

Hessen – Gateway to Contract Research in Europe

A practical Guide to Sites and Services, second edition



Hessen – there's no way around us.

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Imprint

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Volume 8 of the series Aktionslinie Hessen-Biotech of the Hessian Ministry of Economics, Transport, Urban and Regional Development

Publisher

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Listing of a company profile within this publication is strictly voluntary, all Contract Research Organizations in Hessen have the opportunity of being entered in this database since its online version is being continually expanded and updated. The publisher does not take any responsibility for correctness and preciseness of the give information.

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TransMIT Gesellschaft für Technologietransfer mbH, Gießen

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Urban and Regional Development
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Kaiser-Friedrich Ring 75
65185 Wiesbaden | GERMANY
www.wirtschaft.hessen.de

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Design

ansicht kommunikationsagentur, Wiesbaden | GERMANY

Photos

HA Hessen Agentur GmbH
fotolia | NiDerLander | moodboard | mario beauregard
©iStockphoto.com | DivaNir4a | DavidBGray
PhotoDisc

Translations

Language Service Center, Gießen | GERMANY

Print

Werbedruck Schreckhase GmbH, Spangenberg | GERMANY

May 2009

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Some basics on Clinical Research

CLINICAL RESEARCH IN HESSEN

• Health is no longer just a highly private affair, it is also a major economic factor. The health business is growing at a very considerable rate. In 2007, for example, the statutory health insurance funds in Germany spent almost 28 billion euros on medicaments alone. To secure a share in this market, companies need not only good products but also an excellent infrastructure and reliable business conditions. Unless these are available, research-based pharmaceutical companies will hardly be prepared at all to start out on the highly long-term and cost-intensive processes culminating in the authorisation of a new active ingredient.

Not many regions offer excellent and reliable business conditions of this kind. The Federal State of Hessen is with certainty one of them, with its economic centre Frankfurt/Rhine-Main and its pharmaceutical industry with a tradition going back over one hundred years. It is not for nothing that the region, one of the economically most powerful centres in Europe, bears the title of "Germany's chemist shop".

It is now one hundred years since the first Nobel Prize winner for medicine, Emil von Behring, established the world's first "biotech start-up" – the Behringwerke AG – in Marburg and began with the production of vaccines through the immunisation of horses. In 1909, Paul Ehrlich, the Nobel Prize winner resident in Frankfurt, started on the production of the world's first chemical therapeutic agent "Salvarsan" for the treatment of syphilis. His success formed the basis for the rise of Farbwerke Hoechst as the world's leading pharmaceutical concern.

Nowadays the pharmaceutical industry in Hessen employs over 29,000 people, who in 2008 generated a turnover of around 11 billion euros

– that is more than a quarter of the turnover of the entire German pharmaceutical industry. Of this, pharmaceutical products to a value of 7 billion euros were exported throughout the world from Hessen. Companies such as Sanofi-Aventis, Merck Serono, Fresenius, Novartis-Behring, CSL-Behring, Lilly, Merz or Abbott are just a few examples of internationally successful concerns researching and producing in Hessen.

Biotechnology is assuming a constantly increasing share in all this. Over 200 companies are engaged in biotechnology. Most of them are service providers, whether in contract research, production, the growing field of quality management or the performance of clinical trials. This mix, covering the entire range of the pharmaceutical value chain, is unique in Europe.

Important factors for the growth of companies are also created by an attractive regulatory framework. The responsibilities for implementing the requirements of gene technology legislation in Hessen were centralised in a single authority, with the result that companies need to approach only one contact partner. The times necessary for approval of new plants are among the shortest in Germany.

Companies benefit from the international character of the Frankfurt/Rhine-Main region. No other region in Germany houses so many companies from abroad. More than 700 American firms are located in Hessen, and just on 20 percent of all American direct investments in Germany find their way here.

Frankfurt has the largest Korean community in Europe, the Chinese and Japanese communities are growing steadily. The many international schools enable expatriates to have their children educated in same way as they would be in their own countries. This is one reason why employees of foreign companies are so willing to live here.

One factor which makes the region so attractive is the excellent transport infrastructure. The Frankfurt Rhine-Main airport, with about 54 million passengers per year, is among the largest airports in Europe after London and Paris. It offers 4,375 direct flights a week to all major international centres, and to many of them several times daily. Frankfurt is also Europe's largest air freight

Minister of Economics,
Transport, Urban and Regional
Development in Hessen



Dieter Posch

transshipment centre.

These connections guarantee the opportunities for rapid travel which are so important for internationally operating companies. With 40 contract research organisations (CROs), it is no coincidence that clinical research is centred in the region.

It is clear that effective research, especially into the development of new therapeutic active ingredients, cannot be done without academic research and training of high quality. Here, again, the excellent infrastructure in this area becomes evident. In less than one hour it is possible to reach a large number of maximum care hospitals with about 35,000 beds. In Hessen, relevant subjects such as human medicine, pharmacy, biology, chemistry or process engineering are taught at as many as twelve universities and high schools. More than 600 professors teach nearly 17,000 students in these subjects. Every year, companies can draw on a pool of almost 3,000 highly qualified graduates.

The State of Hessen has set up an Initiative for the Development of Scientific and Economic Excellence (LOEWE) with a view to establishing new leading-edge technology centres. Additional resources were made available with the explicit intention of turning already existing strong points into real centres of excellence. The maximum benefit of this will accrue to the Life Sciences.

In addition to the universities and high schools, there are also the four Max Planck Institutes, where high-end research is carried out. Among their principal focuses are biophysics, physiological research, brain research and microbiology.

The close interlocking of business and science, of research and application, is already producing visible results in Hessen – in a nation-wide contest, Hessen was chosen to establish an excellence cluster in the promising future field of white biotechnology. This is now engaged in developing the most recent methods for the biotechnological production of fine and specialty

chemicals.

Backed up by these resources, Hessen is in a good position to expand its position as a biotech production industry region. The pharmaceutical concerns based here are extending their production capacities – Novartis Behring in Marburg, Abbott in Wiesbaden, and Sanofi-Aventis in Frankfurt.

All this speaks for the quality of Hessen in the fields of pharmaceuticals and biotechnology. This is doubtless one of the reasons why the CROs stated in their replies to a questionnaire that Hessen is unusually well positioned and can be considered as a first-class competence centre able to stand any international comparison.

I would like, therefore, to invite you to use this brochure as a source of information about the opportunities for clinical testing in Hessen. I greatly hope that you will be convinced by what we have to offer and would be very glad if we could extend a welcome to your company also.



Dieter Posch
Hessian Minister of Economics, Transport,
Urban and Regional Development

HESSEN: GATEWAY TO CLINICAL RESEARCH IN EUROPE

- Clinical research is beyond all doubt one of the most important phases in the development of a new medicament. Mistakes made at the beginning – whether in the planning of the study, the choice of suitable cooperation partners or the drafting of the test schedules – can lead to considerable costs and lengthen the time needed for registration.

For this reason it is important for small and medium-sized biotech and pharmaceutical companies to find speedy and uncomplicated access to networks offering high-quality advisory services in connection with clinical tests and their performance. In this brochure you will find a list of the Contract Research Organisations (CROs) in Hessen and the test centres at Hessen's university clinics.

Access to 500 million consumers

Hessen, with its economic centre Frankfurt, is one of the centres of the European chemical and pharmaceutical industry. It is ideally situated in the middle of a pharmaceutical market with 500 million consumers. These are joined by just on another 300 million consumers in the non-EU Eastern European states. These countries, which include Russia and the Ukraine, are noted for their high concentration of hospitals and practising physicians.

Region	Consumers
USA	283 million
European Union (27 States)	501 million
Eastern Europe	300 million

All these markets can be reached from Frankfurt in less than two to three hours. Compared with the USA, a greater number of patients can be reached over a smaller area. These facts are becoming increasingly important in the growing markets of Eastern Europe because, before new medicaments are approved in these countries, the authorities expect to receive data which have been generated there.

Thanks to the numerous local CROs, and also to transport facilities unequalled anywhere in Europe, 800 million consumers/patients can be reached by air in less than three hours. The CROs based here already have very close contacts with

Eastern Europe. This was made very much easier by the history and culture shared by European countries. Next to Russian, German is the most widespread foreign language in Eastern Europe.

Hessen - The centre of the CROs in Germany

More than 40 CROs are based in the region around Frankfurt. In addition, there are many providers who help to ensure the quality of testing either by consultancy services in this context or through the provision of software and quality management products.

These CROs employ 1,700 people in Hessen, and more than 38,000 worldwide. This indicates how well Hessen's CROs are netted globally and what potentials this centre has to offer.

A look at the adjoining map (illustration with the dots on the Hessen map) will clearly show how greatly these companies can benefit from the geographical nearness to the authorities and the transport connections.

CROs give the region an excellent rating

The CROs based in Hessen have stated with conviction that they are entirely satisfied with Hessen as a location. They rate it better than other German regions and consider it to be fully competitive at international level. Hessen scores very well most especially for qualified personnel and for cooperation with the authorities. It is the internationally active CROs which have given the best ratings here. They emphasise in particular the transport infrastructure and the cooperation with the ethics commissions. This can be taken as evidence for the high quality and professionalism in Hessen.



The region offers the best conditions for finding **qualified and well-trained personnel**. The long-standing structures of medium-size and large companies, together with the high concentration of research facilities, are constantly producing a large number of highly qualified employees. Coordination centres for clinical research which have been set up at the universities act as direct contact partners. New study courses have been initiated for qualifying as study nurses or research physicians. The universities in Hessen have adapted their courses to fit in with the internationally customary master and bachelor degrees. This will ensure greater relevance for everyday practice.

Hessen is one of the first German states to have reorganised and simplified the work of the **ethics commissions**. Multicentric studies can be set in motion much more rapidly through the binding vote of an executive committee. A standard format has been agreed on, and the work is closely supervised by Hessen's Ministry of Health.

Unbureaucratic access to authorities

Hessen's central situation makes it an ideal location for clinical tests.

The Paul Ehrlich Institute (PEI), one of Germany's leading authorisation authorities and at the same time an internationally renowned research centre, is situated very near to Frankfurt airport. It is competent for the particularly innovative recombinant drugs, for gene therapy and stem cells. This close vicinity is of great advantage for the CROs. The PEI actively seeks contact with the CROs and sponsors, it offers advice at every stage of the application process, and provides training programmes for research physicians. The PEI is integrated in the work of the German and European regulatory authorities by voicing recommendations and also by offering advisory support for the legislature.

Bonn, just over an hour's journey from Frankfurt, is the seat of the Federal Institute for Drugs and Medical Devices (BfArM), the German regulatory authority. The European regulatory authority EMEA, based in London, can be reached by air in just under one and a half hours.

Once the studies have been authorised, they are supervised by a central authority in Hessen with experts of its own who have themselves gathered extensive experience in the pharmaceutical

industry. The CROs have given Hessen a very high rating at international level for cooperation with the authorities.

Frankfurt - Germany's centre for CROs

The highest concentration of CROs in Germany lies within a one hour's drive from Frankfurt. The companies in this area are distinguished by their great variety and by the comprehensive range of services they have to offer. Practically all use areas are covered, and many of the companies are highly specialised. This high degree of professionalism is enhanced by the close networking of the CROs. More than half of the CROs work on a cooperative basis.

As the most important customer group, the large pharmaceutical concerns play a major role. However, the small pharmaceutical and biotech firms are becoming an increasingly important target group. In the meantime, more than half of the CROs have gained intensive experience with small biotech firms. Operating conditions like these are highly useful especially for biotech firms newly breaking into the European market.

The Hessen-based CROs are innovative, and they are striking out on new paths. A service offered by one third of the CROs is to take over the entire preparation and handling of the CTD (Common Technical Document) and forward it to the regulatory authorities in electronic form (eCTD).

Hessen - Gateway to Europe



A large number of companies, engaged up to now in the classical tasks of supporting clinical studies for new medicaments, have now turned additionally to medical products or even specialised in them. These new fields of business also include studies for the food industry to deal with health claims in connection with functional foods.

Access to clinics in Hessen

"Investigator-initiated trials" are assuming increasing importance. As many as one quarter of the CROs stated them to be their major focus, or have declared universities, university clinics and scientific study groups as their clientele. This reflects the high quality and creativity of medical research at Hessen's universities and institutes.

The Centre for Drug Research, Development and Safety (ZAFES) is a model project in the southern region of Hessen in which 24 clinics and research institutes and the locally based pharmaceutical companies have joined forces under the aegis of the Frankfurt University Clinic. In the field of clinical research, they offer a complete package of clinical services over all phases of the project. This encompasses a variety of different things, ranging from chemical analysis to the provision of beds in individual clinics.

