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Clinical Research – Changes arising from the new EU Regulation No. 536/2014

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A Farewell to Referencing the Declaration of Helsinki of 1996, Somerset West

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Synopsis

At the moment, it is expected that EU Regulation No. 536/2014 on clinical trials on medicinal products for human use will repeal Directive 2001/20/EC relating to the implementation of Good Clinical Practice in the conduct of clinical trials on medicinal products for human use in 2019. The new EU regulation will introduce novel concepts and requirements, such as risk proportionate approaches in clinical trials, the provision of layperson summaries of clinical trial results, and the definition of Auxiliary Medicinal Products (formerly referred to as Non-Investigational Medicinal Products) in clinical trials. The European clinical trial environment will benefit from the EU Regulation No. 536/2014 in several ways. The most important improvements and advantages of the new regulation seem to be the harmonization in study application procedures and the partial mutual recognition of review procedures across the Member States.

This article provides an overview of the regulation to come in relation to the EU directive to be repealed and presents a detailed outline of the changes and their implications.

Preparatory Period

In contrast to EU directives, EU regulations, such as the new EU Regulation No. 536/2014[i], are binding supranational European legislative acts that directly apply to all EU Member States without the need of being transposed into national law.

The moment EU Regulation No. 536/2014 on clinical trials on medicinal products for human use becomes applicable, it will repeal the longstanding EU Directive 2001/20/EC[ii] relating to the implementation of Good Clinical Practice (GCP) in the conduct of clinical trials on medicinal products for human use. This new EU regulation will harmonize assessments and supervision processes of clinical trials throughout the EU, employing an EU portal and database. EU Regulation No. 536/2014 was first introduced on 16 April 2014, but the actual date of its application depends on the full functionality of the EU portal and database. Due to technical difficulties with the development of the IT systems, the regulation is expected to come into application not earlier than July 2019.

In July 2017, the responses to the public consultation on EU Regulation No. 536/2014 were published by the European Commission after release of the final recommendations of the European Commission expert group. As is the custom with EU regulations, several comments on the document were submitted and all submissions were at least commented upon, if not incorporated.

The new EU regulation will have a major effect on the clinical trial environment in the EU, particularly due to the requirements and clarifications resulting from the multiple review and commentary cycles. In 2017, risk proportionate approaches in clinical trials, layperson summaries of clinical trial results, and the definition of Auxiliary Medicinal Products in clinical trials were amongst the concepts and requirements further defined and clarified. Changes in Good Manufacturing Practice (GMP) for

investigational medicinal products, detailed arrangements for clinical trial inspection procedures - including the qualification and training requirements for inspectors - and aspects regarding ethical considerations for clinical trials on medicinal products conducted with minors had already been finalized and implemented in 2016.

Before looking into the details of the new EU regulation to come and the reasons behind the changes, a retrospective view on the still effective EU directive should be made and is presented below.

Retrospective View - Directive 2001/20/EC

Although all EU Member States were obliged to adapt any law, regulation and administrative provision necessary to comply with Directive 2001/20/EC at the latest with effect from 1 May 2004, some of these national implementations were delayed considerably[iii]. One can conclude from this that the key intention of Directive 2001/20/EC, namely the introduction of GCP into European clinical research, was not accomplished without difficulty. It was a major act and thus took a while to be entirely implemented within the Member States.

GCP in the context of trial design, trial conduct and trial result reporting was defined as having uniform rules within the EU. Moreover, it was stipulated to conduct as few trials with vulnerable subjects (e.g., children, patients with dementia, etc.) as possible. If, however, such investigations needed to be made, it was detailed how to protect clinical trial subjects and how to perform clinical trials on minors and on incapacitated adults not able to give informed legal consent. Furthermore, it was stated not to conduct any obsolete or repetitive tests, also not outside the EU, and that all test and trial results should be submitted when applying for marketing authorization.

In order to guarantee civil and criminal liability of the sponsor, it was specified that the sponsor or a legal representative of the sponsor had to be located in the European Community.

