A Review of the Latest FDA Communication Regarding Exosomes

On December 6th 2019, the FDA issued a public safety notification regarding exosome products. In this document, the FDA reviewed a series of companies after a case in Nebraska. While Liveyon received a warning letter, Chara Biologics and RichSource Stem Cells Inc. received untitled letters. In this communication from the FDA that can be reviewed at the bottom of this letter you can read exactly what the FDA said.

Within the letter are some key points that help to explain what the FDA is saying, and why Direct Biologics is in complete agreement with the FDA's position. We view these measures as helping to call out many of the bad actors in this market and guide the companies that work diligently to educate and hold themselves to the highest standards.

First and foremost, this letter addressed a safety concern arising from reported adverse events concerning patients in Nebraska who received a treatment that was "marketed as containing exosomes." These events required a response from the FDA. Here is our understanding of what FDA's key points mean:

FDA Communication	What it means
The Food and Drug Administration (FDA) is informing the public, especially patients, health care practitioners, and clinics, of multiple recent reports of serious adverse events experienced by patients in Nebraska who were treated with unapproved products marketed as containing exosomes. These reports were brought to the agency's attention by the Centers for Disease Control and Prevention, among others, and the agencies worked with the Nebraska Department of Health and Human Services. FDA is carefully assessing this situation along with our federal and state partners.	There are currently no approved products with exosomes. Just like there are no approved 361 HCT/P allograft cell or tissue products. HCT/Ps are registered with the FDA and do not require prior FDA approval so long as they are intended for homologous use, are minimally manipulated, and meet certain other regulatory criteria. The most current guidance document for 361 HCT/Ps, "Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue Based Products: Minimal Manipulation and Homologous Use, Guidance for Industry and Food and Drug Administration Staff," was issued in November 2017 (and was corrected in December 2017). This 2017 Guidance for HCT/Ps has not changed and has been referenced repeatedly in all subsequent letters or actions by the FDA.
There are currently no FDA-approved exosome products.	FDA approval comes after a biological product that does not qualify as a 361 HCT/P has successfully completed human testing under an IND and after FDA has reviewed and approved a BLA, or if the product is a medical device, after FDA has either cleared a 510(k) or approved a PMA.

Certain clinics across the country, including some that manufacture or market violative "stem cell" products, are now also offering exosome products to patients. They deceive patients with unsubstantiated claims about the potential for these products to prevent, treat or cure various diseases or conditions. They may claim that they these products do not fall under the regulatory provisions for drugs and biological products – that is simply untrue.	Any HCT/P marketed for the "treatment, prevention, or cure" of a disease or condition is not intended for homologous use (same use in the donor as in the recipient), and must have an IND or BLA. If it does not, it cannot be marketed as having an "indication" for the treatment, prevention or cure of a disease or condition. An example of such improper marketing would be a sales rep telling a physician that a product can "treat" specific diseases such as Autism or Parkinson's Disease.
As a general matter, exosomes used to treat diseases and conditions in humans are regulated as drugs and biological products under the Public Health Service Act and the Federal Food Drug and Cosmetic Act and are subject to premarket review and approval requirements.	As discussed above, if an exosome product is marketed for treating a disease or condition, it does not meet the homologous use requirement, and therefore constitutes a drug or biological product that requires a BLA. However, the phrase "As a general matter" indicates that there are exceptions to the general rule that exosomes are drugs or biologics. We intend our exosomes to be used for what we believe are valid homologous uses and that our marketed exosomes are an exception to the general rule.
Patients considering treatment with exosome products in the United States should: *Ask if the FDA has reviewed the treatment. You also can ask the clinical investigator to give you the FDA-issued Investigational New Drug Application (IND) number and the chance to review the FDA communication acknowledging the IND. Ask for this information before getting treatment and follow up with your personal health care provider to confirm this information.* *Request the facts and ask questions if you don't understand. To participate in a clinical trial that requires an IND application, you must sign a consent form that explains the experimental procedure.*	Again, as before, if a patient has been told that a product can be used for the "treatment" of a disease, the FDA recommends that patients ask if the FDA has formally approved the product and/ or to see an IND number associated with an FDA-authorized clinical trial of the product being studied for that treatment.

About Direct Biologics:

1. Direct Biologics processes all exosomes at a cGMP facility. This is the highest standard of processing and manufacturing controls.
2. Direct Biologics' ExoFlo is marketed solely for homologous use
    a. There are NO approved indications for the use of ExoFlo or XoFlo
3. Direct Biologics' ExoFlo is a minimally-manipulated single-donor-per-lot tissue and contains no animal products, chemicals or drugs in the processing and isolation of the exosome products.
4. Direct Biologics is actively preparing to pursue FDA approval and will be submitting its first of several applications for IND clinical trials in various indications.

Original Communication from FDA

Public Safety Notification on Exosome Products

December 6, 2019

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There are currently no FDA-approved exosome products. Certain clinics across the country, including some that manufacture or market violative "stem cell" products, are now also offering exosome products to patients. They deceive patients with unsubstantiated claims about the potential for these products to prevent, treat or cure various diseases or conditions. They may claim that these products do not fall under the regulatory provisions for drugs and biological products – that is simply untrue. As a general matter, exosomes used to treat diseases and conditions in humans are regulated as drugs and biological products under the Public Health Service Act and the Federal Food Drug and Cosmetic Act and are subject to premarket review and approval requirements.

The clinics currently offering these products outside of FDA's review process are taking advantage of patients and flouting federal statutes and FDA regulations. This ultimately puts at risk the very patients that these clinics claim to want to help, by either delaying treatment with legitimate and scientifically sound treatment options, or worse, posing harm to patients, as evidenced by these recent reports of adverse events.

Health care professionals and consumers should report any adverse events related to exosome products or any other unapproved product to the FDA's MedWatch Adverse Event Reporting program. To file a report, use the MedWatch Online Voluntary Reporting Form. The completed form can be submitted online or via fax to 1-800-FDA-0178. FDA monitors these reports and takes appropriate action necessary to ensure the safety of medical products in the marketplace.

Patients considering treatment with exosome products in the United States should:

- Ask if the FDA has reviewed the treatment. You also can ask the clinical investigator to give you the FDA-issued Investigational New Drug Application (IND) number and the chance to review the FDA communication acknowledging the IND. Ask for this information before getting treatment and follow up with your personal health care provider to confirm this information.
- Request the facts and ask questions if you don't understand. To participate in a clinical trial that requires an IND application, you must sign a consent form that explains the experimental procedure. The consent form also identifies the Institutional Review Board (IRB) that assures the protection of the rights and welfare of human subjects. Make sure you understand the entire process and known risks before you sign. You also can ask the study sponsor for the clinical investigator's brochure, which includes a short description of the product and information about its safety and effectiveness.

Patients considering treatment using an exosome product in another country should:

- Learn about regulations that cover products in that country.
- Know that FDA does not have oversight of treatments done in other countries. FDA typically has little information about foreign establishments or their products.
- Be cautious. If you're considering an exosome product in a country that may not require regulatory review of clinical studies, it may be hard to know if the experimental treatment is reasonably safe.

FDA remains committed to protecting patients. Our work to ensure compliance with the law does not take away from our firm commitment to advance an efficient path for the safe and effective development of novel regenerative medicine therapies and to help foster beneficial new innovations. We'll continue to work closely with investigators and firms legitimately working in this field and will do so in the most effective manner possible, while meeting the FDA's standards for safety and efficacy. We look forward to working with those who share our goal of bringing safe and effective products to market to benefit individuals in need.