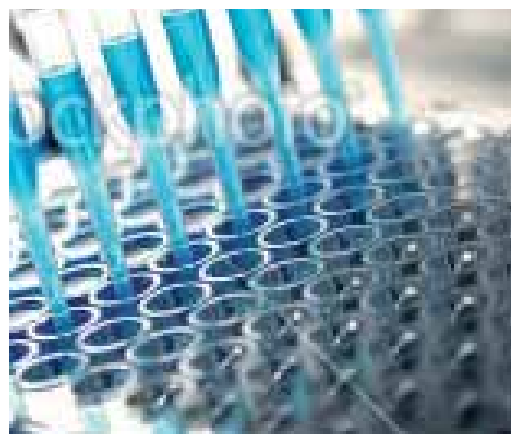
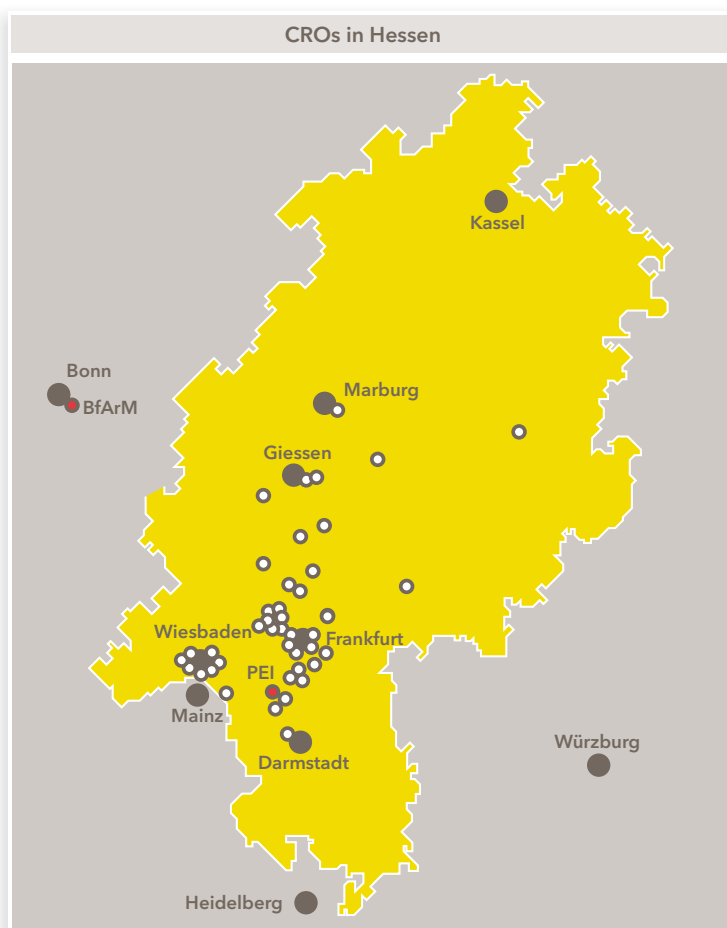
The central contact partner for the university clinics in Marburg and Giessen is the Coordination Centre for Clinical Trials (KKS), which also makes important contributions in the area of personnel training. The most recent legal and professional aspects are integrated in the training of research physicians, study directors or study nurses.

Hessen: Your Gateway to Clinical Research in Europe

Germany remains the European reference market for therapeutic agents. It is here that the specifications for other European markets are very largely set. A number of unique advantages makes Hessen the ideal starting point for access to this enormous market. What sets Hessen apart are the best travel connections in Continental Europe, the close cooperation with all authorities, and the wide choice of highly qualified and motivated employees.

In addition to its excellent resources in the area of clinical research, Hessen can offer more than one hundred years of pharmaceutical experience. And with regard to research, scale-up, production, distribution or marketing, there is hardly another region which can bear comparison with Hessen.

Hessen-Biotech is your contact partner for integrating you in this network. This brochure gives you all the information you need. Dynamic companies need an environment to match, and we will open up the way for you.



• The development of a medicinal product and its establishment in standard medical use is a complex process which includes research and discovery, non-clinical development, testing in clinical trials, finally marketing authorisation and post-marketing follow-up.

The development process is legally regulated to ensure safety and efficacy of new medicines for maximum benefit of the patients. Non-clinical testing allows insight into the pharmacology and toxicology of a new medicinal product. Clinical testing for safety, optimal or feasible dosing, environmental risks and efficacy in controlled clinical trials provides data for a thorough risk-benefit assessment. An acceptable risk-benefit ratio is the basis for marketing authorisation, for either Germany only or also for other EU member states. Scientific research provides the necessary know-how for the experimental testing and evaluation of biomedicines. A modern research and regulatory institute like the Paul-Ehrlich-Institut therefore carries out experimental scientific research on an internationally competitive level and is a major player in the European network of medicinal product regulatory agencies.

In Germany, human medicinal products are regulated by authorities of the Laender and by two higher competent authorities. While the Federal Institute for Drugs and Medical Devices (BfArM) is concerned with chemical medicinal products, many recombinant proteins, cytokines and medical devices, the Paul-Ehrlich-Institut in Langen near Frankfurt/Main is responsible for vaccines and biomedicines. Within the network of EU member state agencies, the Paul-Ehrlich-Institut provides expertise to the European Medicines Agency (EMA), for example by assessing centralised marketing authorisation applications and by contributing to scientific advices. Furthermore, scientists from the Paul-Ehrlich-Institut are experts frequently consulted by and active in international organisations such as the World Health Organisation or the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Due to its experience in the area of blood products and *in vitro* diagnostic tests for pathogens, the Paul-Ehrlich-Institut has been designated "WHO Collaborating Centre for Quality Assurance of Blood Products and *in vitro* Diagnostic Devices" in 2005. Within this function, the Paul-Ehrlich-Institut supports the WHO in the organisation of training courses and meetings, and also organises and performs laboratory studies and standardisation exercises in order to establish internationally accepted test standards. This ensures a harmonized global view on the safety and efficacy of medicines and their optimal regulation.

PAUL-EHRlich-INSTITUT: A FEDERAL RESEARCH AND REGULATORY INSTITUTE WITH INTERNATIONAL COMPETENCE FOR VACCINES AND BIOMEDICINES

Jens Reinhardt, Evelyne Kretzschmar, Klaus Cichutek

Regulatory activities of the Paul-Ehrlich-Institut

Marketing authorisation of safe and efficacious biomedicines

The Paul-Ehrlich-Institut is the Federal Institute for vaccines and biomedicines in Germany. Biomedicines are derived from biological organisms and include vaccines, allergens, blood products, sera and monoclonal antibodies, gene therapy, cell therapy and tissue engineered products as well as classical tissue preparations. The Paul-Ehrlich-Institut carries out important regulatory activities on the national level such as authorisation of clinical trials, marketing authorisation, experimental and batch release testing of biomedicines and pharmacovigilance (see below). Moreover, the Paul-Ehrlich-Institut plays an important role in regulating biomedicines on the European level. Here, the European Medicines Agency (EMA) in London co-ordinates the centralised procedure for marketing authorisation and provides scientific advice during medicinal product development. The scientific assessment of the centralized marketing authorisation applications, which contain all data collected and evaluated during medicinal product development, are conducted by experts from the Paul-Ehrlich-Institut and other EU member state regulatory authorities. The proposal for authorising marketing

The Process of Drug Development

Research and Discovery

Development

- Non Clinical Tests
(Cell Culture, Animal Studies)

- Clinical Trials (Patients)

Phase I

Phase II

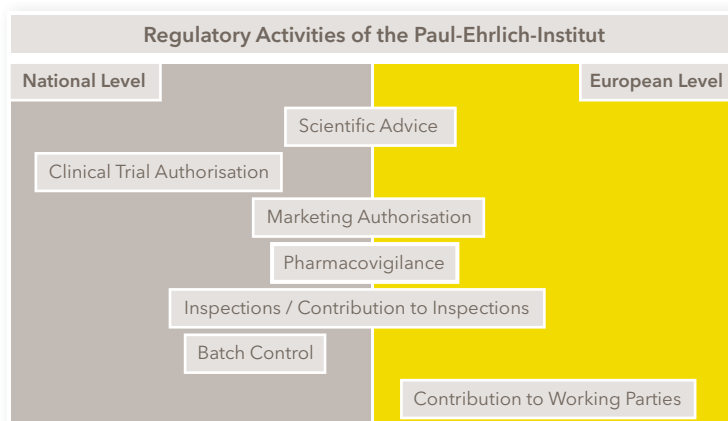
Phase III

Marketing Authorisation Application

Postmarketing Activities



The buildings of the Paul-Ehrlich-Institut in Langen near Frankfurt/Main.



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of a new medicinal product is made by the Committee for Medicinal Products for Human Use (CHMP) at the EMEA followed by provision of the marketing authorisation by the European Commission. An expert from the Paul-Ehrlich-Institut is a co-opted member of the CHMP. A single marketing authorisation application to EMEA allows marketing of a new medicinal product in all EU member states and thus standard use in medical care.

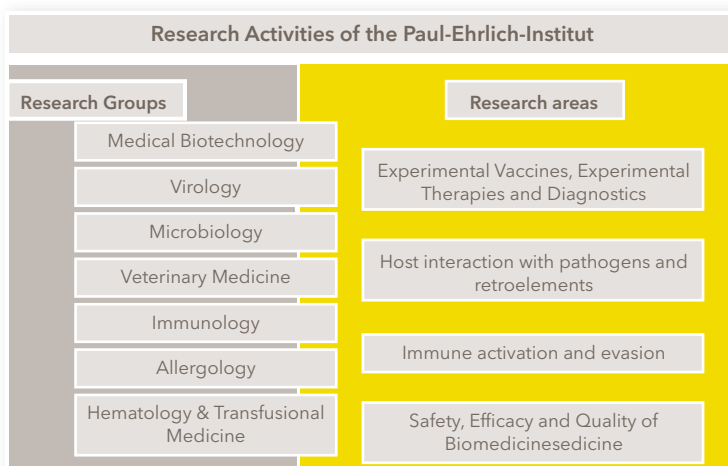
Experts from the Paul-Ehrlich-Institut are also members in most of the currently 12 Working Parties that support the CHMP. The Paul-Ehrlich-Institut is involved in up to 50 % of all procedures coordinated by the EMEA concerning these biomedicines. Furthermore, the co-opted CHMP member from the Paul-Ehrlich-Institut is also a member of the newly formed Committee for Advanced Therapies (CAT). The CAT will play a central role in the assessment of innovative medicines such as gene therapy, somatic cell therapy and tissue engineered medicinal products, which are termed advanced therapy medicinal products (ATMPs).

Scientific Advice supporting rapid and efficient biomedicines development

As the complexity of biomedicines differs considerably from chemical drugs, the conventional test methods used for the final chemical drug product are often not appropriate for biomedicines and they also vary depending on the nature of the given biomedicine. Therefore, the regulatory requirements for biomedicines need to be more flexible and different testing strategies may be applied. However, this flexibility may create uncertainty in whether a chosen development and testing strategy will be appropriate. To address this uncertainty, the Paul-Ehrlich-Institut provides guidance and scientific advice to pharmaceutical or biotechnological companies and academic research groups to their medicinal product development. Scientific advice at the Paul-Ehrlich-Institut is provided during an open and informal discussion meeting where product experts from the Paul-Ehrlich-Institut meet face to face with applicants to discuss all scientific and medical topics relevant for biomedicine development, clinical testing and marketing authorisation. One of the experts of the Paul-Ehrlich-Institut is also a member in the Scientific Advice Working, which coordinates the scientific advice provided by EMEA. The EMEA scientific advice focuses on technical requirements and development strategies presented by the pharmaceutical company with a view to a future centralised marketing authorisation. Furthermore, for ATMPs of small or medium-sized enterprises, the newly established CAT will also certify the data collected on the quality and non-clinical pharmacology-toxicology of a new product. Certificates are intended to allow these companies to get additional support, also financially, for their product development.

Clinical trial authorisation

As a pre-requisite to marketing authorisation, biomedicines, just like all medicinal products, are tested in controlled clinical trials. Initiation of clinical trials of biomedicines in Germany requires a positive appraisal by the local ethics committee and authorisation by the Paul-Ehrlich-Institut. The applicant has to provide data on quality and non-clinical studies that support safety and provide a proof of concept for the medicinal product, which has to be in accordance with the current state of scientific knowledge. To facilitate successful clinical trial applications, the Paul-Ehrlich-Institut has issued a guidance document termed Third Notification on the Clinical Trial of Medicinal Products for Human Use, jointly published with the BfArM. Here, the requirements of the German Medicinal Product Act and references to the relevant EMEA



guidelines are laid down to reflect the current state of scientific knowledge.

Pharmacovigilance

The Paul-Ehrlich-Institut is also responsible for the pharmacovigilance of biomedicines. The adverse effects of medicinal products, observed by and collected from healthcare providers, pharmaceutical industry and patients, are continuously monitored and evaluated to identify unexpected adverse reactions associated with medicines in order to prevent harm from patients. Necessary actions are taken by the Paul-Ehrlich-Institut or coordinated in conjunction with other authorities. Thus, by continuously monitoring risk-benefit, the Paul-Ehrlich-Institut ensures the safety and efficacy of medicinal products, thereby contributing to patient safety and public health.

Official biomedicines control by experimental testing of medicinal products

Vaccines and some other biomedicines require that each new production batch has to be tested or assessed and officially released by the Paul-Ehrlich-Institut before it may be marketed. The Paul-Ehrlich-Institut also carries out experimental testing of some centrally authorised medicinal products. Experimental testing of biomedicines by a governmental authority parallels in-process control and release testing by the manufacturer to ensure the quality and efficacy of each individual product dose. For vaccines, for example, this provides a high level of confidence for patients and public health because vaccines with low efficacy would not protect individual recipients from infectious disease, nor would they inhibit spread of infectious diseases in a population. Unsafe vaccines would possibly harm healthy individuals and children receiving vaccines to protect their health.

Research at the Paul-Ehrlich-Institut

Right from the beginning the Paul-Ehrlich-Institut has focused its research on applied and basic topics related to biomedicines. This goes back to its founder, Paul Ehrlich, whose fame is based on his success with experimental testing of diphtheria toxin as a biomedicine and on his visionary contributions to immunology. Currently, the different research groups at the Paul-Ehrlich-Institut are working in four main areas in the field of "experimental vaccines, therapies and diagnostics", scientists study, e.g., the mechanisms of gene

transfer and cell therapy medicinal products. "Host interactions with pathogens and retroelements" are important because understanding the mechanisms by which different pathogens cause diseases may lead to novel treatment and prevention strategies. Studying "immune activation and evasion" fosters a better understanding on how the immune system is activated to respond to pathogens. This knowledge may also contribute to vaccine development against novel targets such as certain viruses or tumours. Another area of the research in the Paul-Ehrlich-Institut focuses on "safety, efficacy, and quality of biomedicines" by developing and validating novel test methods for the appropriate examinations of biomedicines. This is particularly important for innovative medicinal products, and for new emerging diseases. An illustrative example for research performed at the Paul-Ehrlich-Institute is the development of new lentiviral vectors for gene transfer. The idea of gene transfer is to treat inherited diseases by replacing the defect gene with a functional copy of this gene. Lentiviral vectors are frequently used for these genetic modifications since they can enter cells of the haematopoietic system. Current safety and efficacy limitations of these viral gene vectors are for example due to the broad range of cells that can be infected. Paul-Ehrlich-Institut researchers are engineering lentiviral vectors to restrict the gene transfer to a targeted cell population of interest. This work not only helps to facilitate gene transfer, but also contributes to the understanding of the possibilities and challenges with which the manufacturers of gene therapy products are confronted. The Paul-Ehrlich-Institut also develops tools to assure the safety of biological and biotechnological medicinal products. As already described, the Paul-Ehrlich-Institut performs official experimental batch testing for biomedicines such as immunoglobulins or vaccines, independent of the manufacturer, thus providing an essential contribution to the safety of the biological medicinal product. The experimental research conducted at the Paul-Ehrlich-Institut is an indispensable basis for the fulfilment of its duties, ensuring excellent knowledge and expertise of the scientific staff, to base their assessment of the dossiers of biomedicines on first-hand research experience. It also allows the Paul-Ehrlich-Institut to provide health policy decision-makers with competent expert advice on biomedicine-relevant issues.