Detailed measures regarding trial regulation were introduced and implemented. According to the directive, also an all-compassing European Database was to be established. Moreover, it was defined that all study participants should have the same information and that the Investigational Medicinal Products (IMPs) had to be manufactured according to GMP, incl. import, labelling and verification of compliance with GMP. Directive 2001/20/EC also made provisions for non-commercial trials, subjects' data protection as well as monitoring and notification of adverse events and (serious) adverse reactions. Multiple definitions were given in accordance with US American standards and became customary in the entire EU.

The directive also specified how to gain authorization to conduct a trial within the EU. In case of multi-center trials, the clinical trial could begin after obtaining one single opinion for all EU Member States involved. Moreover, an implicit authorization, i.e., if there had been a vote in favor by the EC and the Competent Authority (CA) did not object within a given period, was also possible.

Just the awareness that any arbitrary or willfully originated decision made by any authority regarding a clinical trial – no matter if arbitrariness or willfulness were indeed present – would not be acceptable and sustained easily any longer, stimulated the entire clinical research in the EU. The skepticism that usually accompanies the introduction of an entirely new directive was partially balanced by this prospect.

The content of Directive 2001/20/EC was completed by clarifications regarding the conduct of a clinical trial and amendments to the protocol (substantial or not) as well as provisions regarding the notification of the end of a trial, the exchange of information between Member States and the suspension of the trial or infringements. Also, guidance concerning reports and general provisions regarding civil and criminal liability of the sponsor or the investigator were given.

The basic idea, the introduction of GCP into EU clinical research is based on the protection of the rights and dignity of the human being as reflected in the Declaration of Helsinki (DoH). More specifically, Directive 2001/20/EC directly refers to the DoH amendment made at Somerset West in 1996[iv]. The reference needed to be that specific because of the imperfections contained in the DoH version made at Edinburgh in the year 2000 (use of placebo as control arm and information of patients about outcome of the study, e.g., regarding the best identified treatment, intervention, etc.), which were only belatedly noticed and corrected by notes of clarification in 2002 and 2004 (Washington and

Tokyo). Due to the fact that the new EU Regulation No. 536/2014 apparently will not be implemented prior to 2019, the essential reference to the newest version of the DoH (version Fortaleza 2013[v] or later) and its subsequent insertion into every Trial Master File will not be made until then. All in all, it will have been a long farewell to the DoH version of 1996, Somerset West.

Figure: Somerset West – Hello in 1996, Goodbye in 2019 (?) [Source: H. Schwabedissen, 2013]

Another remnant from the individual national legislations within Europe, prior to the first harmonization in 2004, is the "Chief Investigator" (CI). From 2004 onwards, this title was mostly converted to "Coordinating Investigator of *Member State Concerned*".

Originally, the "*Leiter der klinischen Prüfung – LKP*", as the CI was called in Germany and Austria, the "Chief Investigator"[vi] in the United Kingdom, "*le Chercheur Investigateur*" in France, and so on, started out as the only person who – besides the sponsor – had the right to terminate a clinical trial/investigation for good, even without the sponsor's consent. On the other hand, the CI was to be held liable in case of non-appropriate treatment or inadequate subject information. Like this, all the CIs had an enormous responsibility and authority at the same time until 2004.

Then, the CI gradually lost its former functions and was reduced to a more central administrative role in nearly all EU Member States. Currently, the CI is – for the most part – the person authorized to conduct a trial at a trial site or, if the trial is conducted by a team of authorized health professionals at a trial site, to be the leader responsible for that team. Additionally, the CI is one of the persons to sign the trial protocol, the person according to whose residency the leading ethics committee is chosen (if appl.), and the primary contact person for the leading EC. The CI retained its original responsibility and authority in Germany only.

What's new and different?

In 2017, three major contributions were made to the new EU Regulation No. 536/2014 as discussed below.

The benefit/risk assessment has gotten special importance in the new regulation. This aspect is also reflected in the guidance paper "Risk proportionate approaches in clinical trials"[vii] developed at the beginning of the year 2017 to explain in more depth how the requirements from the new EU regulation regarding risk proportionate approaches might be implemented in actual clinical trials. Different approaches are presented therein – all within the regulatory framework – taking into account a number of factors, such as the design, the conduct, the evaluation and the reporting foreseen, which may affect the risk posed to a clinical trial subject and/or trial integrity. The possible variations in how to adapt the clinical trial with respect to the risks identified are described within this guidance. It is explained that the complexity and number of documents, control steps and reporting requests required might depend on the status and properties of the IMP planned to be used in the clinical trial. The risks associated with the IMP need to be assessed based on its marketing status and properties, the intended trial population, and the planned exposure, for example. All these details shall become part of the trial protocol. Also, the actual difference between the planned trial interventions and normal practice shall be defined therein. Further, it is recommended that the approaches taken regarding risk assessment during the development of new medications should already be considered and detailed in the clinical development plan. It remains to be seen whether the risk proportionate procedures in clinical trials will really advance clinical research or just lead to a replication of study approaches from earlier times.

