Stem-cell Breakthrough in the EU

The first veterinary stem cell products are reaching the EU market now. Two products for treatment of joint disease in horses have received positive opinions and will present an innovative option in the veterinary field. This should be acknowledged as a major achievement by the companies behind the products, who made it through the EU authorisation process despite limited published guidance and regulatory experience.

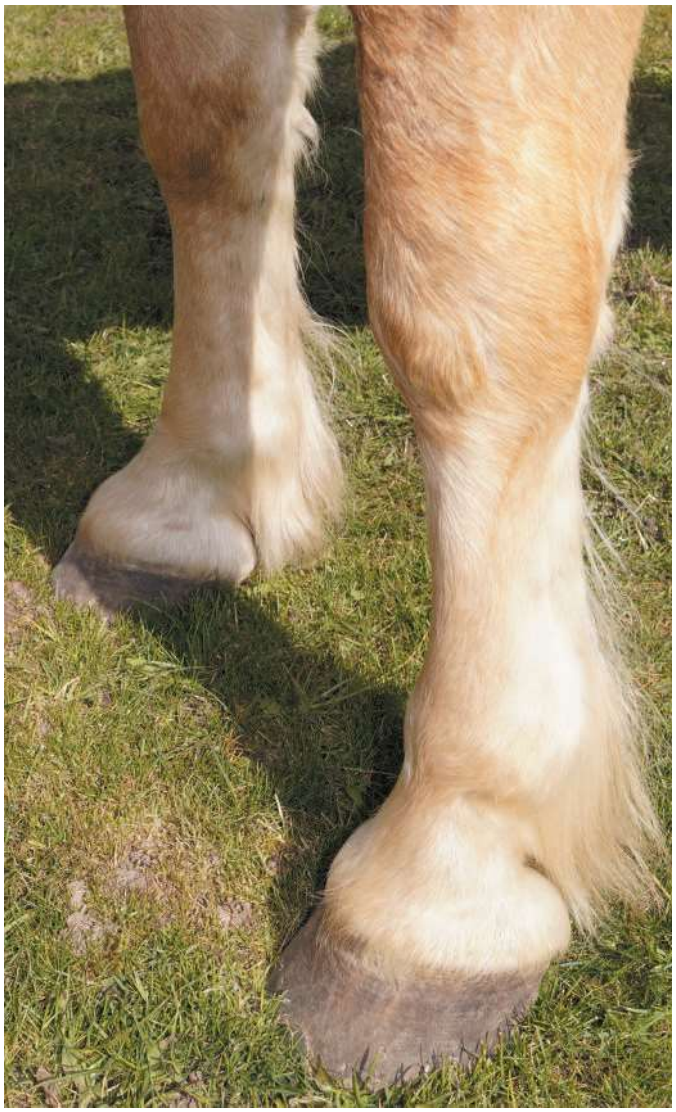
Stem cells are non-terminally differentiated, self-renewing cells that harbour the ability to produce mature, differentiated daughter cells. They serve to regulate or participate in normal tissue homeostasis and embryonic and foetal development. They can be harvested from a variety of tissues, e.g. bone marrow, umbilical cord, blood, fat, or embryos, and subsequently produced in a manufacturing facility. Although stem cells share the same principal characteristics of self-renewal potential and differentiation, stem-cell-based medicinal products do not constitute a homogeneous class.

Stem cell therapy is intended for mitigating, treating, or preventing disease in animals or humans. They hold considerable promise for therapeutic applications in various conditions, including metabolic, degenerative and inflammatory diseases, and for the repair and regeneration of damaged or lost tissues. The stem cells now produced as veterinary medicines are allogeneic stem cells, i.e. those in which the cells are collected from a donor animal and used in a recipient animal of the same species. Stem cell treatments may lower symptoms of the disease or condition that is being treated, which may also allow reduce the drug intake.

The first human stem cell product in the EU, Holoclar, was designated as an orphan medicine and recommended for conditional approval in 2014. This allowed the EMA to provide support including free scientific advice during Holoclar's development. Holoclar is used in the eye to replace damaged cells on the surface (epithelium) of the cornea, the transparent layer in front of the eye covering the iris, to treat moderate to severe limbal stem cell deficiency due to physical or chemical burns to the eye.