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REGULATORY COMPLIANCE AS A PREREQUISITE FOR LEAN DRUG DEVELOPMENT

Dr. Julia Wellsow

- When developing a drug product, every company aims for a lean development process, which is focused on the target to obtain an international marketing authorisation within the shortest possible time. One important measure speeding up the development and authorisation process is ensuring regulatory compliance as early as possible during drug development.

What is regulatory compliance?

Regulatory compliance means the adherence to all regulatory requirements relevant for the respective drug product throughout the complete life cycle of the drug product. This includes not only legal and marketing authorisation aspects, classically referred to as regulatory affairs, but does in fact comprise the complete package of pharmaceutical, toxicological, medical, and regulatory affairs. A vast variety of regulations, directives and guidelines exist with regard to the drug development and authorisation process in Europe.

To ensure drug product approval within the shortest possible time and thus an early market entry, substantial understanding of regulatory requirements for development and for the drug authorisation processes is most important. While larger drug companies can usually afford bundling this knowledge within various departments of their enterprise, smaller companies such as biotech or advanced therapy start-ups may not have the resources to set up a modern "all-in-one" regulatory affairs department and therefore would most often need to rely on external consulting by specialised experts and contract organisations. Since the necessity to comply with regulatory requirements begins early on in the drug development process, it is generally advisable to integrate regulatory competence as early as possible.

Biotechnological and other innovative drug products, such as e.g. advanced therapy medicinal products, present a special challenge in this respect, since the products are much more complex than small molecule products, and so are the respective regulatory requirements.

How can external regulatory experts help ensure regulatory compliance?

At the latest when the proof-of-concept has been established for a new drug, the following steps including preclinical and clinical studies will need careful planning. Very often a first-in-human Phase I study is seen as a first milestone to be reached. In most cases a Scientific Advice at a competent authority is useful at some stage(s) during the development process. The most suitable approach ensuring a lean development process varies from drug product to drug product, and identifying essential development steps requires substantial experience with regard to regulatory needs. Experienced regulatory consultants can help with the coordination of the development and ensure that regulatory needs are suitably considered.

At various stages during a drug products' life cycle the need will arise to submit certain documentations to the competent authorities. This is not only the actual submission of the application for marketing authorisation in CTD structure (Module 1 - 5), but also during the development process submissions will have to be made, e.g. before a Scientific Advice and before starting clinical studies in form of an Investigational Medicinal Product Dossier (IMPD) and an Investigator's Brochure (IB). Once the drug product is authorised, pharmacovigilance observations will need to be documented and reported. These documentations need to comply with very specific requirements, which raises the need that data are recorded and processed in compliance with these requirements as early as possible during drug development. While a large drug company might have suitable documentation systems available, this will be more difficult for smaller drug companies which may want to outsource data organisation for regulatory purposes.

In the following specific aspects of regulatory compliance with regard to pharmaceutical quality, preclinical studies, clinical studies, and data documentation are discussed.

Why consider pharmaceutical quality early in the development?

Concerns regarding pharmaceutical quality run like a thread through the complete development process and the life cycle of a drug product. According to our long experience, these are unfortunately often missed in the beginning of the development process, which can have substantial impact on later stages of the development, particularly in the case of complex biotechnological and other innovative drug products.

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The pharmaceutical quality of the drug product used for preclinical studies should be comparable to the pharmaceutical quality of the drug product used for clinical studies and for the market once the drug product is authorised. Comparability in terms of pharmaceutical quality needs to be documented. This means that consideration has to be given to the pharmaceutical quality of the drug substance and the drug product before the start of preclinical studies and any modification during development must be continuously assessed with regard to their scientific and regulatory impact.

One needs to be aware of the fact that the pharmaceutical quality of the drug product and the drug substance can have substantial influence on the outcome and interpretation of preclinical and clinical studies. The rationale behind it is that, for instance, the impurity profile of a drug substance or drug product may influence the toxicity and even the efficacy of a drug product. This is particularly the case for biotechnological products where the drug substance is rarely a pure protein, but often a mixture of various protein variants. The immunogenicity of a protein product may also be strongly influenced by its impurity profile.

For biotechnological products, the composition of the drug substance in terms of protein variants and the impurity profile strongly depends on the synthesis and purification process. During early development of a biotechnological drug product the synthesis and purification process and the analysis of the drug substance may not have been ultimately optimised and will be subject to change at a later stage. Most often an upscale of the synthesis process has not yet taken place.

The above considerations not only apply to biotechnological products, but also to the broad variety of advanced therapy medicinal products.

With regard to the required comparability of drug product(s) used during the development stages, reference samples of the drug substance and drug product(s) used during all studies should be retained in order to be able to re-analyse these samples, e.g. in case more sensitive analytical methods have been developed. In case the applicant is not able to show comparability, it cannot be excluded that the authorities request that e.g. certain preclinical studies are repeated before the clinical studies can be started, and even clinical studies may require repetition.

Moreover, the chosen packaging for the drug substance and the drug product needs careful consideration. In case plastic packaging materials are chosen, the drug product may need to be investigated with regard to leachables from the plastic that may have effects on the safety of the

drug product. In addition, particularly with proteins administered in low doses, the observation that the drug substance is adsorbed to the plastic packaging material is not uncommon, and can result in loss of efficacy. The stability of drug substance and drug product in the chosen packaging material needs to be addressed before clinical studies can be started.

Manufacture in a GMP regulated environment is mandatory for drug products used in clinical studies. In order to ensure comparability it is always advisable to start production in a (c)GMP regulated environment as early as possible.

The pharmaceutical quality of the drug substance and the drug product needs to be documented within the IMPD before a clinical study can be started. The complexity of the documentation for pharmaceutical quality depends on the type of the investigational medicinal product and also on the clinical study phase. The IMPD needs to be compiled in accordance with relevant regulations and guidelines, which regulate the structure of presentation and the level of detail needed at a certain stage.

When suitably planned, the IMPD can later be used as a basis for the more comprehensive pharmaceutical quality documentation of drug substance and drug product required for marketing authorisation in CTD format.

What needs to be considered during preclinical development?

Particularly for biotechnological and other innovative drug products the general concepts of designing preclinical studies as applicable for small molecules cannot be followed without being critically surveyed, and most often preclinical study programmes specific for the particular drug product have to be designed. This includes, for instance, choosing a relevant animal species and considering specific risks associated with the particular drug product. Close cooperation with toxicological experts is advisable. In order to plan the preclinical study design, the target disease, the route of administration, and the intended dosage regimen should ideally be known for the drug product.

Since very often no specific guidelines exist for innovative biotechnological drug products with regard to toxicological studies, a Scientific Advice at a competent authority may be advisable. This ensures that the chosen preclinical study programme will be acceptable when submitting the IMPD for clinical studies. A Scientific Advice meeting at a competent authority needs careful preparation. The authorities expect that the applicant only discusses those questions that are not



covered by regulatory guidelines. Early involvement of an experienced regulatory specialist is strongly recommended in order to maximise the company's benefit from such meetings.

What is important with regard to clinical studies?

Protection of the people enrolled in a clinical study should be of highest priority. Toxicological results from preclinical studies should therefore be the basis for dose finding and implementing safety measures. This is particularly important for highly effective drug products, and special guidelines exist for these kinds of products, all of them focussing on enhancing drug safety, i.e. assessing potential risks and implementing measures for a safe use. Since very often a case-by-case approach is necessary, experienced regulatory specialists can help enhancing interpretation of these guidance documents.

The study design of clinical studies is no trivial task and requires a certain amount of experience. The relevant patient population, suitable study endpoints, and the location for the study need to be chosen. Clinical studies with conceptual weaknesses should be avoided as these may fail to demonstrate the efficacy of the drug product. A Scientific Advice with a competent authority may prove useful to ensure acceptance of the study during drug product authorisation.

Quality management during conduct of the clinical study is most important and should be surveyed by experienced experts. This includes e.g. monitoring of the study and process audits. Study results have to be adequately processed and study reports have to be compiled following the relevant regulatory requirements. Since many clinical studies are conducted within classical research environments, the awareness towards regulatory requirements with regard to data documentation and reporting should be sufficiently supported. Current studies not being conducted and reported according to GCP/ICH requirements will not be accepted as pivotal data and may not even be considered as supportive data.

Moreover, one should be aware of the fact that when developing a new drug product the potential use in children needs special consideration, which requires approaching early the paediatric committee and, usually at the end of Phase I, submitting a Paediatric Investigation Plan (PIP).

What are the requirements regarding data documentation?

Complete electronic submission in eCTD structure is required for EMEA submissions within the centralised procedure from July 2009 onwards,

and also for submission to national authorities (e.g. within a decentralised procedure (DCP) or a mutual recognition procedure (MRP)) electronic submission is increasingly required. This poses additional and complex demands on document preparation.

It makes sense to put all data in a central repository already at an early stage during drug development. All data will then need to be processed in accordance with ICH eCTD requirements.

This means, for instance, the use of a certain file structure and certain file names, the creation of searchable pdf files, bookmarking and tagging, and the use of defined hyperlinks and cross-references. Use of that database can already be made for the IMPD and later for preparation of the files for marketing authorisation.

What post-approval activities are required?

The risk management plan that must be submitted with the application for marketing authorisation describes the risk management system chosen for the specific drug product. This includes post-authorisation studies (Phase IV studies) with much larger patient populations in order to further evaluate the risk-benefit ratio of the new drug product as well as all pharmacovigilance activities planned. Risk management is a continuous process throughout the life cycle of a medicinal product and requires timely planning, involving regulatory expertise.

Complex and continuous safety data management according to legal stipulations and regulatory standards is necessary within the pharmacovigilance activities including e.g. safety signalling, database searches, CIOMS and E2B reporting. This requires access to relevant data bases and certain technological equipment which may not be profitable for smaller companies. Therefore various possibilities exist to outsource certain or all pharmacovigilance activities.

Conclusion

To speed up the entire drug product authorisation process, regulatory compliance should be ensured as early as possible and at all relevant steps of the drug product's life cycle. This includes the areas pharmaceutical quality, pre-clinical and clinical studies, data documentation and post-authorisation activities within the risk management system.

Integration of a regulatory full-service provider proved to be one factor of success for small and medium sized enterprises (SMEs) and should be sought as early as possible during the development in order to ensure a lean development process and an early market entry.



• sterna biologicals is a young entrepreneurial company dedicated to the development of third generation anti-sense therapy for the causative treatment of chronic inflammatory diseases, in particular bronchial asthma, atopic dermatitis and rheumatoid arthritis.

Based on more than a decade of biological and medical research sterna was founded as a spin-off of the Department of Clinical Chemistry and Molecular Diagnostics at the Philipps University of Marburg and the TransMIT GmbH - Center for Immunomodulation (an institution promoting the transfer of academic research results into economic applications).

sterna biologicals has established a novel class of therapeutic compounds for the key indications bronchial asthma, atopic dermatitis, and rheumatoid arthritis representing a highly attractive pharmaceutical market.

The rationale of sterna biologicals' approach for identifying desirable therapeutic compounds is to interfere with the most relevant key events in the disease causing cascade that are responsible for the development of the inflammatory response. This has been achieved by sterna biologicals' patented third generation anti-sense molecules, so-called DNAzymes. The novel approach - as the name already indicates - is that these compounds are enzymatically active DNA structures with all the inherent advantages of this type of compound which contrasts well with other anti-sense therapies.

This principle has already been successfully proven for the GATA 3 mRNA-specific DNAzyme with regard to efficacy, side effects, off-target effects including escalating dose response in a variety of validated animal disease models for acute and chronic bronchial asthma.

The key success factors of sterna biologicals are related to the unique mode of action allowing intervention at a point of the natural course of the inflammatory diseases resulting in a causative treatment effect without stimulation or suppression of other immunological mechanisms. The causative effect stems from catalytic elimination/destruction of mRNAs that encode early key molecules in the signaling cascade that cause and maintain each specific inflammatory process. Thus, the cascade is interrupted at the earliest possible point at the origin of the disease.

The corporate goal is to develop therapeutic DNAzymes from animal models to Clinical Phase II trials. But especially for a small start-up company it's a long and winding road to get there. First (and big) step is to manage preclinics and file a sufficient and promising submission of the study to the ethics commissions and the regulatory authorities.

