Four phases of clinical trials in humans

Medicinal products are funnelled through a series of different types of studies and tests. The series of clinical trials also represent a selection process. As the exposure of patients increases, so does the demand for proving a favourable benefit / risk ratio. The overall likelihood of approval of a drug from Phase I for all developmental drug candidates is only around 10%. Rare disease programmes and clinical trial programmes utilizing biomarkers tend to have higher success rates at each phase of clinical development.

By Charlotte Strøm, MD PhD Journalist

Phase I studies assess the safety of a drug or device and represent an initial phase of testing, only including a small number of healthy volunteers. The study determines the effects of the drug or device in humans including how it is absorbed, metabolized, and excreted in addition to side effects that occur as dosage levels are increased. About 70% of experimental drugs pass this phase of testing.

Phase II studies test the efficacy of a drug or device and involves up to several hundred patients. Most phase II studies are randomized trials in which one group of patients receives the experimental drug, while a control group receives a standard treatment or placebo in a double-blinded manner, allowing for comparative information about the relative safety and effectiveness of the new drug. About 33% of experimental drugs successfully complete both phase I and II studies.

Phase III studies involve randomized and blinded testing in several hundred to several thousand patients. Large-scale investigation that may last several years provides a more thorough understanding of the effectiveness of the drug, the benefits, and the range of possible adverse reactions. 70% to 90% of drugs that enter phase III studies successfully complete this phase. Application for marketing authorization is applied for after the completion of phase III.

Phase IV studies, often called post marketing surveillance, are conducted after a drug or device has been approved by the national or international regulatory authorities. The objective may be a) to compare a drug with other drugs already in the market; b) to monitor long-term effectiveness and impact on patients' quality of life, or c) to determine the cost-effectiveness of a drug relative to other traditional and new therapies. Phase IV studies can result in a drug being taken off the market or restrictions of use could be placed on the product depending on the findings in the study. Regulatory authorities may approve a medicinal product for the market, while connecting the sustained marketing authorization to the results of post approval phase IV studies. ■

Prepare for the future legal framework for clinical trials in Europe

The current voluntary harmonization for approval of clinical trials within the European Union (EU) will take a step further when the new legal frame Work comes into effect around 2019. Starting right –regulatory documentation is more important than ever.

Lillan Rejkjær, Managing Partner and Head Regulatory & Medical Development

Any type of testing in humans bears significance to the marketing authorization of the medicinal product or device, as the documentation is part of the regulatory file. Lillan Rejkjær, Managing Partner and Head Regulatory & Medical Development at IWA Consulting is keeping an eye on the progress of putting clinical trials into a new legal framework within the EU. The law is expected to come into act in 2019.

-At IWA Consulting we stress the urgency of starting the clinical documentation in a correct manner, ensuring that the study protocol, the data collection, the description of the study conduct etc. are all in compliance with the requirements, Lillan Rejkjær says and continues,

-In particular the small or midsize biotech and pharma companies or the non-commercial sponsors who may run clinical testing before a university spin out or divestment of the compound may have difficulties in overlooking the full process from the first-in-man phase I trial to the submission of an electronic marketing authorization application (MAA) with the European Medicines Agency (EMA) or a national authority. It takes a thorough regulatory understanding to do it all right from the very start of the clinical development process.

More than words

The future clinical trial legal framework will be based on an approval procedure similar to the assessment of a decentraliced marketing authorization procedure. However, the choice of words appears to slightly differ.

-Some may argue that it is just about words, the point is that an applicant for a clinical trial, is helped by being aware of this similarity, which eases the understanding of the new clinical trial approval process., Lillan Rejkjær says and refers to a tabulated overview from IWA Consulting.

Aim for the MAA

-The aim of a clinical trial result being a part of an MAA is important, irrespective of the origin of the sponsor, says Lillan Rejkjær.

She's hoping that the centralisation and harmonization within a legal framework for clinical trials in Europe will enable a smooth and rapid work flow to the benefit of the life science industry and to patients to whom the new medicines will hopefully become available sooner than what is the case today. Moreover, she believes it will strengthen the pharmacovigilance and overall surveillance of adverse effects and also hopes that the understanding of the need of thinking ahead will settle.

-In general, the harmonization is likely to create a greater awareness of the close connection between clinical trials and the regulatory set up among the different stakeholders of the life science industry. The simple advice is, to aim for the MAA.

About IWA Consulting

- The IWA Consulting Team is a dedicated group of regulatory affairs specialists providing expert services to a range of international private and public clients.
- We do that based on our long term regulatory experience, in-depth knowledge, and expertise.
- We assist biotech, pharma, and medtech companies in achieving their major regulatory milestones, knowing and thoroughly understanding the sense of urgency that applies to this business area. Regulatory affairs – in every aspect of the discipline – are our core competence.

That is – at the end of the day – the goal. And my job is to ensure that our clients understand enough about the process to choose a regulatory pathway that is well thought through from the very beginning, Lillan Rejkjær ends.

Decentralised Procedure (DCP)	Clinical trial
Reference member state (RMS)	Reporting member state
Concerned member states (CMS)	Member states concerned
Common documentation	Scientific part (Part I)
National documentation	National part (Part II)
Preliminary assessment report	Draft part I of the assessment report
	Request of additional information
Final assessment report	Final part I of the assessment report
	Part II of the assessment report
RMS approval	Conclusion of part I of the assessment report
National phase	Decision phase

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