In June 2018, the first veterinary stem cell product, Arti-Cell Forte, received a positive opinion from the EMA, followed by an EU marketing authorisation in spring 2019. Arti-Cell Forte contains chondrogenic induced equine allogeneic peripheral blood-derived mesenchymal stem cells as the active substance and is given as a single injection into an affected joint for reduction of mild to moderate lameness linked to joint inflammation in horses. The stem cells are treated so that they develop towards cartilage cells, which can assist in repairing damaged cartilage in the joint and aims to activate chondroprotective mechanisms, such as producing extracellular matrix and influencing the inflammatory process in the joint.

In February 2019, HorStem received a positive opinion, after a first negative opinion in 2018. HorStem contains



equine umbilical cord mesenchymal stem cells as active substance, which has immunomodulatory and anti-inflammatory properties. It reduces lameness associated with mild to moderate degenerative joint disease (osteoarthritis) in horses. At the time of writing, the European Commission had not yet issued the marketing authorisation, but this is expected to happen soon.

Another stem cell product, Horse Allo 20, received a negative opinion from the EMA in June 2018. This product contained allogeneic equine adipose-derived mesenchymal stem cells with potential immunomodulatory and anti-inflammatory properties for tissue regenerative properties.

The task for the innovative companies is large and challenging. Not only must they develop innovative science for the product and the assays to control production, but they face a regulatory landscape with very little guidance. Stem cells fall between existing legal classifications, being a biological product without a distinct immunologic mechanism and without clear chemical/pharmaceutical

characteristics. To a large extent, the novel product development takes place in a foggy environment, where guidance and advice must be patched together from different sources.

It is self-evident that for new innovations, the regulators do not have the expertise and cannot issue strong guidance. In the EMA, the CVMP's Ad Hoc Expert Group on Veterinary Novel Therapies (the ADVENT group) has developed Q&A documents with partial pieces of advice. Four problem statements related to stem cells were published for consultation in 2016, asking for input from experts, and three corresponding Q&As were published in 2017; Stem cell Sterility, Extraneous agents and Tumorigenicity. Specific questions on target animal safety in relation to stem cell products are under finalisation.

To illustrate some of the challenges in stem cell production, sterility makes a good example. As allogenic stem cell-based products are veterinary medicinal products to be administered parenterally, they should be sterile. The active substances of stem cell-based products are living cells which themselves cannot be sterilised by physical or chemical methods, and the final product can neither be terminally sterilised nor sterilised by filtration. Microbiological contamination can occur at various steps during the manufacturing process but particularly at the initial sampling of the cells/tissue, which may take place in a horse stable when collecting the umbilical cord after the birth of a foal. A stable is never a sterile, or even clean, environment.

The US FDA, Center for Veterinary Medicines, in 2015 issued Guidance for Industry #218, Cell-Based Products for Animal Use. Here it is clarified that cell-based products meeting the definition of a new animal drug are subject to the same statutory and regulatory requirements as other new animal drugs.

For products for human use, EMA guidance from 2008 (EMEA/CHMP/410869/2006) on human cell-based medicinal products, including quality and manufacturing aspects, non-clinical and clinical development exists, but does not always apply to veterinary topics. In 2011, the Committee for Advanced Therapies issued a reflection paper (EMA/CAT/571134/2009) comprising topics related to embryonic stem cells, induced pluripotent stem cells, adult stem cells, somatic stem cells, marketing authorisation application, quality, non-clinical, clinical considerations for human medicines.

Innovation is often driven by small companies with a highly competent scientific background. They draw on their scientific understanding but run into conflict with the lack of experience on the specialised field in regulatory authorities. Instead, regulators draw on a broad understanding of other types of medicines and a "regulator's mindset", trying to foresee obstacles or uncertainties in the product manufacture and use. The skills of translating between the scientific understanding of an innovative product and the regulators' need for firm and controllable processes may be absent in small companies, which causes miscommunication and frustrations on both sides. The fact that two stem cell products from small innovative companies now is entering the EU market for the benefit of animals and owners, deserves loud applause. It would be great to see more new medicines in the future and an increased effort to facilitate this process would be welcome.

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