BIOTECH START-UPS AND CONTRACT RESEARCH ORGANIZATIONS FORMING WINNING TEAMS

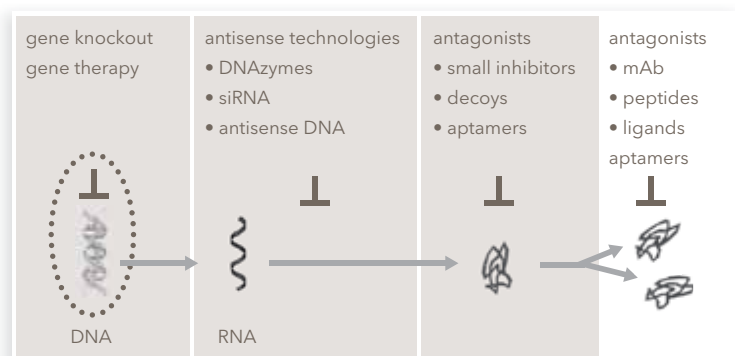
A CASE STUDY

PD. Dr. Holger Garn, Dr. Joachim Bille

Because of the newness of both, class of sterna's therapeutic molecule and therapeutic approach, there was few experience regarding preclinical study outlines as well on the side of service providers (e.g. for toxicological studies) as on the side of the authorities. So we early decided to get the help of an experienced and well established CRO (from Hessen) to achieve our aim: to get as quick and as cost effective as possible into a First-in-Man study. The experts helped us to structure steps and milestones. Together we prepared for and obtained an invaluable Scientific Advice from the BfArM regarding toxicological studies and currently are preparing another regarding pharmaceutical quality. The CRO-team taught us to plan preclinics from the sight of the needs of later clinical studies (application route, estimation of dosing in man, favoured inhalation device etc.). They helped us avoiding short-term AND long-term costs by concentration on the minimum requirements for an early approval of the First-in-Man study, but not disregarding necessary preclinical work which may be essential for later clinical phases (e.g. repeated dose toxicology). Summing up, our urgent advice to biotech start ups in the field of therapeutics is to get expert monitoring by an experienced (in the field of clinical AND preclinical studies) contract research organization.

Figure:

Potential points of therapeutic interference within and outside the cell to block the generation of proteins involved in the inflammatory cascade. Whereas interference at the DNA level is a more hypothetical possibility due to its irreversibility the direct interference with the mRNA is the earliest point of action to inhibit the generation of a specific protein.



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INVESTIGATOR-INITIATED TRIALS

Dr. Torsten Arndt, Dr. Silke Busch

● Academia has been and still is the pool for innovative therapies and clinical trials, which are crucial for medical progress and the development of novel therapeutic concepts. Investigator-initiated trials (IITs) have a long tradition at University hospitals and represent an important aspect of medical research, translating discoveries made in basic science into novel therapies, new drugs or devices. IITs are clinical studies set off by physicians at academic medical centers. The goal of IITs is to advance and improve existing therapeutic concepts by supporting investigator-initiated research that will enhance the understanding of disease entities and provide clinicians with the most reliable evidence for careful decision-making at the bedside. A major advantage of academic translational research, particularly in a hospital setting, is direct access to patients for clinical studies. By contrast, research at pharmaceutical companies is focused on gaining knowledge of a new compound and bringing out new products, however, IITs are patient-oriented and designed to optimize an already known therapy.

To further address the benefit for patients, especially in indications with so far unmet medical need, it is crucial to come up with novel innovative therapeutic concepts. These include studies such as diagnostic and therapy optimizing trials, applying modern genotyping and phenotyping methods of important polymorphisms (SNPs), personalized medicine and adaptive study designs, investigating the combination of existing drugs and the development of orphan drugs. Patients will benefit due to early access to novel, innovative therapies that is provided by these dynamic clinical research efforts. Most significantly, IITs represent the clinical translational efforts of academic centers and underline researchers' commitment to innovation for patients.

Many times IITs address issues with only marginal prospect of revenue, but commonly investigate so far inadequately solved clinical questions and enhance knowledge of particular disease mechanisms. IITs enable uncommitted clinical research and provide an environment for unbiased clinical trials. Of particular note in this respect is the need of adequate public funding. Obtaining funding for research is the greatest impediment. Generally, funding for IITs is provided by public institutions like the Federal Ministry for Education and Research (BMBF), German Research Foundation (DFG) or foundations to support non-commercial,

scientifically compelling and innovative clinical research within various fields of interest.

However, beside IITs of pure non-commercial interest, some IITs are entirely funded by industry. As the pharma industry continues to struggle to launch new drugs, it has to rely on life-cycle management of existing products to meet economic aims. In this respect, IITs became a tangible asset and are rather regarded as part of a sophisticated product development strategy by the pharmaceutical industry, than a non-profitable, science-focused merit. IIT findings not only provide clinical data to expand scientific knowledge of marketed drugs, but also further the extension of on- and off-label use in new indications to reach larger patient groups. Furthermore, IITs generate data for scientific publications and establish fruitful relationships with academic key opinion leaders. Hence, IITs proposing unique applications, possibly leading to new indications for the drug, are willingly funded by the pharmaceutical industry.

A main drawback of translational studies and related personalized medicine approaches in industry is the mandatory economical interest, whereas IITs unravel all sophistications of drug profiling narrowing medical applications. Obviously, both interests aren't necessarily mutually compatible.

However, commercial and academic research should not be considered as opponents, because both are interdependent and complementary and close ties between both partners should be encouraged.

Recently the regulatory environment for IITs has been reformed substantially. The 12th amendment of the German Drug Law (Arzneimittelgesetz, AMG) was implemented to comply with the requirements of the European Union's Clinical Trials Directive 2001/20/EC for all clinical studies on medicinal products. It defines comprehensive administrative legal requirements with regard to academic clinical research with the intention to stipulate and harmonize regulations for clinical research in respect of Good Clinical Practice (GCP).

Undeniably, compliance with GCP-guidelines ensures a valid design of the study, reliable data management and monitoring, as well as qualified analysis of study results, therefore enhancing the value and significance of the collected data. More likely, these trials generate reliable data to improve disease understanding and increase confidence in new therapeutic treatments. Therefore, investigators appreciate the importance of methodological rigour.

But the increased regulatory burden confronts investigators with almost unsolvable tasks and is regarded to substantially hamper independent

clinical research. Due to the stringent regulations, a basic prerequisite for IITs is adequate assistance of the investigator in fulfilling the regulatory requirements, guidelines and procedures. Planning and implementation of an IIT demands specialized knowledge of regulatory issues, drug safety and quality management. In this respect, performing an IIT according to the new legal environment requires a service for clinicians and academic researchers to tackle the increased regulatory obligations. It requires professional organisational structures, a highly trained staff and close cooperation with specialised experts, such as project managers, statisticians, data managers, pharmacists and monitors. Based on the emerging recognition of the value of non-industry originating studies, the structures and resources for investigator driven trials in academia are increasingly provided, especially through translational medicine centers like the Center for Drug Research, Development and Safety (Zentrum für Arzneimittelforschung, -Entwicklung und -Sicherheit, ZAFES), leading to the implementation of centralized service institutions.

Clinical Trial Center Rhine-Main (Klinisches Studienzentrum Rhein-Main, KSRM)

The KSRM, as an integral part of ZAFES, provides a competent staff, the expertise and efficient management structure regarding the conception, implementation and monitoring of clinical studies to support independent patient-oriented clinical research by physicians. The KSRM was supported by a triennial grant of the Hessen Ministry of Economics, Transportation and Regional Development (Hessischen Ministerium für Wirtschaft, Verkehr und Landesentwicklung, HMWVL) in order to implement a sustainable infrastructure for clinical research in the Rhine-Main region. The network build up by the KSRM integrates mainly university teaching hospitals, but is in principle

open to all regional hospitals and physicians in private practice and therefore provides a large patient pool crucial for considerably faster execution of clinical studies. Notably, the in-house Phase I unit provides capacities customized for most Phase I trial designs, continuous safety monitoring and is backed up by the cooperating hospital emergency care unit, to assure a high degree of individual medical care for all trial subjects. Within this setting there is the option to conduct first-in-man trials, bioavailability/bioequivalence and PK/PD studies, to rapidly translate therapeutic concepts from the laboratory to the clinic. The KSRM guarantees a close contact to opinion leaders in the respective field and substantially contributes to the competitive position of the Frankfurt region in the field of clinical research. The KSRM aims to represent a balanced portfolio of both innovative publicly funded IITs and clinical trials on behalf of sponsors from the pharmaceutical industry, the latter to continuously benchmark quality measures against industry standards.

Coordination Centers for Clinical Trials (Koordinierungszentren für Klinische Studien, KKS)

In addition to the KSRM in Frankfurt the Coordination Center for Clinical Trials (KKS) in Marburg complements the highly competitive environment for compelling science-initiated trials in Hessen. The KKS Marburg belongs to the KKS network of 12 sites throughout the country, funded by the BMBF, as a platform for transparent, patient-oriented development of new drugs and therapeutic principles in Germany. Furthermore, within the KKS network paediatric trials are supported in special modules to enable the conduct of ethi-



cally sound and qualified drug trials with children, to counteract the common practice to translate results from studies with adults to children, often inadequately taking into account the unique pharmacology of children. In addition to that, the KKS network is engaged in the organisation of training and further education in the areas of clinical pharmacology, investigator courses, study nurses, documentation, quality management, regulatory guidelines, monitoring, data management and biometrics.

ZAFES

Excellent academic networks are the key for innovative drug discovery and development projects. Academic medical centers can actively promote the discovery and development of novel drugs by combining their expertise in basic and clinical science with the know-how of pharmaceutical and biotechnology companies. To effectively manage this interface, ZAFES was launched at the Goethe University of Frankfurt integrating hospitals and academic centers to develop, manage, and implement corporate alliances, design the optimal structure for cooperations, negotiate actual partnership agreements and provide project management for collaborative projects. ZAFES implemented a structure to collect, integrate, and disseminate the intellectual, organizational, and resource infrastructure needed to promote and support multidisciplinary research collaborations, being considered to be a key factor for successful translational research. The ZAFES platform promotes university research ideas and inventions, expands and manages industry-academic collaborations and accelerates the translation of biomedical research into therapeutic applications to rapidly deliver new drugs to the patients. In addition the KSRM enables researchers to

evaluate a scientific rationale in a clinical research setting seamlessly, thus supporting a bench to bedside approach. Furthermore, ZAFES trains the next generation of clinical and translational researchers and creates an environment in which investigators have a clearer career path in the highly rewarding discipline of translational research. ZAFES is a partner for the pharmaceutical industry and biotech companies for joint-projects at all stages of the value chain of drug discovery and drug development and provides essential academic core technology facilities.

In conclusion, there is a continuous need for conducting IITs to assess novel and complex therapeutic concepts to enable evidence based decision-making in medical care, whether in a completely independent manner funded by public grants or sponsored by the pharmaceutical industry. As compared to international standards clinical research in Germany is only mediocre regarding number of scientific publications, quantity and impact of clinical studies across the board. There is a distinct awareness to substantially further expertise in clinical research and effectively counteract the increasing allocation of clinical trials abroad. Therefore it is of strategic interest to address the establishment of the required infrastructure for clinical research and continuous education and training of physicians in the field of study concept development, coordination and regulatory processes. Of particular note in this respect is Hessens special position, because the large number of resident pharmaceutical companies, biotech firms and CROs along with a vital academic research environment represent a unique cluster for compelling biomedical research and constitute the driving force for novel, innovative medical therapies.

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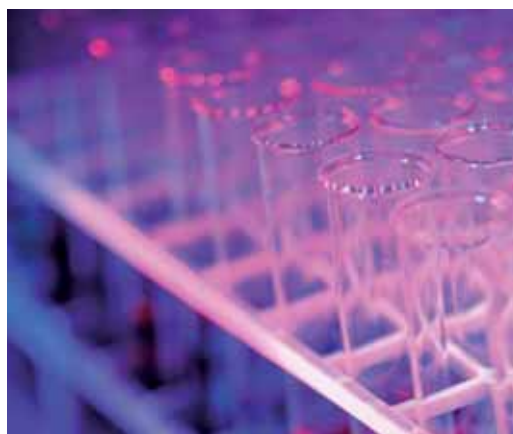
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• The protection of patients during a clinical trial is one of the most important issues in human research; this has been addressed by the Declaration of Helsinki, the European Convention of Bioethics and also in many statutes of medical science. In accordance with European guidelines, the latest amendment of the German Drug Law (AMG § 40) requires the explicit approval of an ethics committee (EC) for a clinical study with drugs. The trial has to be submitted by the sponsor of the trial and the submission has to be addressed to the EC responsible for the principal investigator of a single center study or the principal coordinating investigator of a multi-center trial. Such ethics committees are present at almost every medical faculty (according to the university laws of each province state) and for non-university researchers at each chamber of physicians of a province state. Further details on the work and coordination of these ethics committees are outlined in a guideline supplementary to the German drug law (GCP-V). These procedures ensure a standardized process for the trial (i.e. all study documents such as patient information and consent forms will be similar nationwide) in a timely fashion (usually, 30 days for single center trials and 60 days for multi-center trials). Further EC-activities are the review of substantial protocol amendments and the appraisal of the suitability of a study site and the qualification of the investigator. Since adoption of the new guidelines in 2004, the submission procedure and requirements for the study documents between the different committees throughout Germany have now been widely harmonized, facilitated by the activities of the so called "Arbeitskreis Medizinischer Ethik-Kommissionen in Deutschland".

The EC review of a study protocol and related documents is done by competent experts in the corresponding clinical field of the research project. The (honorary) members are nominated by the governing bodies of the medical faculties or the Physicians Chamber. The composition of an EC follows the requirements of the AMG and ICH-GCP. At least one member is independent from the institution, at least one has a primary area of interest in a nonscientific area, one is a pediatrician and one is an expert in methodology (e.g. biometrician or pharmacologist).

The review focuses on the validity of study rationale, the adequacy of the study design and sample size for reaching the study goals, the risk-benefit ratio and the documents used for the informed consent. Several reference guides have been published which describe the principles of the review process (see Reference List). The appraisal of the study site and its investigators base on the review of its technical equipment incl. resuscita-

THE WORK OF THE ETHICS COMMITTEES IN HESSEN

Prof. Dr. med. Sebastian Harder

tion facilities, the experience of the investigator in the field of clinical trials, the number of parallel studies performed in this center (to ensure fair allocation of eligible patients) and the certification of the trial staff.

