

August 16, 2013

### Regenerative Cell Therapy: Osiris Graffix highlights a Back Door. Is there an Achilles heel in Cell Therapy with a KISS? (keep It Simple Stupid).

Companies mentioned include:

Athersys, Inc. (ATHX) – \$1.89 – Buy  
 Baxter (BAX) – \$72.33 – NR  
 Capricor (private)  
 Cardio3 Biosciences (CARD.BR) – €16.50 – NR  
 Cytomedix (CMXI) – \$0.43 – NR  
 Cytora Therapeutics (CYTX) – \$2.21 – Buy  
 Dendreon (DNDN) – \$3.15 – Sell  
 IntelliCell Biosciences (SVFC) - \$0.02 – NR  
 Lonza (LONN.VX) – CHF69.50 – NR  
 Mesoblast Ltd. (MBLTY) – \$26.95 – Buy  
 NeoStem, Inc. (NBS) – \$7.16 – NR  
 Osiris (OSIR) – \$19.76 – NR  
 Pfizer (PFE) – \$28.80 – NR  
 Pluristem (PSTI) – \$3.14 – Hold  
 RTI biologics (RTIX) - \$3.52 – NR  
 Teva Pharmaceuticals (TEVA) – \$40.38 – Buy  
 \*Closing prices (8/15/2013)

Jason Kolbert



Unlocking a Rich commercial Pathway through a backdoor?  
 Source: Cartoonstock

- This week Osiris Therapeutics Inc. (OSIR - \$19.76 - NR) demonstrated the utility of Graffix, the company's allogeneic product for diabetic foot ulcers (DFU), long a graveyard of failed therapies. Graffix, 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 examine this regulatory pathway and try to make sense of what implications does it have in cell therapy space?
- The FDA has allowed this "back door" as a pathway into the market place with no pre-market review or approval. If they are regulated solely under PHS sec. 361 and 21 C.F.R. Part 1271. To meet this criteria: 1) the cells have to be minimally manipulated 2) Homologous use 3) not combined with another article (with limited exceptions) 4) Either (i) cells do not have a systemic effect and is not dependent upon the metabolic activity of living cells for its activity or (ii) does have a systemic effect or is dependent upon the metabolic activity for its primary function, and is for autologous, allogeneic or reproductive use.
- In addition to marketing of Osiris' Graffix under 361, recently RTI biologics (RTIX -\$3.52 - NR) may also be in the market shortly with map3 cellular allogeneic bone graft, which incorporates Athersys (ATHX - \$1.89) MAPC stem cells, under 361 as well. This opens the question what other cell therapy products can come to the market under 361. For example we believe the stromal vascular fraction that IntellicellBioscience (SVFC) qualifies under these rules.
- **Our conclusion:** Under this regulatory framework, companies can claim that that a product meets the "361" requirements which leaves the FDA to confirm the claim or enforce (block) the products sale. This opens up a backdoor for companies to bring products to market simply by claiming that they fall under the PHS sec. 361 and 21 C.F.R. Part 1271 and then simply wait and see if the FDA agrees or disagrees. In meantime the product can be marketed. We believe many products do meet these standards such as Osiris Graffix and RTIX's bone graft. We also believe that the stromal vascular fraction made by IntellicellBioscience meets this definition. With that said "361" does not allow product claims (without a supporting trial). So is Graffix showing us an Achilles heel and can it be so simple as a KISS of Stromal Vascular Fraction? Only clinical trials will tell us.

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SEE PAGE 5 FOR IMPORTANT DISCLOSURES AND DISCLAIMERS

**INVESTMENT SUMMARY**

Osiris reported breakthrough data earlier this week; however, the company has already been marketing and selling Grafix without the typical pre-market review process. The company has been marketing Grafix under PHS sec. 361 and 21 C.F.R. Part 1271. As we understand under this regulatory framework, company can claim that that a product is “361” compliant, which leaves the FDA to confirm the claim. Osiris is not obligated to seek a designation by the FDA that it agrees with the company’s designation of the product. Therefore this opens up what is in essence a “backdoor pathway” for a company to bring products to market simply by claiming that they fall under the PHS sec. 361 and 21 C.F.R. Part 1271 and then simply wait and see if the FDA agrees or disagrees. In meantime the product can be marketed.

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 an MSC-based cells in a combination product such as - Nuvasive's (NUVA-\$23.59-NR) Osteocel and Orthofix's (OFIX-\$22.64-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, 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, separated by density gradient and selective removal of cells (B cells, T cells or platelets).

Our understanding is that Osiris’ Grafix does not expand MSC so they could be considered minimally processed. RTI is using Athersys’ technology to isolate MAPC-based cells from a qualified donor, and to combine that with bone material taken from the same organ donor. Since RTI is not expanding the isolated cells, they can be considered as minimally processed. So as the regulation is written they will meet the first criterion. On the other hand, Athersys MAPC, Mesoblasts 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 (SVC) and Cytori’s adherent stromal cells (ASC) may be considered as “minimally manipulated.” Except that 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 mute point). How does Intellicell remove the “fat” IntelliCell 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. As we have mentioned, according to the FDA cell separation techniques this does constitute minimal manipulation. Therefore IntelliCell stromal vascular cells will satisfy the first criterion.

### Homologous Use

The second criterion is homologous use. Endogenous MSC have been shown to be involved in wound repair so Grafix can claim to be homologous. 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, increase in blood perfusion, angiogenesis and tissue differentiation. Therefore the scope of the use of stem cells for homologous use is broader compared 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 IntelliCells SVC 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 MSC, 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 is not dependent upon the metabolic activity of living cells for its activity or (ii) does have a systemic effect or is dependent upon the metabolic activity for its primary function, and is for autologous, allogeneic or reproductive use.**

The last criterion is two pronged but only one prong must be satisfied. Grafix satisfies 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 is allogeneic.

Based on our understanding Stem cells will qualify the last criterion, since they have a systemic effect and are dependent on their metabolic activity (cells act as drug factories) and they 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 lot of flexibility built into them and most importantly it puts the onus 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 other(s) do not. The answer may or may not lie in the definition of Homologous use. Under current FDA guidance gleaned 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 gleaned 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 product used as a bone graft substitute for the repair, replacement, or reconstruction of musculoskeletal defects is not a 361 HCT/P because it is dependent upon the metabolic activity of living cells for its primary function and is 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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