A recent EU regulation brought in to standardise control of ATMPs - medicinal products for human use, based on gene therapy, somatic cell therapy or tissue engineering – has divided opinions. Although having had a mainly positive effect, some within academia felt that the regulation had overlooked them and that the regulation was unclear in points. We spoke to **Martin Hildebrandt** about Academic GMP, a project which aimed to investigate these issues.

Investigating the impact of EU ATMP legislation

Photo caption here

Advanced therapy medicinal products, or ATMPs, represent the forefront of medical research, blurring the lines between medicinal products and medical devices. They are comprised of cell-based therapies - gene transfer medicinal products, cell-based medicinal products and tissue engineered products - derived from living human tissue which is then manipulated in such a way that it can then be used in a therapeutic setting.

For instance, Dr Mark Lowdell of University College London has recently been focusing on a tissue engineered product that has helped to make trachea transplants possible. After first decellularising a donor windpipe, leaving just the connective tissue, Lowdell is then able to seed this structure with cells from the recipient, after which the trachea can be implanted by surgeons without the normal issue of immune rejection.

Another group of treatments which comes under the label of ATMPs is somatic cell therapy. For example, taking stem cells from a patient's bone marrow and then injecting them into the patient's ischemic heart is thought to help to


Photo caption here

repair the failing organ. This is known as heterologous use - transferring cells from one part of the body to the other for therapeutic purposes.

Gene therapy makes up the final group of ATMPs, and in December 2008 a regulation was put in place to define ATMPs not only as tissues but also as drugs. This has led to a rise in the required safety standards needed due to the more stringent regulations placed upon drugs. However, for one reason or another, this regulation failed to take into account or even mention academia, despite it being the main provider of these therapeutic concepts and complex drugs. Professor Martin Hildebrandt, a haematologist at the Technical University Munich, decided that this needed to be investigated and so, together with a few like-minded colleagues, started the Academic GMP project.

"We set out on this project because we wanted to give academic institutions a voice," says Hildebrandt. "With the rise in genuine scientific interest in these products, GMP facilities – places where drugs are produced - are appearing more and more in universities and public hospitals. This has helped fill the gaps in which the pharmaceutical industry has no interest; for instance, patients with extremely rare diseases often require these types of complex treatments, but because there is very little money to be made from producing a medicine which only ten or twenty people can use, the industry will not produce it."

Initiating the project by conducting a Europe-wide survey among the non-industrial facilities in the sector, Hildebrandt and his colleagues were aiming not only to build a comprehensive map of the activity within this field, but also to gather people's opinions on how the recent legislation – Regulation (EC) No 1394/2007 – has affected the facilities.

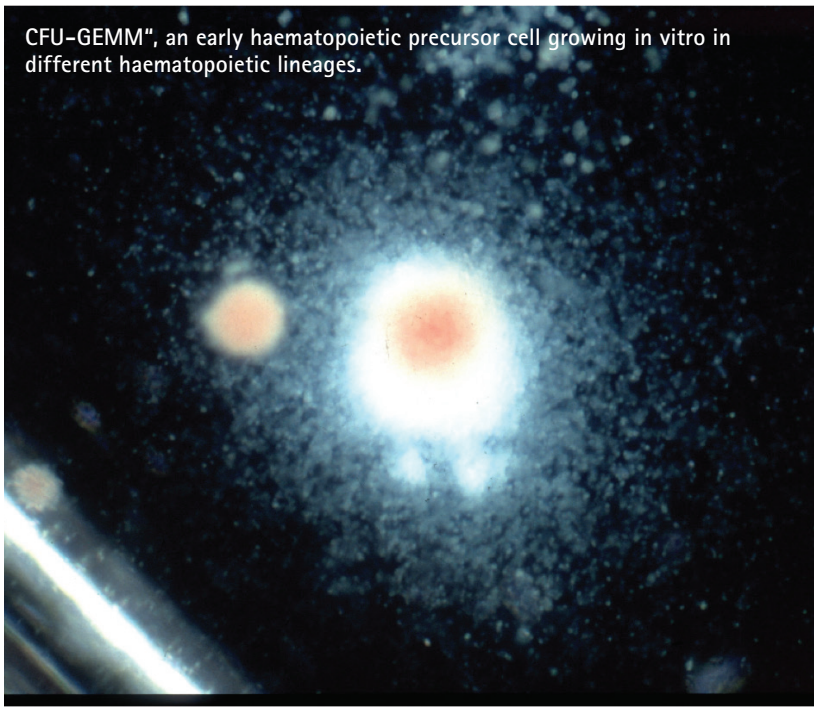
"With the rise in genuine scientific interest in these products, GMP facilities – places where drugs are produced – are appearing more and more in universities and public hospitals"

"The general consensus was that the current legislation has in fact helped to improve the situation in a number of ways," says Hildebrand. "All of the EU member states have been forced to address the issue of manufacturing ATMPs, and we are consequently seeing GMP facilities arise in academic institutions and hospitals throughout the EU.