In the federal state of Hessen, there is an ethics committee at each of the 3 medical faculties (Frankfurt, Gießen, Marburg) and one ethics committee at the physicians' chamber of Hessen located in Frankfurt (application and addresses see below). The two ethics committees in Frankfurt share some members, but work independently. However, the principal rules for the format and wording of study documents, e.g. the informed consent are the same, and there is close cooperation between these two ECs, as many clinical trials are performed at the medical department, but involve co-investigators from adjacent teaching hospitals. There is also close cooperation with the other ECs which is coordinated by the Ministry of Social Affairs (which is responsible for the Health Sector). Recently, all ECs in Hessen adopted a common format for the submission and the submission fees. All ECs are accredited by the competent authorities (i.e. BfArM or PEI) and working in compliance with FDA regulations. Thus, in Hessen, a high degree of cooperation within the ECs and the applicants is ensured.

Application procedure for studies, according to the German Drug Law (AMG): Each EC has a detailed web-site which gives clear instructions on how to submit a study and the format of the application (see below). EC meetings are usually in monthly intervals. Furthermore, EC staffs will advise applicants (sponsors and investigators)



who are not familiar with the German or EU regulations e.g. the EudraCT registry, the application to the competent authorities (see above) and registration with the local administration authorities (RP).

If the coordinating or principal investigator is affiliated with the university hospital of Frankfurt (Klinikum der J.W.Goethe-Universität), the responsible EC is that of the medical department (<http://ethik-kommission.klinik.uni-frankfurt.de>). If the coordinating or principal investigator is affiliated with the university hospital of Gießen (Klinikum der Justus-Liebig-Universität) or one of the official teaching hospitals of this medical faculty, the responsible EC is that of the medical department of Gießen (<http://www.med.uni-giessen.de/infoweb/intranet/ethik>). If the coordinating or principal investigator is affiliated with the university hospital of Marburg (Klinikum der Philipps Universität Marburg) or one of the teaching hospitals affiliated with this medical faculty, the responsible EC is that of the medical department of Marburg (<http://www.med.uni-marburg.de/stpg/zentr/ethikkomm/webneu/index.html>). The EC of the Physicians' Chamber (http://www.laekh.de/Aerzte/Aerzte-Rund-ums-Recht/Aerzte-Rund-ums-Recht-Ethik-Kommission/Rund_ums_Recht_cat367.html) is the responsible EC for all other study sites (hospitals or ambulatory care) in Hessen. After confirmation of receipt of a valid submission (i.e. all documents required according to § 7 of the national GCP-directive), applicants will get their approval or rejection within 30 days for single center and 60 days for multi-center studies, unless the submitted documents are subjects of concern or not complete enough to fulfill GCP-requirements. However, any objections by the EC can only be made once,

and the time frame for notification of approval or rejection is expanded until the applicant has supplemented the documents or otherwise responded. The submission to the competent authorities has to be made simultaneously, and, after getting approval of the study, the study has to be registered with the local administration authorities (i.e. Regierungspräsidium RP). The application procedure for studies according the German Law for Medicinal Products (MPG) follows a similar pathway, with some variations (see websites for detailed guidelines).

Since the substantial changes of the AMG in 2004, time and experience with the new regulations has elapsed. Although the EU-wide harmonization has been welcomed by most pharmaceutical companies, smaller companies and particularly independent researchers of so called "Investigator Initiated Trials" (IIT) have criticized the burden caused by e.g. the requirements of SUSAR-reporting, the need for extensive labeling of the study medication or the EC appraisal of each single investigator. The Commission Directive 2005/28/EG and a draft guidance on 'specific modalities' for non-commercial clinical trials (Title: draft guidance on 'specific modalities' for non-commercial clinical trials referred to in Commission Directive 2005/28/EC laying down the principles and detailed guidelines for good clinical practice; disseminated in June 2006 but not adopted yet) have taken these concerns into consideration, but several problems regarding harmonization of procedures remain unsolved.

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• The Regional Board Darmstadt, the largest of the three Hessian Regional Boards, has more than 5,000 functions in the areas of health, integration, aliens law, regional planning, building and construction trades, economy, transport, labor and environmental safety, agriculture, forestry, nature conservation and consumer protection.

The employees provide contact points for 3.8 million citizens, for cities and municipalities, the economy, industry, service industry, associations, as well as other organizations in the region Rhine-Main / Southern Hesse.

The Regional Board Darmstadt has currently approx. 1,600 employees with a wide range of experts in the fields of legal, administrative, economical, natural and engineering sciences, human medicine, veterinary medicine and pharmacy.

Principal services of the Regional Board Darmstadt are:

- active participation in and shaping of regional development
- safeguarding of the business location, as well as the international competitiveness of Hessian companies
- preventive risk minimization, also in complex approval procedures
- supervision in the interest of security and quality of life

The exercise of functions of the Regional Board Darmstadt is carried out:

- in accordance with the rule of law
- cooperatively
- in a citizen-oriented manner
- securing a balance of interests

COMPETENCE AND COMMUNICATION

MISSION STATEMENT OF THE MONITORING AUTHORITY

Some functions are carried out for the entire state of Hesse. These include pharmacovigilance.

The following activities of the two pharmaceutical departments of the Regional Board Darmstadt are a priority:

- supervision of the traffic of drugs and active agents at manufacturers, pharmaceutical entrepreneurs, wholesalers and retailers as well as in pharmacies
- execution of permission, approval and certification procedures required according the Arzneimittel- und Apothekengesetz (the German Drug and Pharmacy Law) for the production and distribution of drugs on the national, European and international market
- supervision of clinical trials of drugs on humans for approx. 1,500 clinical trial physicians, approx. 50 commission research institutes and approx. 40 sponsors

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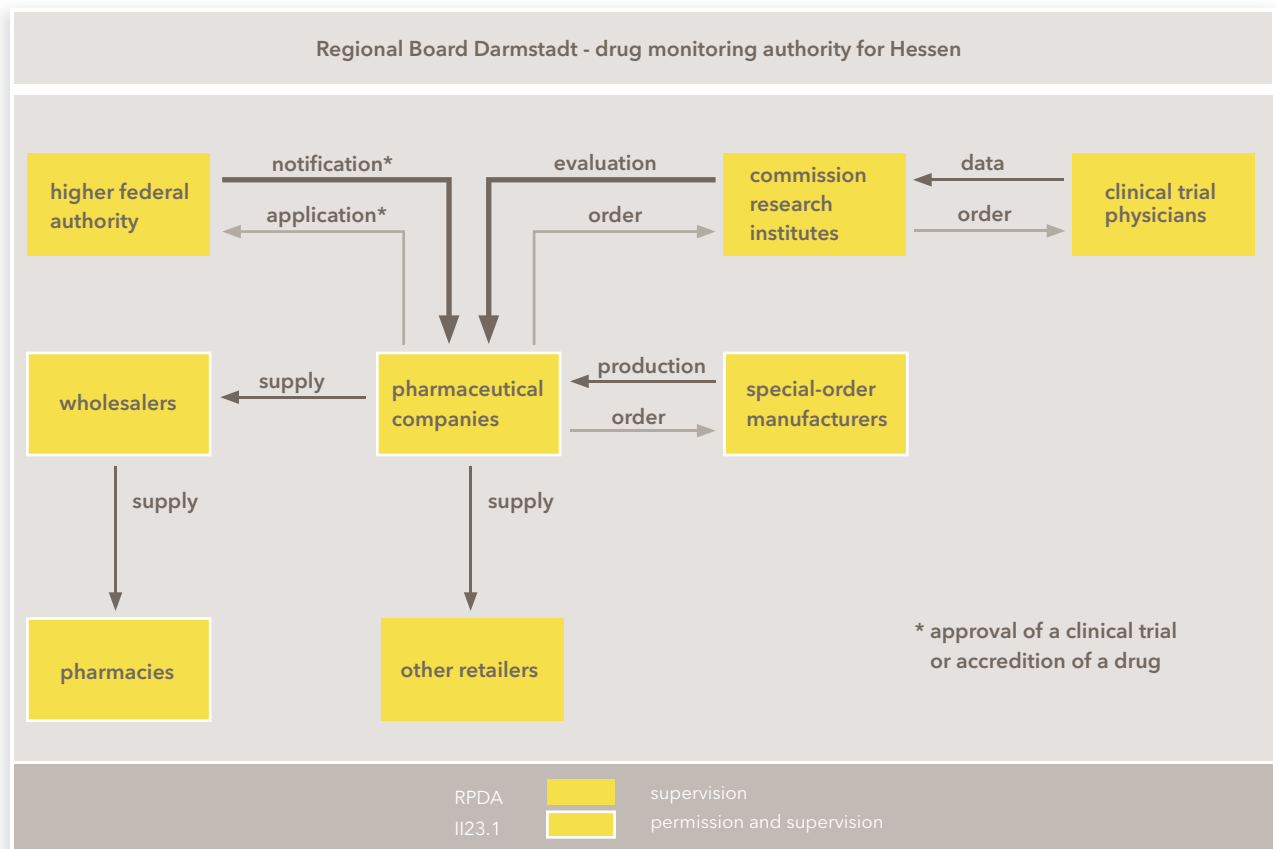
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Susanne Huber





Within the framework of supervision of clinical trials of drugs on humans, the Regional Board Darmstadt mediates between the interests of public welfare and the interests of institutions and people involved and works towards a fair balance of interests, although the protection of patients and test persons has the highest priority.

During the supervision of clinical trials of drugs on humans, the Regional Board Darmstadt focuses particularly on:

- an optimum of patient protection through a systematic and risk-based supervision approach
- effective and committed communication with clinical trial physicians, commission research institutes, sponsors, collegiate authorities and higher federal authorities
- quality and transparency during inspections in order to ensure compliance with national and international normative provisions

- competence, qualification and independence of inspectors
- modern data techniques
- orientation of the extent of supervision on the degree of autonomy and readiness to cooperate
- solution-oriented and constructive conflict resolution
- active and continuous dialogue through the organization of specialist conferences in order to discuss the regulatory rules
- quality assurance through defined standards and target agreements
- stable presence in the federalwide professional group of experts

Company Profiles

A.CRO Clinical Research Services
Accovion GmbH
Alcedis GmbH
Amantec GmbH
Averion Europe
Chiltern International
clinicalworks GmbH
C.R.O.Cont(r)acts
DR. RIETHMÜLLER M/R/S
ECRON ACUNOVA
ERGOMED
GBG Forschungs-GmbH
ICON Clinical Research GmbH
Koordinierungszentrum für klinische Studien
Klinisches Studienzentrum Rhein-Main (KSMR)
Medical Consulting - Klaus Goldschmidt
NeuroCode AG
Omega Mediation GmbH
Omnicare Clinical Research GmbH
PAREXEL International GmbH
PAZ Arzneimittelentwicklungsgesellschaft mbH
PharmaPart GmbH
PharmaProjekthaus GmbH & Co. KG
Praxis Klinische Arzneimittelforschung
Premier Research Germany
Quintiles GmbH
SciNuTec GmbH
SCRATCH Pharmacovigilance Services
SKM Oncology Research GmbH
Trilogy Writing & Consulting GmbH
YES Pharmaceutical Development Service GmbH
Zentrallaboratorium Deutscher Apotheker e. V. GmbH

A.CRO Clinical Research Services GmbH

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Type and range of services provided

- General consultation in the area of clinical research
- Trial plan: design of the trial protocol
- Trial plan: design of the CRF (Case Report Files)
- Training and further education (e.g. training in GPC etc)
- Audit- and compliance services
- Monitoring
- Selection and acquisition of trial centers and physicians
- Acquisition of patients
- Data management / databases / biostatistics etc.
- Supervision of procedures for authorization of the study:
Submission to the Senior Federal Authority
- Supervision of procedures for notification of the Regional
Supervising Authority

Customer Groups

- Start-up
- Producers of Generics
- Mid-sized pharmaceutical companies
- Big Pharma
- Other CROs

Type and range of services provided

- General consultation in the area of clinical research
- Trial plan: design of the trial protocol
- Trial plan: design of the CRF (Case Report Files)
- Training and further education (e.g. training in GPC etc)
- Audit- und Complianceleistungen
- Monitoring
- Selection and acquisition of trial centers and physicians
- Acquisition of patients
- Data management / databases / biostatistics etc.
- eCTD (Electronic Common Technical Document)
- Supervision of procedures for authorization of the study:
Submission to the Senior Federal Authority
- Supervision of procedures for notification of the Regional
Supervising Authority
- Approval of Drugs / Medical devices

Clinical Phases covered

- Preclinical I, II, III, IV

Customer Groups

- Start-up
- Mid-sized Pharmaceutical Companies
- Big Pharma

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Type and range of services provided

- General consultation in the area of clinical research
- Trial plan: design of the trial protocol
- Trial plan: design of the CRF (Case Report Files)
- Training and further education (e.g. training in GPC etc)
- Audit- and compliance services
- Monitoring
- Selection and acquisition of trial centers and physicians
- Acquisition of patients
- Data management / databases / biostatistics etc.
- eCTD (Electronic Common Technical Document)
- Supervision of procedures for authorization of the study: Submission to the Senior Federal Authority
- Supervision of procedures for notification of the Regional Supervising Authority
- Approval of Drugs / Medical devices
- Other Services: web-based tumor documentation system for online conference systems , web-based study documentation, web-based registry

Clinical Phases covered

- I, II, III, IV

Indication areas

- Oncologie

Customer Groups

- Start-up
- Big Pharma
- Other: Universities

Type and range of services provided

- General consultation in the area of clinical research
- Trial plan: design of the trial protocol
- Trial plan: design of the CRF (Case Report Files)
- Training and further education (e.g. training in GPC etc)
- Audit- and compliance services
- Monitoring
- Selection and acquisition of trial centers and physicians
- Acquisition of patients
- Data management / databases / biostatistics etc.
- Supervision of procedures for authorization of the study: Submission to the Senior Federal Authority
- Supervision of procedures for notification of the Regional Supervising Authority
- Approval of Drugs / Medical devices
- (Quality) management of distribution of clinical trial supplies
- (Quality) management of storage of clinical trial supplies
- (Quality) management of import of clinical trial supplies
- Security supervision and coverage

