

■ PHARMAZEUTISCHE MEDIZIN

Challenges faced during Process Development and Manufacturing

Combined ATMPs Containing Genetically Modified Cells

Patrick Bittorf^{1}, Martin Zierau², Dr. Ralf Sanzenbacher³, Prof. Dr. Heike Walles¹, Dr. Joris Braspenning¹*

¹University Hospital Würzburg, Chair Tissue Engineering and Regenerative Medicine, Würzburg, Germany

²IMS Integrierte Management Systeme e. K., Heppenheim, Germany

³Paul-Ehrlich-Institut, Langen, Germany

The first two authors contributed equally to this work.

References

[1] Paul-Ehrlich-Institut Innovationsbüros (2012), Arzneimittel für neuartige Therapien ATMP - Advanced Therapy Medicinal Products Regulatorische Anforderungen und praktische Hinweise. URL:

www.pei.de/SharedDocs/Downloads/pu/innovationsbuero/broschuere-atmp-anforderungen-hinweise.pdf?__blob=publicationFile&v=1 (accessed on 12.09.2017).

[2] European Medicines Agency (2015), Reflection paper on classification of advanced therapy medicinal products (EMA/CAT/600280/2010 rev.1). URL:

www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/06/WC500187744.pdf (accessed on 12.09.2017).

[3] European Medicines Agency. Advanced therapy medicinal products. [08.09.2017]; available from:

www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000294.jsp&mid=WC0b01ac05800241e0 (accessed on 12.09.2017).

[4] Sanzenbacher R, et al., European regulation tackles Tissue Engineering. Nature Biotech, 25 (10): 7-9.

[5] HemAcure. HemAcure Development of a novel cell based therapy for the treatment of sever haemophilia A. [29.03.2017]; available from: www.hemacure.eu/ (accessed on 12.09.2017).

[6] Andrew R. Pepper, et al., Diabetes Is Reversed in a Murine Model by Marginal Mass Syngeneic Islet Transplantation Using a Subcutaneous Cell Pouch Device. Transplantation 2015;99: 2294–2300.

[7] Schenke-Layland K and Walles H (2013), Strategies in tissue engineering and regenerative medicine. Biotechnol J. 8(3):278-9.

- [8] Anliker B, Renner M, and Schweizer M (2015), Genetisch modifizierte Zellen zur Therapie verschiedener Erkrankungen. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 58: 1274-1280.
- [9] Blümel J and Stühler A (2009), Wichtige Aspekte der Virussicherheit bei Neuartigen Therapien. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 53:38-44.
- [10] European Commission (2012), Commission Directive 2012/39/EU of 26 November 2012 amending Directive 2006/17/EC as regards certain technical requirements for the testing of human tissues and cells Text with EEA relevance. URL: <http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32012L0039&from=EN> (accessed on 12.09.2017).
- [11] Bundesministerium der Justiz und für Verbraucherschutz (2008), Verordnung über die Anforderungen an Qualität und Sicherheit der Entnahme von Geweben und deren Übertragung nach dem Transplantationsgesetz (TPG-Gewebeverordnung - TPG-GewV) vom 26. März 2008 (BGBl. I S. 512), zuletzt durch Artikel 5 des Gesetzes vom 21. November 2016 (BGBl. I S. 2623) geändert.
- [12] Council of Europe (2017), Raw materials of biological origin for the production of cell-based and gene therapy medicinal products, in European Pharmacopoeia, 9th Ed.: Council of Europe, Strasbourg, 01/2017:50212.
- [13] Stühler A and Blümel J (2015), Spezifische Aspekte zur Virussicherheit von Produktionshilfsstoffen für somatische Zelltherapie-Arzneimittel. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 58:1233-1238.
- [14] European Medicines Agency (2013), Guideline on the use of bovine serum in the manufacture of human biological medicinal products (EMA/CHMP/BWP/457920/2012 rev). URL: www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/06/WC500143930.pdf (accessed on 12.09.2017).
- [15] Council of Europe (2015), Bovine serum (serum bovinum), in European Pharmacopoeia, 8th Ed.: Council of Europe, Strasbourg, 01/2008:2262.
- [16] European Medicines Agency (1999), ICH Topic Q 6 B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products (CPMP/ICH/365/96). URL: www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002824.pdf (accessed on 12.09.2017).
- [17] European Medicines Agency (2012), Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials (EMA/CHMP/BWP/534898/2008 rev.). URL: www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/07/WC500209618.pdf (accessed on 12.09.2017).
- [18] European Medicines Agency (2008), Guideline on human cell-based medicinal products (EMA/CHMP/410869/2006). URL: www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003898.pdf (accessed on 12.09.2017).
- [19] European Medicines Agency (2012), Quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells (EMA/CAT/GTWP/671639/200). URL: www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/05/WC500126836.pdf (accessed on 12.09.2017).