"However, where we have seen real problems has been in the harmonisation of the regulation across the different member states. As a regulation, it took immediate effect at the moment it was implemented, but what we have seen in reality has ranged wildly, with some countries taking it very seriously, others simply disregarding it and all of them interpreting it slightly differently."

The disparity in interpretation of the regulation between member states has led to some almost farcical situations, with certain examples being treated as ATMPs in one country but not even regarded as medicines in others. Indeed, some member states accused academia of being incapable of handling the manufacture of such complex products and denied its claim to produce them, despite academia often having more experience in the matter. With the current buzzword coming out of Brussels being "simplification", it would seem that this regulation has failed in its attempt to clarify how these therapies are defined, treated and manufactured.

Another main issue with the regulation noted in the survey is its perceived failure to involve academia, or even recognise it as the main proponent of



CFU-GEMM", an early haematopoietic precursor cell growing in vitro in different haematopoietic lineages.

ATMP development. Despite a fast-growing network of GMP-compliant academic/hospital units working at the same standards as industry emerging across the EU, these facilities cannot yet have their products certified by the European Medicine Agency as having complied with the standards required by the regulation. "We want to encourage interaction between the pharmaceutical industry and academia, and to do this we need to define the point at which they work together better," says Hildebrandt.

Costs were also highlighted as an issue, mostly related to GMP-grade starting materials, the personnel required to run a facility efficiently and in compliance with current regulation, and to the infrastructure needed for aseptic manufacture and proper quality control of medicinal products. Although costs are beneficial when adequate standards of quality are assured, a risk-based and less costly approach could allow for the manufacture of a certain product even when GMP compliance is not entirely maintained as long as the safety of the product is not affected.

After having spoken to members of European parliament about the issue, Hildebrandt is aware that these types of issues could be avoided with increased participation of academic scientists in political discussions. "These members of parliament told us that the only people who bother to turn up are the industry representatives," says Hildebrand, "and that is one of the reasons why we have ended up with this legislation which is good in parts but too industry-oriented."

Academic GMP officially ended in May, and has succeeded in creating a map of ATMP centres in Europe as well as demonstrating the elements of success for ATMP development. Importantly, it has also brought together academia, the pharmaceutical industry and regulators. The workshops and conferences organised by the Academic GMP consortium have helped raise awareness to the hindrances faced by researchers and clinicians in this promising medical field.

AGORA, a recently approved FP7 project, will continue and expand on the work accomplished by Academic GMP. AGORA will focus on "undertaking a series of specific actions to address each of the current unmet needs and critical issues" that arose from the results of the surveys conducted by Academic GMP, and on "building a network of academic and commercial partners working together and individually to provide a sustainable service, including training and a document "toolbox" for the development of new ATMPs to clinical trial and their delivery to commercial supply".

AT A GLANCE

Project Information

Project Title:
ACADEMIC GMP: The impact of Regulation (EC) No 1394/2007 on the development of Advanced Therapy Medicinal Products (ATMPs) - an academic perspective

Project Objective:
Advanced Therapy Medicinal Products (ATMPs), the next generation of complex medicines, pose particular challenges to medicines regulation. Regulation (EC) No 1394/2007 defines ATMPs and has been designed to foster competitiveness while guaranteeing the highest level of health protection. We studied its impact on Academic facilities, the main source of ATMPs.

Project Duration and Timing:
Starting September 2010, the project lasted until May 31, 2013 (33 months)

Project Funding:
HEALTH 2010.4.2-6

Project Partners:
Lund University, Sweden (Stefan Scheding); University of Newcastle upon Tyne, UK (Anne M. Dickinson, Kim F Pearce); University College London, UK (Mark W. Lowdell); Imperial College London, UK (Jane Apperley); Medical School Hannover, Germany (Eva Mischak-Weissinger, Ulrike Köhl); University Hospital Regensburg, Germany (Andrea Hauser, Matthias Edinger); Medical University Vienna, Austria (Hildegard Greinix, Nina Worel); Technical University Munich, Germany (Martin Hildebrandt)

MAIN CONTACT

Martin Hildebrandt
Martin Hildebrandt is a Haematologist and was in charge of GMP Facilities in Berlin and Hannover before moving to Munich. He is a member of the working group on blood-associated infectious risks at the Federal Ministry of Health, of the State of Berlin's ethics committee, and of several professional societies.

Contact:
Tel: 0049-(0)89-4140-7810
Email: martin.hildebrandt@lrz.tum.de; info@academic-gmp.eu
Web: www.academic-gmp.eu