Customer Groups

- Start-up
- Producers of generics
- Mid-sized pharmaceutical companies
- Big Pharma
- Other CROs
- Other: Medicinal Products

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Type and range of services provided

- General consultation in the area of clinical research
- Trial plan: design of the trial protocol
- Trial plan: design of the CRF (Case Report Files)
- Training and further education (e.g. training in GPC etc.)
- Audit- and compliance services
- Monitoring
- Selection and acquisition of trial centers and physicians
- Acquisition of patients
- Data management / databases / biostatistics etc.
- eCTD (Electronic Common Technical Document)
- Supervision of procedures for authorization of the study: Submission to the Senior Federal Authority
- Supervision of procedures for notification of the Regional Supervising Authority
- Approval of Drugs / Medical devices
- (Quality) management of production of clinical trial supplies
- (Quality) management of distribution of clinical trial supplies
- (Quality) management of storage of clinical trial supplies
- (Quality) management of import of clinical trial supplies
- Security supervision and coverage
- Electronic Reporting (e-Pharmacovigilance and E2B)
- Other: EDC; IVRS (Interactive Voice Response System); Pharmacovigilance; Endpoint Adjudication Committees; Medical Writing; Training

Clinical Phases covered

- Preclinical I, II, III, IV

Indication Areas

- Cardiology, Oncology, Medical Devices, Vaccines, Neurology, Dermatology

Groups of agents / substances

- Biopharmaceuticals, Small Drugs, Dietary Supplements, Functional Food, Medical Devices, Diagnostics

Customer Groups

- Start-up
- Mid-sized Pharmaceutical Companies
- BigPharma
- Other: Medical Devices; Other medical centers (for investigator initiated trials)

Type and range of services provided

- General consultation in the area of clinical research
- Trial plan: design of the trial protocol
- Trial plan: design of the CRF (Case Report Files)
- Training and further education (e.g. training in GPC etc.)
- Audit- and compliance services
- Monitoring
- Selection and acquisition of trial centers and physicians
- Data management / databases / biostatistics etc.
- Supervision of procedures for authorization of the study: Submission to the Senior Federal Authority
- Supervision of procedures for notification of the Regional Supervising Authority
- Approval of Drugs / Medical devices
- Security supervision and coverage
- Other
- EDC Support

Clinical Phases covered

- I, II, III, IV

Indication areas

- Oncology, Central Nervous System, Infectious diseases, Pediatrics, Women's health

Customer Groups

- Start-up
- Mid-sized pharmaceutical companies
- Big Pharma

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Type and range of services provided

- General consultation in the area of clinical research
- Trial plan: design of the trial protocol
- Trial plan: design of the CRF (Case Report Files)
- Monitoring
- Selection and acquisition of trial centers and physicians
- Acquisition of patients
- Data management / databases / biostatistics etc.
- Supervision of procedures for authorization of the study:
 Submission to the Senior Federal Authority
- Supervision of procedures for notification of the Regional
 Supervising Authority
- Approval of Drugs / Medical devices
- Security supervision and coverage

Clinical Phases covered

- Preclinical, II, III, IV

Customer Groups

- Start-up
- Mid-sized Pharmaceutical Companies
- Big Pharma
- Other CRO
- Other: Universities, Medical-Centers for IITs,
 Producer of Medical Devices

Type and range of services provided

- General consultation in the area of clinical research
- Electronic Reporting (e-Pharmacovigilance and E2B)
- Laboratory services

Clinical Phases covered

- I, II, III, IV

Customer Groups

- Start-up
- Producers of Generics
- Mid-sized Pharmaceutical Companies
- Big Pharma
- Other CROs

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Type and range of services provided

- General consultation in the area of clinical research
- Trial plan: design of the trial protocol
- Trial plan: design of the CRF (Case Report Files)
- Training and further education (e.g. training in GPC etc.)
- Audit- and compliance services
- Selection and acquisition of trial centers and physicians
- eCTD (Electronic Common Technical Document)
- Supervision of procedures for authorization of the study:
Submission to the Senior Federal Authority
- Approval of Drugs / Medical devices

Clinical Phases covered

- I, II, III, IV

Customer Groups

- Start-up
- Producers of generics
- Mid-sized pharmaceutical companies
- Big Pharma
- Other CROs
- Other: Universities

Type and range of services provided

- General consultation in the area of clinical research
- Trial plan: design of the trial protocol
- Trial plan: design of the CRF (Case Report Files)
- Training and further education (e.g. training in GPC etc.)
- Audit- and compliance services
- Monitoring
- Selection and acquisition of trial centers and physicians
- Data management / databases / biostatistics etc.
- Supervision of procedures for authorization of the study:
Submission to the Senior Federal Authority
- Supervision of procedures for notification of the Regional
Supervising Authority
- Other: Submission to ethics committees, project management, medical writing, pharmacovigilance, peri-approval studies, rescue studies

Clinical Phases covered

- I, II, III, IV

Indication areas

- Allergology, cardiovascular diseases, clinical immunology/ infectiology, dermatology, diagnostic imaging, endocrinology, ENT, gastroenterology, gynaecology, metabolic disorders, nephrology, neurology, nutrition, oncology, ophthalmology, peripheral arterial diseases, psychiatry, pulmonology, rheumatology, urology, surgery, women's health

Groups of agents / substances

- Pharmaceuticals, biopharmaceuticals, herbal medicines, small drugs, serological products, medical devices, generics, dietary supplements, nutraceuticals

Customer Groups

- Start-up
- Producers of Generics
- Mid-sized Pharmaceutical
- Big Pharma
- Other: Medical device companies, Food Industry

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Type and range of services provided

- General consultation in the area of clinical research
- Trial plan: design of the trial protocol
- Trial plan: design of the CRF (Case Report Files)
- Training and further education (e.g. training in GPC etc.)
- Audit- and compliance services
- Monitoring
- Selection and acquisition of trial centers and physicians
- Acquisition of patients
- Data management / databases / biostatistics etc.
- eCTD (Electronic Common Technical Document)
- Supervision of procedures for authorization of the study: Submission to the Senior Federal Authority
- Supervision of procedures for notification of the Regional Supervising Authority
- Approval of Drugs / Medical devices
- (Quality) management of import of clinical trial supplies
- Security supervision and coverage
- Electronic Reporting (e-Pharmacovigilance and E2B)
- Other
- Pharmacovigilance-Management

Clinical Phases covered

- I, II, III, IV

Indication areas

- Oncology, Neurology, Immunology / Allergy

Customer Groups

- Start-up
- Producers of Generics
- Mid-sized Pharmaceutical Companies
- Big Pharma
- Other CROs

GBG Forschungs-GmbH

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Type and range of services provided

- General consultation in the area of clinical research
- Trial plan: design of the trial protocol
- Trial plan: design of the CRF (Case Report Files)
- Training and further education (e.g. training in GPC etc.)
- Monitoring
- Selection and acquisition of trial centers and physicians
- Acquisition of patients
- Data management / databases / biostatistics etc.
- Supervision of procedures for authorization of the study: Submission to the Senior Federal Authority
- Supervision of procedures for notification of the Regional Supervising Authority
- (Quality) management of distribution of clinical trial supplies
- Other
- Academic Research Organization for Investigator initiated and sponsored trials

Clinical Phases covered

- I, II, III, IV

Indication areas

- Breast cancer

Groups of agents / substances

- Chemotherapy, Hormonal therapy, Immunotherapy

Customer Groups

- Big Pharma

ICON Clinical Research GmbH

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Type and range of services provided

- General consultation in the area of clinical research
- Trial plan: design of the trial protocol
- Trial plan: design of the CRF (Case Report Files)
- Training and further education (e.g. training in GPC etc.)
- Audit- and compliance services
- Monitoring
- Selection and acquisition of trial centers and physicians
- Data management / databases / biostatistics etc..
- Supervision of procedures for authorization of the study:
 - Submission to the Senior Federal Authority
- Approval of Drugs / Medical devices
- (Quality) management of storage of clinical trial supplies
- (Quality) management of import of clinical trial supplies
- Security supervision and coverage

Clinical Phases covered

- I, II, III, IV

Stoff-/Substanzgruppen

- Biopharmaceuticals, natural products, small drugs, serological products, medicinal devices

Customer Groups

- Start-up
- Mid-sized pharmaceutical companies
- Big Pharma

Type and range of services provided

- General consultation in the area of clinical research
- Trial plan: design of the trial protocol
- Trial plan: design of the CRF (Case Report Files)
- Training and further education (e.g. training in GPC etc.)
- Monitoring
- Selection and acquisition of trial centers and physicians
- Data management / databases / biostatistics etc.
- Supervision of procedures for authorization of the study:
 - Submission to the Senior Federal Authority
- Supervision of procedures for notification of the Regional Supervising Authority
- Approval of Drugs / Medical devices

Clinical Phases covered

- I, II, III, IV

Customer Groups

- Start-up
- Mid-sized Pharmaceutical Companies
- Big Pharma
- Other CROs
- Other:
 - Universities and University Research Hospitals

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Type and range of services provided

- General consultation in the area of clinical research
- Trial plan: design of the trial protocol
- Trial plan: design of the CRF (Case Report Files)
- Audit- and compliance services
- Monitoring
- Selection and acquisition of trial centers and physicians
- Acquisition of patients
- Supervision of procedures for authorization of the study:
Submission to the Senior Federal Authority
- Supervision of procedures for notification of the Regional
Supervising Authority
- (Quality) management of distribution of clinical trial
supplies
- (Quality) management of storage of clinical trial supplies

Clinical Phases covered

- I, II, III, IV

Customer Groups

- Start-up
- Producers of Generics
- Mid-sized Pharmaceutical Companies
- Big Pharma
- Other CROs

Medical Consulting - Klaus Goldschmidt

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Type and range of services provided

- General consultation in the area of clinical research
- Trial plan: design of the CRF (Case Report Files)
- Monitoring
- Selection and acquisition of trial centers and physicians
- Data management / databases / biostatistics etc.
- Supervision of procedures for authorization of the study:
Submission to the Senior Federal Authority
- Supervision of procedures for notification of the Regional
Supervising Authority
- Approval of Drugs / Medical devices

Indication areas

- Cardio-Vascular System

Groups of agents / substances

- Medical devices

Customer Groups

- Start-up

NeuroCode

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Type and range of services provided

- General consultation in the area of clinical research
- Trial plan: design of the trial protocol
- Trial plan: design of the CRF (Case Report Files)
- Selection and acquisition of trial centers and physicians
- Acquisition of patients
- Data management / databases / biostatistics etc..
- Supervision of procedures for authorization of the study:
 - Submission to the Senior Federal Authority
- Supervision of procedures for notification of the Regional Supervising Authority
- Approval of Drugs / Medical devices
- Laboratory services: - EEG, Psychophysiology
 - Sleep laboratory
 - Tele-stereo EEG
 - Hippocampal slice

Clinical Phases covered

- Preclinical, I, II, III, IV

Indication areas

- Psychiatry, Central Nervous System, Sleep disturbances, Migraine

Groups of agents / substances

- Biopharmaceuticals, Natural products, Small drugs, Dietary supplements, Functional food etc.

Customer Groups

- Mid-sized pharmaceutical companies
- Big Pharma
- Other CROs

Type and range of services provided

- General consultation in the area of clinical research
- Trial plan: design of the trial protocol
- Trial plan: design of the CRF (Case Report Files)
- Training and further education (e.g. training in GPC etc.)
- Audit- and compliance services
- Monitoring
- Selection and acquisition of trial centers and physicians
- Acquisition of patients
- Data management / databases / biostatistics etc.
- eCTD (Electronic Common Technical Document)
- Supervision of procedures for authorization of the study:
 - Submission to the Senior Federal Authority
- Supervision of procedures for notification of the Regional Supervising Authority
- Electronic Reporting (e-Pharmacovigilance and E2B)

Clinical Phases covered

- Preclinical, I, II, III, IV

Indication areas

- Neurology, Oncology, Diabetes

Customer Groups

- Start-up
- Producers of Generics
- Mid-sized Pharmaceutical Companies
- Big Pharma
- Other CROs

Omnicare Clinical Research GmbH

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Type and range of services provided

- General consultation in the area of clinical research
- Trial plan: design of the trial protocol
- Trial plan: design of the CRF (Case Report Files)
- Training and further education (e.g. training in GPC etc.)
- Audit- and compliance services
- Monitoring
- Selection and acquisition of trial centers and physicians
- Data management / databases / biostatistics etc.
- eCTD (Electronic Common Technical Document)
- Supervision of procedures for authorization of the study:
 - Submission to the Senior Federal Authority
- Supervision of procedures for notification of the Regional Supervising Authority
- Approval of Drugs / Medical devices
- (Quality) management of distribution of clinical trial supplies
- (Quality) management of storage of clinical trial supplies
- (Quality) management of import of clinical trial supplies
- Security supervision and coverage
- Electronic Reporting (e-Pharmacovigilance and E2B)

Clinical Phases covered

- I, II, III, IV

Customer Groups

- Start-up
- Producers of Generics
- Mid-sized Pharmaceutical Companies
- Big Pharma
- Other CROs
- Other: University Research Hospitals, Medical Device Companies

PAREXEL International GmbH

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Type and range of services provided

- General consultation in the area of clinical research
- Trial plan: design of the trial protocol
- Trial plan: design of the CRF (Case Report Files)
- Training and further education (e.g. training in GPC etc.)
- Audit- and compliance services
- Monitoring
- Selection and acquisition of trial centers and physicians
- Data management / databases / biostatistics etc.
- Supervision of procedures for authorization of the study:
 - Submission to the Senior Federal Authority
- Supervision of procedures for notification of the Regional Supervising Authority
- Approval of Drugs / Medical devices
- (Quality) management of import of clinical trial supplies

Clinical Phases covered

- I, II, III, IV

Customer Groups

- Start-up
- Producers of Generics
- Mid-sized Pharmaceutical Companies
- Big Pharma
- Other CROs