Another novelty is the request for summaries of clinical trial results understandable to a layperson (Article 37). The guidance paper "Summaries of Clinical Trial Results for Laypersons"[viii] was

developed at the beginning of the year 2017 to explain in more depth how the requirements from EU Regulation No. 536/2014 regarding this layperson's summary are to be understood. Annex V of the new EU regulation describes several items that shall be part of this summary. Besides information on the sponsor and the identity of the IMP, the layperson's summary shall contain items such as the title of the trial, the protocol and EU trial numbers, the time and sites of trial conduct, information and comments on subject populations, the overall results as well as a description of adverse reactions and their frequency. The guidance paper clearly states that "consistency in the way trial results are presented will help improve familiarity and comprehension by the general public, participants, patients, and others"[viii].

The third contribution relates to the introduction of "Auxiliary Medicinal Products (AxMPs)" – formerly called Non-Investigational Medicinal Products ("NIMPs")[ix] and can be regarded as an especially huge step forward. The main objective of this addition was to harmonize the EU regulation with the newest scientific understanding. Also, a clear differentiation between IMPs and NIMPs has sometimes been problematic in the past. Even within the same authority, depending on the person being in charge with handling the submission, a different understanding of what was to be regarded as an IMP or NIMP occasionally resulted in multiple contradictory communications.

In the new EU regulation, an AxMP is defined as "a medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product". Examples of AxMPs are medicinal products used as rescue medication, challenge agents or background treatment. To clarify further which types of medical products may fall under the category of AxMP in a clinical trial, examples are provided in Annex 1 of the new regulation and in the guidance paper "Auxiliary Medicinal Products in Clinical Trials"[x]

The new regulation states that in general only authorized AxMPs can be used in clinical trials. Unauthorized AxMPs – definition to be found in [x] – may be used within clinical trials only in special cases. Similar to IMPs, all AxMPs should be traceable and accounted for by subject.

As mentioned above, some important contributions to EU Regulation No. 536/2014 were already made in 2016. On the one hand, inspection procedures throughout the EU will be harmonized, as well as training and qualification requirements for inspectors will be specified throughout the EU by implementing acts (Articles 78 and 88).

On the other hand, the most necessary changes in GMP for IMPs were made. The new EU regulation states that the following activities shall be exempt from the holding of a manufacturing authorization if they are carried out in hospitals, health centers or clinics, by pharmacists or other persons legally authorized in the Member State concerned to carry out such processes, and if the investigational medicinal products are intended to be used exclusively in hospitals, health centers or clinics taking part in the same clinical trial in the same Member State:

- Re-labelling or re-packaging,
- The preparation of radiopharmaceuticals used as diagnostic investigational medicinal products.

Also, the preparation of medicinal products referred to in paragraphs (1) and (2) of Article 3 of Directive 2001/83/EC[1] for use as investigational medicinal products shall be exempt from the holding of a manufacturing authorization if those processes are carried out in hospitals, health centers or clinics legally authorized in the Member State concerned to carry out such processes, and if the investigational medicinal products are intended to be used exclusively in hospitals, health centers or clinics taking part in the same clinical trial in the same Member State (Article 61, Paragraph 5)[i].

On second thought, it becomes clear that the wording in Article 61 of the new EU regulation is more or less identical with the changes described in Article 13 of the 16th amendment to the German Drug

[1] Paragraphs 1 and 2 of Article 3 in Directive 2001/83/EC refer to the "*magistral formula*" (any medicinal product prepared in a pharmacy in accordance with a medical prescription for an individual patient), respectively to the "*officinal formula*" (any medicinal product which is prepared in a pharmacy in accordance with the prescriptions of a pharmacopoeia and is intended to be supplied directly to the patients served by the pharmacy in question)[1].