- [20] Heinz S and Braspenning J (2015), Measurement of Blood Coagulation Factor Synthesis in Cultures of Human Hepatocytes. *Methods in Molecular Biology* 1250:309-16.
- [21] European Medicines Agency (2008), Guideline on the non-clinical studies required before first clinical use of gene therapy medicinal products (EMA/CHMP/GTWP/125459/2006). URL: www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003942.pdf (accessed on 12.09.2017).
- [22] Bundesministerium der Justiz und für Verbraucherschutz (1993), Gesetz zur Regelung der Gentechnik (Gentechnikgesetz - GenTG) in der Fassung der Bekanntmachung vom 16. Dezember 1993 (BGBl. I S. 2066), zuletzt durch Artikel 4 Absatz 13 des Gesetzes vom 18. Juli 2016 (BGBl. I S. 1666) geändert.
- [23] Wuchter P, et al., Standardization of GMP-compliant production of bone marrow derived human mesenchymal stromal cells (MSCs) for immunotherapeutic applications. *Cytotherapy* 0: 1-12.
- [24] European Commission (2012), Annex 2 Manufacture of Biological active substances and Medicinal Products for Human Use (SANCO/AM/sl/ddg1.d.6(2012)860362). URL: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/vol4-an2_2012-06_en.pdf (accessed on 12.09.2017).
- [25] Ph.D. Maria Cristina Galli, Manufacturing of gene therapy products common issues and advices, in Session 2: Gene Therapy: Non-Clinical Development of Gene Therapy Medicinal Products.
- [26] European Medicines Agency (2005), Development and manufacture of lentiviral vectors (CHMP/BWP/2458/03). URL: www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500003984.pdf (accessed on 12.09.2017).
- [27] European Commission. Revisions of Medical Device Directives. [07.05.2017]; Available from: http://ec.europa.eu/growth/sectors/medical-devices/regulatory-framework/revision_de (accessed on 12.09.2017).
- [28] Sernova Corp. Improving the Quality of Life for Patients with Chronic Diseases. [11.05.2017]; Available from: www.sernova.com/ (accessed on 12.09.2017).
- [29] BVMed Bundesverband Medizintechnologie e.V. CE-Kennzeichnung. [07.05.2017]; Available from: www.bvmed.de/de/recht/ce-kennzeichnung (accessed on 12.09.2017).
- [30] European Commission (2012), Proposal for a Regulation of the European Parliament and of the Council on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009. URL: <http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52012PC0542&from=EN> (accessed on 12.09.2017).
- [31] European Medicines Agency (2015), Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products (EMA/CAT/80183/2014). URL: www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/05/WC500187020.pdf (accessed on 12.09.2017).
- [32] Concept Heidelberg GmbH. Neue EMA Guideline - GMP für Neuartige Therapien (ATMP). [09.05.2017]; Available from: www.gmp-navigator.com/dnews_05777_Neue-EMA-Guideline---GMP-f%C3%BCr-Neuartige-Therapien--ATMP-.html (accessed on 12.09.2017).

[33] Heinz-Stempel S (2016), GMP for ATMPs - Quo vadis?, in "The Product is the Process - Is it?" Qualitätsaspekte bei der Herstellung von ATMPs.

[34] Uta Schurig, et al., Aktuelles Konzept zur mikrobiologischen Sicherheit von zellbasierten Arzneimitteln. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 58:1225-1232.

[35] Montag T, et al., Microbial safety of cell based medicinal products – What can we learn from cellular blood components? Clin Chem Lab, 46(7): 963–965.

ENDE