PAZ Arzneimittelentwicklungs- gesellschaft mbH

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Type and range of services provided

- General consultation in the area of clinical research
- Trial plan: design of the trial protocol
- Trial plan: design of the CRF (Case Report Files)
- Data management / databases / biostatistics etc.
- Supervision of procedures for authorization of the study:
 - Submission to the Senior Federal Authority
- Supervision of procedures for notification of the Regional Supervising Authority
- Approval of Drugs / Medical devices
- (Quality) management of production of clinical trial supplies
- (Quality) management of distribution of clinical trial supplies
- (Quality) management of storage of clinical trial supplies
- Security supervision and coverage
- Laboratory services: - EEG, Psychophysiology
 - Bioanalytics (Analytics of substances in body fluids)
 - Pharmaceutical analytics

Clinical Phases covered

- I, II, III, IV

Indication areas

- Pain and inflammation

Groups of agents / substances

- Enantiomerically pure active agents

Customer Groups

- Start-up
- Producers of Generics
- Mid-sized Pharmaceutical Companies
- Big Pharma
- Other CROs
- Other: Public authorities

Type and range of services provided

- General consultation in the area of clinical research
- Trial plan: design of the trial protocol
- Trial plan: design of the CRF (Case Report Files)
- Training and further education (e.g. training in GPC etc.)
- Audit- and compliance services
- Monitoring
- Selection and acquisition of trial centers and physicians
- Acquisition of patients
- Data management / databases / biostatistics etc.
- eCTD (Electronic Common Technical Document)
- Supervision of procedures for authorization of the study:
 - Submission to the Senior Federal Authority
- Supervision of procedures for notification of the Regional Supervising Authority
- Approval of Drugs / Medical devices
- (Quality) management of production of clinical trial supplies
- (Quality) management of distribution of clinical trial supplies
- (Quality) management of storage of clinical trial supplies
- (Quality) management of import of clinical trial supplies
- Security supervision and coverage
- Electronic Reporting (e-Pharmacovigilance and E2B)

Clinical Phases covered

- II, III, IV

Indication areas

- Oncology, Cardiology, Neurology, Diabetology, Vaccines, Dermatology, Gastrointestinal Disorders, Infectiology, Pneumology, Rheumatology

Groups of agents / substances

- Biopharmaceuticals, natural compounds, chemical drugs, medicinal products

Customer Groups

- Start-up
- Producers of Generics
- Mid-sized Pharmaceutical Companies
- Big Pharma

PharmaProjekthaus GmbH & Co. KG

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Type and range of services provided

- General consultation in the area of clinical research
- Trial plan: design of the trial protocol
- Training and further education (e.g. training in GPC etc.)
- Selection and acquisition of trial centers and physicians
- Supervision of procedures for authorization of the study:
 - Submission to the Senior Federal Authority
- Supervision of procedures for notification of the Regional Supervising Authority

Clinical Phases covered

- I, II, III, IV

Indication areas

- Cardiology, Dermatology, Endocrinology, Gastrointestinal Disorders, Infectious Diseases including HIV and other viral infections, Oncology, Pediatrics - Vaccines and Therapeutics
- Psychiatry and Neurology, Respiratory Disorders, Urology

Customer Groups

- Start-up
- Mid-sized Pharmaceutical Companies
- Big Pharma

Praxis Klinische Arzneimittelforschung

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Type and range of services provided

- Data management / databases / biostatistics etc.

Groups of agents / substances

- natural compounds

Customer Groups

- Start-up
- Producers of Generics
- Mid-sized Pharmaceutical Companies

Premier Research Germany

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Type and range of services provided

- General consultation in the area of clinical research
- Trial plan: design of the trial protocol
- Trial plan: design of the CRF (Case Report Files)
- Training and further education (e.g. training in GPC etc)
- Audit- and compliance services
- Monitoring
- Selection and acquisition of trial centers and physicians
- Acquisition of patients
- Data management / databases / biostatistics etc.
- eCTD (Electronic Common Technical Document)
- Supervision of procedures for authorization of the study:
 - Submission to the Senior Federal Authority
- Supervision of procedures for notification of the Regional Supervising Authority
- Approval of Drugs / Medical devices
- Security supervision and coverage
- Electronic Reporting (e-Pharmacovigilance and E2B)

Clinical Phases covered

- I, II, III, IV

Indication areas

- Pain (general), Oncology, Neurology, Dermatology

Groups of agents / substances

- Drugs and Medical devices, Medicinal products

Customer Groups

- Start-up
- Producers of Generics
- Mid-sized Pharmaceutical Companies
- Big Pharma

Type and range of services provided

- General consultation in the area of clinical research
- Trial plan: design of the trial protocol
- Trial plan: design of the CRF (Case Report Files)
- Training and further education (e.g. training in GPC etc.)
 - Monitoring
- Selection and acquisition of trial centers and physicians
- Acquisition of patients
- Data management / databases / biostatistics etc..
- eCTD (Electronic Common Technical Document)
- Supervision of procedures for authorization of the study:
 - Submission to the Senior Federal Authority
- Supervision of procedures for notification of the Regional Supervising Authority
- Approval of Drugs / Medical devices

Clinical Phases covered

- I, II, III, IV

Customer Groups

- Start-up
- Producers of Generics
- Mid-sized Pharmaceutical Companies
- Big Pharma

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SCRATCH**Pharmacovigilance Services GbR**

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 Phone +49 6033 974777
 Fax +49 6033 974778
 s.kienzle@scratch-services.de
 www.scratch-services.de

Type and range of services provided

- General consultation in the area of clinical research
- Trial plan: design of the trial protocol
- Trial plan: design of the CRF (Case Report Files)
- Monitoring
- Selection and acquisition of trial centers and physicians
- Acquisition of patients

Clinical Phases covered

- Preclinical, I, II, III, IV

Indication areas

- Clinical Studies on functional; new ingredients in "infant formulas".

Groups of agents / substances

- functional food, prebiotics, n-3 fatty acids, functional carbohydrates, protein hydrolysates, metabolics

Customer Groups

- Start-up
- Big Pharma
- Other: dietetic food industry

Type and range of services provided

- General consultation in the area of clinical research
- Trial plan: design of the trial protocol
- Trial plan: design of the CRF (Case Report Files)
- Training and further education (e.g. training in GPC etc.)
- Supervision of procedures for authorization of the study:
 - Submission to the Senior Federal Authority
- Supervision of procedures for notification of the Regional Supervising Authority
- Security supervision and coverage

Indication areas

- All aspects of pharmacovigilance for both clinical as well as post-marketing

Customer Groups

- Start-up
- Mid-sized Pharmaceutical Companies
- Other CROs
- Other: Manufacturers of phytomedicines

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Type and range of services provided

- General consultation in the area of clinical research
- Trial plan: design of the trial protocol
- Trial plan: design of the CRF (Case Report Files)
- Training and further education (e.g. training in GPC etc.)
- Audit- and compliance services
- Monitoring
- Selection and acquisition of trial centers and physicians
- Data management / databases / biostatistics etc.
- Supervision of procedures for authorization of the study:
Submission to the Senior Federal Authority
- Supervision of procedures for notification of the Regional
Supervising Authority
- Approval of Drugs / Medical devices
- (Quality) management of distribution of clinical trial supplies
- (Quality) management of storage of clinical trial supplies

Clinical Phases covered

- I, II, III, IV

Indication Areas

- Oncology

Groups of agents / substances

- All oncological substances

Customer Groups

- Start-up
- Producers of Generics
- Mid-sized Pharmaceutical Companies
- Big Pharma
- CRO

Type and range of services provided

- General consultation in the area of clinical research
- Trial plan: design of the trial protocol
- Training and further education (e.g. training in GPC etc.)
- eCTD (Electronic Common Technical Document)
- Other: Study Documentation: clinical study reports (CSR),
clinical study protocols (CSP), common technical
documents

Customer Groups

- Start-up
- Mid-sized Pharmaceutical Companies
- Big Pharma

YES Pharmaceutical Development Services GmbH

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Type and range of services provided

- Audit- and compliance services
- eCTD (Electronic Common Technical Document)
- Supervision of procedures for authorization of the study:
Submission to the Senior Federal Authority
- Supervision of procedures for notification of the Regional
Supervising Authority
- Approval of Drugs / Medical devices
- Security supervision and coverage
- Electronic Reporting (e-Pharmacovigilance and E2B)
- Other Services:
Coordination of development with main emphasis on
regulatory compliance
 - identification of essential development steps
 - advice on regulatory needs
 - gap analyses, milestone definition
 - tracking
 - scientific ad

Customer Groups

- Start-up
- Mid-sized Pharmaceutical Companies
- Big Pharma
- Other: Biosimilar companies, SMEs

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Type and range of services provided

- General consultation in the area of clinical research
- Trial plan: design of the trial protocol
- Trial plan: design of the CRF (Case Report Files)
- Training and further education (e.g. training in GPC etc.)
- Audit- and compliance services
- Monitoring
- Selection and acquisition of trial centers and physicians
- Acquisition of patients
- eCTD (Electronic Common Technical Document)
- Supervision of procedures for notification of the Regional
Supervising Authority
- Approval of Drugs / Medical devices
- (Quality) management of production of clinical trial supplies
- (Quality) management of distribution of clinical trial supplies
- (Quality) management of storage of clinical trial supplies
- Laboratory Services:
 - Development and validation of analytical methods for
the determination of substances in biological samples
 - Quality control of active ingredients and finished products
 - Stability studies
 - Bioavailability and Bioäquivalence Studies
 - Permeability studies

Clinical Phases covered

- Preclinical, I, II, III, IV

Groups of agents / substances

- Biopharmaceuticals, natural compounds, small Drugs, me-
dicinal products, Peptides/Oligonukleotide

Customer Groups

- Start-up
- Producers of Generics
- Mid-sized pharmaceutical companies
- BigPharma

SOME BASICS ON CLINICAL RESEARCH

What is clinical research (KliFo – CliRe)

- Clinical research deals with both further and new developments of drugs and therapeutic approaches for the improvement of treatment options of patients and preventive measures. Clinical research does not mean 'research in the hospital'. Naturally, part of the research is carried out in hospitals or university clinics. However, basic research, which forms the fundamentals of clinical research, is carried out in university laboratories or clinics or in special research establishments, e.g. conducted by the pharmaceutical industry. Clinical studies which are carried out on voluntary test subjects and patients are a building block of clinical research. The physical examinations during the clinical studies take place in so-called test centers. These can be research establishments, hospitals, and doctor's offices. The organization, direction, supervision and evaluation of the clinical studies are carried out by a pharmaceutical company and/or a contract research institute working together with physicians, ethics commissions and authorities. Clinical studies are based on knowledge acquisition and are strictly separated from marketing activities.

What is a pharmaceutical?

According to the Arzneimittelgesetz (AMG) (German Drug Law), pharmaceuticals consist of plant, animal or synthetic materials. These are employed for diagnostics or, in suitable dosages, as therapeutics for influencing bodily states and functions, as well as substitutes for substances naturally generated by human or animal bodies or bodily fluids, and for the elimination or neutralization of pathogens, parasites or foreign substances in the body. [Roche Lexikon 3rd Edition]

The path to a new pharmaceutical

After isolation / synthesis of a novel substance, the path to a new pharmaceutical (medicament) leads, according to legal requirements, from a preclinical trial to the clinical trial. These novel substances are examined with established models in the preclinical trial stage. The clinical phase of the development begins after critical evaluation of the results obtained regarding pharmacological efficacy and safety. For that purpose, the substance is tested on humans through so-called clinical studies. These clinical studies must be authorized beforehand by the responsible ethics commissions and authorities; participation as

a test subject or study patient is voluntary. The clinical trial is carried out in three phases, in which safety, dosage, efficacy, as well as tolerance to other drugs and interactions with other diseases are examined. After successful completion of the so-called third phase of the clinical trial, the collected data is submitted to the responsible authorities for obtaining market approval for the drug.

The approval process

After completion of all clinical studies, the data collected for the approval must be correspondingly prepared and forwarded to the responsible authorities. In Germany, the BfArM (Federal Institute for Drugs and Medical Devices) in Berlin/Bonn is responsible for the national approval of pharmaceuticals, and the Paul-Ehrlich-Institut in Langen is responsible for the national approval of vaccines, sera and blood products. Since 1995, applications for EU-wide approvals can be filed by submitting to the central admission's office EMEA (European Medicines Evaluation Agency) in London. Thus, submission in Germany is no longer necessary. Genetically engineered pharmaceuticals must be submitted to the EMEA. Should the submitted data not clearly prove the efficacy and safety according to the discretion of the approval authorities, said authorities can then require further trials/studies. After initial approval, medicaments are available exclusively by prescription.

After initial approval

The authorities continue to supervise medicaments after approval. The pharmaceutical industry and physicians are required to register side effects with the authorities. If required, market approval can be withdrawn. Examinations concerning the long-term relationship between risks and benefits are carried out after market approval by a Phase 4 clinical trial. Every 5 years, an extension must be resubmitted for each medicament. Provided that a medicament is safe, the producer can request to remove the requirement for prescription by the first extension at the earliest. Medicaments available without prescription are referred to as OTC (over the counter) drugs.