Law[xi]. With this amendment dating from 2012, the German Drug Law already anticipated and implemented the provisions specified in Article 61 of the new EU regulation.

Also dating back to 2016 are the changes in provisions for clinical trials on vulnerable populations. In the new EU regulation, the specifications outlined in Directive 2001/20/EC were supplemented to cover clinical trials on multiple vulnerable populations, such as incapacitated subjects, minors, pregnant or breastfeeding women, and subjects in emergency situations (Articles 10 and 31 to 35).

Included from the beginning were the splitting of study application dossiers in two parts and the harmonization of the application procedures for regulatory and EC approval. Both parts of the application dossier can be reviewed either in parallel or consecutively (Part I prior to Part II), depending on the needs or preferences of the sponsor. Part I – Study Specific Documents – will be reviewed by all Member States concerned cooperating in assessing the request for authorization of a clinical trial. Part II – Country/Site Specific Documents (e.g., biological samples, clinical trial agreements, informed consent, recruitment of subjects, etc.) – will be assessed by every Member State concerned individually.

As a concession to the British regulatory agency, it was added to the legislative text that serious breaches of EU Regulation No. 536/2014 or of the protocol – i.e., breaches likely to affect to a significant degree the safety and rights of the subjects or the reliability and robustness of the data generated – must be reported by the sponsor to the Member States concerned through the EU portal within seven days.

Conclusion

In summary, the new EU Regulation No. 536/2014 on clinical trials is expected to be a major improvement over the previous EU directive and will streamline the approval process for studies conducted across EU Member States. With the new regulation, one single application will be sufficient for the conduct of a clinical trial in several Member States. The new legislation will harmonize the regulation of clinical trials across Member States, simplify the reporting procedures, and additionally increase the transparency of clinical trial results.

Table: Content of the new EU Regulation No. 536/2014

CHAPTER I	General Provisions
CHAPTER II	Authorization Procedure for a Clinical Trial
CHAPTER III	Authorization Procedure for a Substantial Modification of a Clinical Trial
CHAPTER IV	Application Dossier
CHAPTER V	Protection of Subjects and Informed Consent
CHAPTER VI	Start, End, Temporary Halt, and Early Termination of a Clinical Trial
CHAPTER VII	Safety Reporting in the Context of a Clinical Trial
CHAPTER VIII	Conduct of a Clinical Trial, Supervision by the Sponsor, Training and Experience, Auxiliary Medicinal Products
CHAPTER IX	Manufacturing and Import of Investigational Medicinal Products and Auxiliary Medicinal Products
CHAPTER X	Labelling
CHAPTER XI	Sponsor and Investigator
CHAPTER XII	Damage Compensation
CHAPTER XIII	Supervision by Member States, Union Inspections and Controls
CHAPTER XIV	IT Infrastructure
CHAPTER XV	Cooperation between Member States
CHAPTER XVI	Fees
CHAPTER XVII	Implementing Acts and Delegated Acts
CHAPTER XVIII	Miscellaneous Provisions
CHAPTER XIX	Final Provisions
ANNEX I	Application Dossier for the Initial Application
ANNEX II	Application Dossier for Substantial Modification
ANNEX III	Safety Reporting
ANNEX IV	Content of the Summary of the Results of the Clinical Trial
ANNEX V	Content of the Summary of the Results of the Clinical Trial for Laypersons
ANNEX VI	Labelling of Investigational Medicinal Products and Auxiliary Medicinal Products
ANNEX VII	Correlation Table

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References:

[i] Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC

[ii] Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use

iii M. Gierend, D. Chase, W. Feuerer (2006): "Experience with the implementation of the EU clinical trials directive – first results of a survey initiated by the BVMA e. V.", Qual Assur J 10, 21-28

iv World Medical Association **Declaration of Helsinki** Recommendations guiding physicians in biomedical research involving human subjects. Adopted by the 18th World Medical Assembly, Helsinki, Finland, June **1964**, and amended by the 29th WMA, Tokyo, Japan, October 1975, 35th WMA, Venice, Italy, October 1983, 41st WMA, Hong Kong, September 1989 and the 48th General Assembly **Somerset West**, Republic of South Africa, October **1996**

