascular cells (SVFC) and Cytori's adherent stromal cells (ASC) may be considered "minimally manipulated." Cytori adds an enzyme to accomplish "digestion" of fat. Because of this, we believe the product does not qualify (and Cytori is not pursuing 361—so it's a moot point). How does IntelliCell remove the "fat"? It physically removes the fat cells from the lipoaspirate using exactly the right amount of sonic energy in a patented process. This leaves only non-structural stromal vascular fraction components that do not contain fat. According to the FDA cell separation techniques, this does constitute minimal manipulation. Therefore, IntelliCell stromal vascular fraction cells will satisfy the first criterion.

Homologous use
The second criterion is homologous use. Endogenous MSCs have been shown to be involved in wound repair so Grafix can claim to be homologus. RTI is using MAPC for the bone application (i.e. homologous use, since the cells are isolated from bone marrow); therefore, it will satisfy the criterion as well.

This opens up question on the role of Stem Cells. Endogenous stem cells have shown to be involved in responding to inflammation to regenerative function. They are involved in immunomodulation, an increase in blood perfusion, angiogenesis, and tissue differentiation. Therefore, the scope of the use of stem cells for homologous use is broader than a bone allograft. Also, the FDA has already clarified that homologous use does not depend upon using the processed cells or tissue in the same physiological location from which they came. Under these guidelines, IntelliCell's SVFC meet this criterion.

Not combined with another article
Under the FDA guidelines, the cells may not be combined with any material that does not raise new clinical safety concerns. Here, we are not sure how Grafix qualifies. Our understanding is that Grafix 3D matrix has growth factors, proteins to support cell migration, proliferation, and maturation—and, in addition, MSCs, fibroblasts, and epithelial cells. So in addition to the cells there are growth factors and proteins which in the way we understand the regulation, Grafix will not be regulated under 21 C.F.R. Part 1271. On the other hand, IntelliCell SVC are only combined with sterile saline.
Either (i) cells do not have a systemic effect and are not dependent upon the metabolic activity of living cells for its activity, or (ii) they have a systemic effect or are dependent upon the metabolic activity for its primary function, and are for autologous, allogeneic, or reproductive use.

The last criterion is two-pronged, but only one prong must be satisfied. Grafix satisfies the second prong. The MSCs have a systemic effect and are dependent on the metabolic activity of the living cells (production of cell factors that speed up wound healing) and are allogeneic.

Based on our understanding, Stem Cells will qualify for the last criterion, since they have a systemic effect, are dependent on their metabolic activity (cells act as drug factories), and can be autologous (IntelliCell SVC and Cytori ASC) or allogeneic (RTI and Atherys' MAPC in map3 bone grafts).

These rules have left us more perplexed than ever. The rules have a lot of flexibility built into them and, most importantly, put the responsibility of defining non-compliance on the FDA rather than the company. We are puzzled on how some can question why some products meet this standard and others do not. The answer may or may not lie in the definition of homologous use. Under current FDA guidance gleamed from the Tissue Reference Group, use of stem cells to treat cancers and MS will not be compliant under 361.

The guidance we have from FDA on non-homologous use is gleamed from the Tissue Reference Group *http://www.fda.gov/BiologicsBloodVaccines/TissueTissueProducts/RegulationofTissues/ucm152857.htm*

- Bone marrow-derived mesenchymal stem cells expanded in culture are more than minimally manipulated and therefore not a 361 HCT/P.
- Adipose-derived mesenchymal stem cells used as a bone graft substitute for the repair, replacement, or reconstruction of musculoskeletal defects are not a 361 HCT/P because they are dependent upon the metabolic activity of living cells for primary function and are not intended for autologous use or allogeneic use in a first- or second-degree blood relative.
- A cell selection process that results in activation of the T-Cell Receptor (TCR) does not meet the definition of minimal manipulation, as defined in 21 CFR 1271.3(f), because TCR activation alters the relevant biological characteristics of the selected cell population.
- Allogeneic adipose-derived stem cells seeded onto a bone scaffold for filling, augmenting, or repair of pathologically or surgically created bony voids is considered a biological product, and not a 361

HCT/P, because the product is dependent upon the metabolic activity of living, unrelated allogeneic cells for its primary function.

- Allogeneic retinal pigment epithelium and neurosensory cell layer for the treatment of patients with retinal degenerative diseases is considered a biological product subject to investigational new drug applications (INDs) and biologic license applications (BLAs), and not a 361 HCT/P because the product is dependent upon the metabolic activity of living (allogeneic) cells for its primary function (systemic effect).
- Umbilical cord stem cells treated with enzyme to increase engraftment are considered biological products and are subject to INDs and BLAs because this processing constitutes more than minimal manipulation.
- Hematopoietic stem cells from first and second-degree blood relatives for induction of tumor regression in cancer patients are considered to be biological products because this intended use is considered a non-homologous use.

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