The effort

Around 10 of approximately 10,000 substances reach the clinical trial after the preclinical trial. Of these 10 substances, 8 to 9 are sorted out in the clinical trial. Only around 1 or 2 of the original 10,000 substance are submitted for approval. Development takes an average of 8 to 12 years. As a rule, this time period is shorter for HIV or cancer. Development expenses are accordingly high:

An overview of the phases of new pharmaceutical developments				
Isolation Synthesis	Preclinical trials	Clinical trials Phase I, II and III	Approval	Clinical trial Phase IV
Isolation / Synthesis of Substances				
Preclinical trial 2 - 3 years		Trials with diverse models <ul style="list-style-type: none"> ↪ isolated cells ↪ cell cultures ↪ tissue ↪ organs ↪ animals 	Safety examinations: <ul style="list-style-type: none"> ↪ toxicology ↪ pharmacology ↪ biochemistry ↪ mutagenicity ↪ carcinogenicity ↪ teratogenicity ↪ fertility ↪ perinatal and postnatal toxicity ↪ pharmacokinetics: absorption, dispersal, metabolism, excretion 	
Clinical trial Phase I-III 3 - 5 years		Trials on humans		
Phase I		approx. 50 healthy test subjects	Examinations: <ul style="list-style-type: none"> ↪ pharmacokinetics ↪ tolerance ↪ effect on bodily functions: cardiovascular, neurological 	
Phase II		approx. 500 chosen patients homogeneous patient population; the latter is affected exclusively by the examined indication	Examinations: <ul style="list-style-type: none"> ↪ efficacy ↪ safety ↪ side effects 	
Phase III Divided into Phase IIIa, relevant for approval: Main focus on efficacy and safety aspects Phase IIIb, approval might already be submitted: Main focus on health economics and quality of life		large number of patients diverse patient populations with diverse diseases	Examinations: <ul style="list-style-type: none"> ↪ efficacy ↪ safety ↪ side effects ↪ interactions with other medications ↪ contraindications ↪ therapeutic advantages ↪ health economics ↪ quality of life 	
Approval process				
Clinical trial Phase IV 2 - 3 years		very large number of patients the most diverse patient population with the most diverse diseases	Completion of the data as described above should the submitted data not clearly be proven (safety, efficacy), then the approval will be withdrawn (negative example: teratogenicity of Contergan)	

in 1999, approx. 23 billion US\$ were invested worldwide in research and development (R+D) by pharmaceutical corporations. Clinical trials account for approx. 14 billion US\$ of this. Other sources allude to costs of over Euro 0.5 billion for the development and marketing of each drug. The costs accrued during the developmental phase must be correspondingly covered after market approval. An important aspect of this is the duration of the patent. When a substance which possesses a possible pharmacological value has been newly discovered or synthesized, it is protected under a corresponding patent application. After the patent has expired, this substance is allowed to be produced and marketed from other companies as well (generics). Therefore, each company is very concerned with having the shortest development time possible for its products, in order to use the duration of the patent, namely the market monopoly, as long as possible.

After approval, post-marketing surveillance studies can also be carried out.

Post-marketing surveillance studies - PMS

Post-marketing surveillance studies (PMS) are carried out exclusively on approved medicaments and are strictly separated from clinical studies. PMS are an additional control instrument of the pharmaceutical industry, in order to collect further knowledge on the efficacy and possible side effects through broad application in the population.

Data from patients who have followed the standard instructions included in the package insert is collected anonymously for PMS and statistically evaluated. There is no study protocol and no additional examinations or other demands on the physician or patient. Documentation of the data is carried out (as in clinical studies) by a physician in a structured and anonymous form on special documentation forms. The burden of documentation for this is significantly less than in clinical studies (approx. 2-5 pages). As a rule, pharmaceutical representatives are highly involved in the support of the physicians. PMS are often carried out retrospectively, i.e. the physician fills out the documentation form based on the patient file after treatment is completed.

Informing the patient is not necessary during PMS, since the patient is receiving an approved medicament in an approved form of therapy and his personal details (patient file) are not disclosed to third parties (monitor, auditor).

Legal basis and guidelines for carrying out clinical studies in Germany

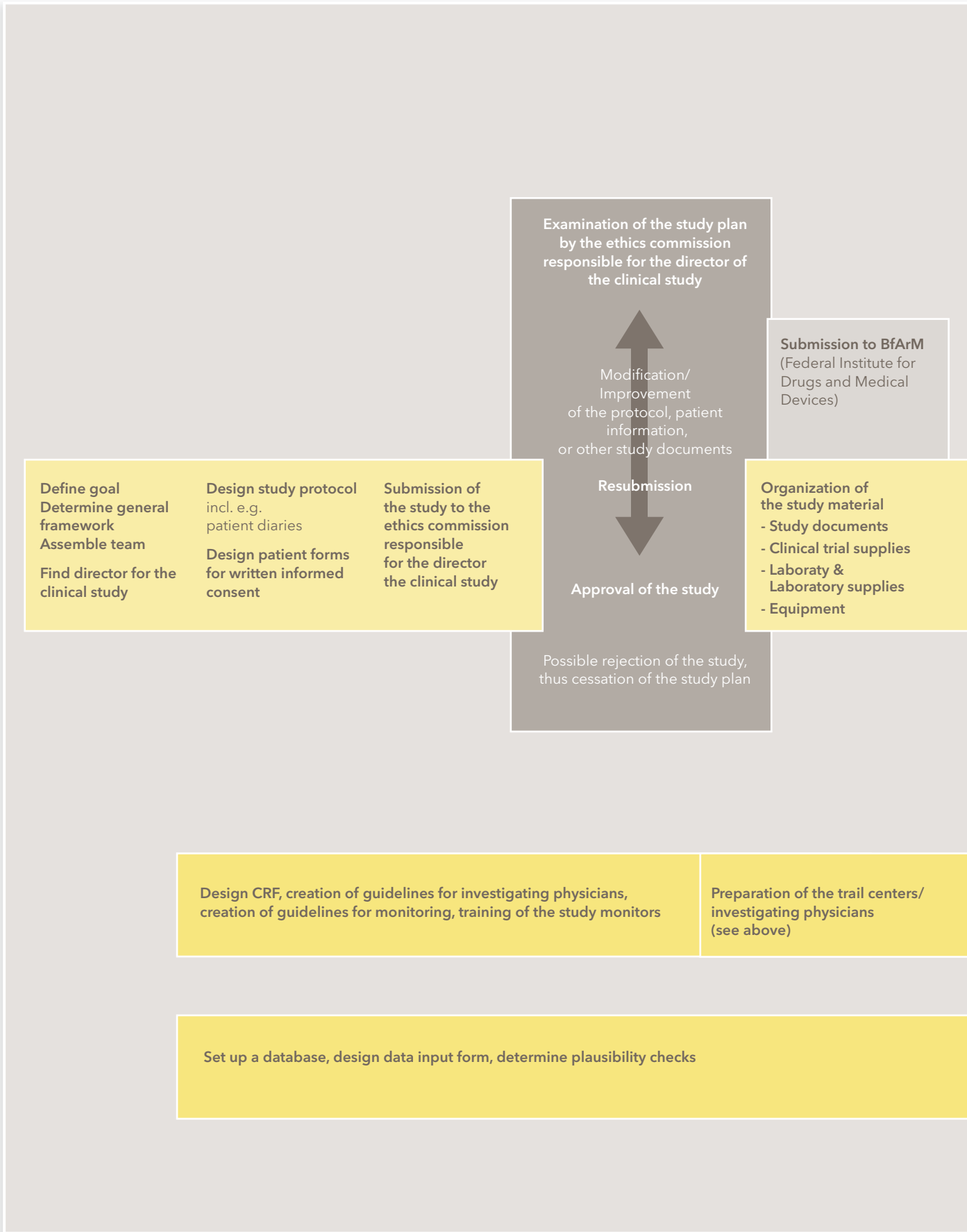
1. German Drug Law (AMG, Law about the commerce of pharmaceuticals)
2. Chamber Law for Health Care Professions
3. Law for Medicinal Products (MPG, Law about medicinal products)
4. German Transfusion Law, Law about regulation of the nature of transfusions
5. German Transplantation Law, Law about the donation, removal, and transfer of organs
6. Genetic Engineering Law (GenTG, Law about regulation of genetic engineering)
7. Embryo Protection Law (ESchG, Law for the protection of embryos)
8. X-ray Ordinance (RöV, Ordinance on the protection from damage caused by X-rays)
9. German Radiation Protection Ordinance (StrlSchV, Ordinance on the protection from damage caused by ionizing radiation)
10. Professional Code of Conduct for German Physicians
11. World Medical Association Declaration of Helsinki
12. Principles for the proper execution of the clinical trial of pharmaceuticals, edited by the Minister for Youth, Family, Women and Health
13. EU guideline for "Good Clinical Practice" (GCP, Guideline for Good Clinical Practice, ICH Harmonised Tripartite Guideline)
14. List of requirements for a "Director of the Clinical Trial", Drug Commission of the German Medical Association
15. Procedure principles of the ethics commission
16. Data Protection Law

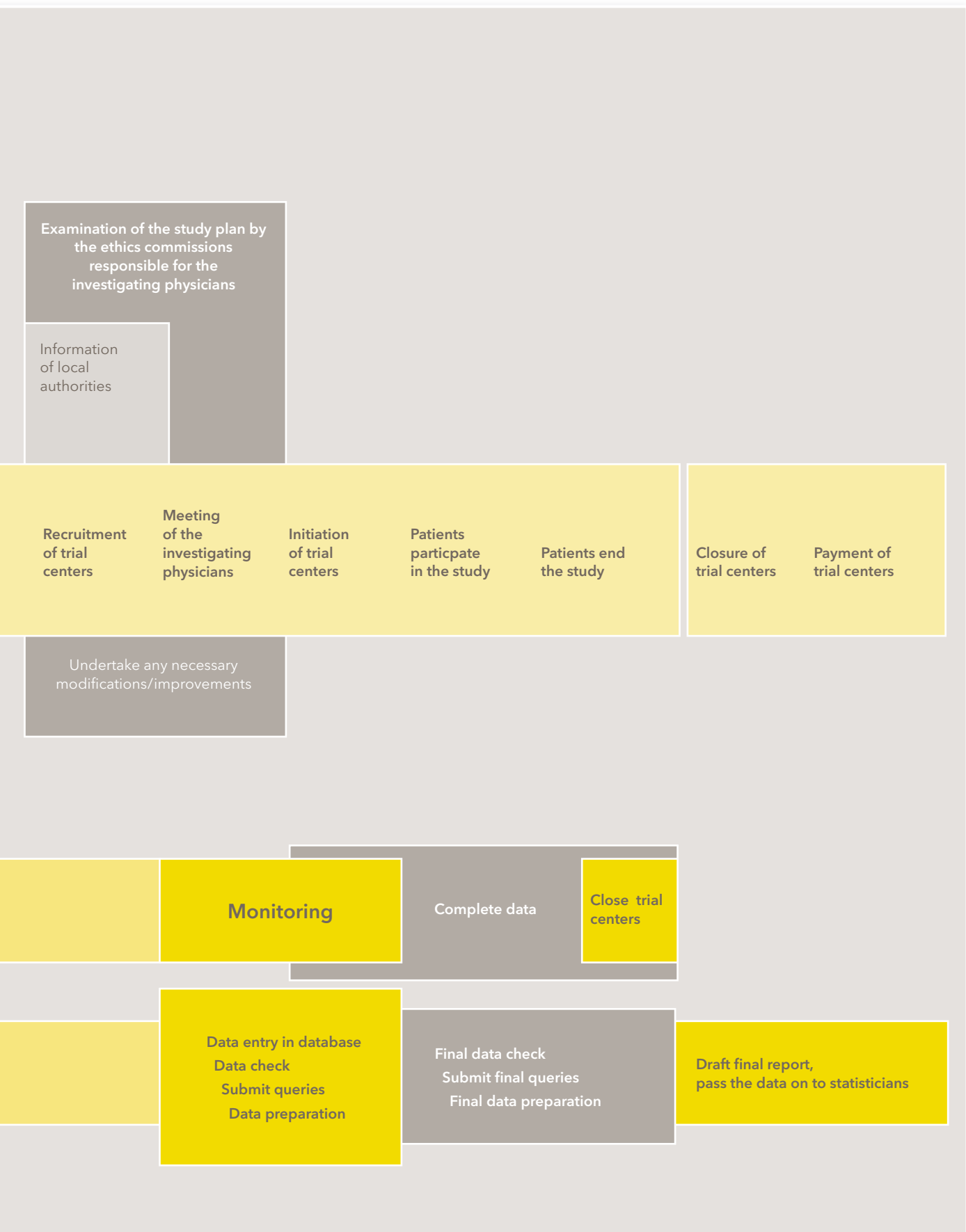
Number of beds in hessian hospitals

Indication	Number of beds
cardiac surgery	274
child and adolescent Psychiatry / Psychotherapy	438
Dermatology and Venerology	324
Intenal Medicine	11.062
Neonatology	156
Neurology	1.716
Neurosurgery	411
Nuclear Medicine	39
Obstetrics and Gynecology	2.723
Ophthalmology	323
Oral and Maxillofacial Surgery	959
Orthopedics	1.731
Other/Miscellaneous	1.085
Otorhinolaryngology	959
Pediatrics	1.097
Pediatric Cardiology	37
Pediatric Surgery	81
Plastic Surgery	83
Psychotherapy and Psychiatry	3.714
Surgery	5.706
Therapeutic Radiology	157
Urology	1.038
Total	34.113

Physicians in private practice in Hessen according to specialities

Anesthesiology	229
Cardiac Surgery	3
Child and Adolescent Psychiatry	51
Dermatology and Venereology	236
General Medicine	2.915
Human Genetics	7
Internal Medicine	1.398
Laboratory Medicine	67
Microbiology and Virology	18
Neurology and Psychiatry	382
Neuropathology	2
Neurosurgery	52
Nuclear Medicine	66
Obstetrics and Gynecology	788
Ophthalmology	373
Oral and Maxillofacial Surgery	63
Orthopedics	405
Otorhinolaryngology	290
Pathology	79
Pediatric Surgery	7
Pediatrics and Adolescent Medicine	437
Phoniatics and Pediatric Audiology	13
Physical and Rehabilitative Medicine	37
Plastic Surgery	14
Psychiatry and Psychotherapy	90
Psychotherapeutic Medicine	239
Radiology and Diagnostic Radiology	259
Surgery	378
Therapeutic Radiology	22
Transfusion Medicine	8
Urology	205
Total approx.	9.100





Hessen

Biotech

www.hessen-biotech.de

Executing organisation of Hessen-Biotech,
a project of the Hessian Ministry of Economics,
Transport, Urban and Regional Development



HessenAgentur

HA Hessen Agentur GmbH