[v] World Medical Association **Declaration of Helsinki** Recommendations guiding physicians in biomedical research involving human subjects. Adopted by the 18th WMA, Helsinki, Finland, June **1964**, and amended by the 29th WMA, Tokyo, Japan, October 1975, 35th WMAy, Venice, Italy, October 1983, 41st WMA, Hong Kong, September 1989 and the 48th General Assembly Somerset West, Republic of South Africa, October 1996, 52nd WMA, Edinburgh, Scotland, October 2000 53rd WMA, Washington DC, USA, October 2002 (Note of Clarification added) 55th WMA, Tokyo, Japan, October 2004 (Note of Clarification added) 59th WMA General Assembly, Seoul, Republic of Korea, October 2008 64th WMA, **Fortaleza**, Brazil, October **2013**

[vi] Statutory Instruments, Medicines: The Medicines for Human Use (Clinical Trials) Regulations, 2004 No. 1031

[vii] Risk proportionate approaches in clinical trials. Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use. 25 April 2017

[viii] Summaries of Clinical Trial Results for Laypersons. Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use. 26 January 2017

[ix] The Rules Governing Medicinal Products in the European Union, Vol. 10 – Guidance Documents Applying Clinical Trials; Guidance on Investigational Medicinal Products (IMPS) and 'Non' AND 'NON' Investigational Medicinal Products (NIMPS); (Rev. 1,March 2011)

[x] Auxiliary Medicinal Products in Clinical Trials. Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use. 28 June 2017

[xi] *2. Änderungsgesetz zu arzneimittelrechtlichen Vorschriften (16. AMG-Novelle),* 19 October 2012

About the Authors

Dr. Heidrun Schwabedissen earned her doctorate in 1989 from the Westphalian Wilhelms-University of Münster, Institute of Botany. After having been granted a post-doctoral fellowship by the renowned German Research Foundation (DFG), she spent parts of her post-doc period at university laboratories in Baton Rouge (LA), East Lansing (MI), and Münster. Afterwards, Dr. Schwabedissen was involved in fundamental research at university and industrial laboratories in Germany and abroad for several years, e.g. at the renowned *Unité Mixte de Recherche* of Rhône-Poulenc Agro in Lyon, France.

In 1999, Dr. Schwabedissen changed into clinical research. She has been working as a Medical Writer, Project Manager and Manager Clinical Affairs at CROs for more than 15 years now and gained experience in the planning, conduct and evaluation of mono-center and multi-center clinical trials with medicinal products from Phase I to Phase IV and in clinical investigations with medical devices of Classes IIa, IIb, III, and implants in multiple indications.

For several years now, Dr. Schwabedissen has been responsible for the Quality Management and Quality Assurance at Inamed and has been working as a GCP- / GMP-Auditor.

Patrick McManus received his diploma in Business Administration and Computational Sciences from the Academy of Public and Business Administration in Munich in 2010. Conducting his studies as dual education, he was working as product manager and application engineer at a mid-size distributor for large format printers and IT-systems during this time.
In 2007, he joined Inamed as Business Development Associate in order to further pursue and promote his career. Learning the CRO business from scratch, he soon gained a broad knowledge of all services required to successfully conducting clinical trials and established a wide network of client contacts. After proving his skills by winning several studies for Inamed, he was promoted to Business Development Manager in 2010.
Since 2014, Mr. McManus has been leading Inamed's BD department as Director Business Development. In this role, he is responsible for establishing Inamed as a market leader in respiratory and early phase clinical trials, as well as further pursuing Inamed's growths.
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About Inamed

For nearly two decades now, Inamed has been supporting various companies in their pharmaceutical and medical device development activities by providing excellent CRO services.

Inamed offers flexible, reliable, high-quality clinical research services, which cover pre-clinical *in-vitro* investigations, followed by mono-center and multi-center clinical trials with medicinal products from Phase I to Phase IV, including Bioequivalence, Pharmacokinetics, Pharmacodynamics and Proof-of-Concept Trials, as well as clinical investigations with medical devices of Classes IIa, IIb, III and implants in multiple indications.

Study conduct, data management, statistical and medical evaluation of study data and medical writing activities complete Inamed's CRO services, although training and auditing activities certainly should also not go unmentioned.

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