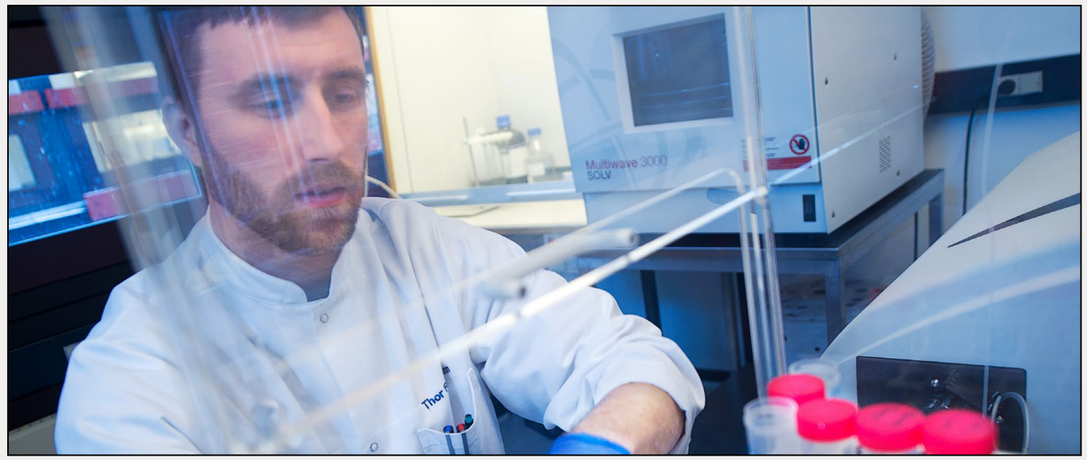
THEME

CLINICAL TRIALS

Clinical trials are often the result of a public-private collaboration. The business area engages a series of life science partners. From pharmaceutical companies, over contract laboratories, logistics, and contract research service partners along with doctors and nurses, testing both new and readily licensed medicinal products and devices in patients to the benefit of society. This series of articles assesses the status of clinical trial activity in Denmark.

THEME CONTENT



Moving day for heavy metals analyses

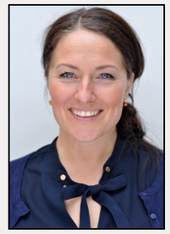
From January 1st 2017, the heavy metal analysis described in the European Pharmacopeia chapter 2.4.8 has been deleted from all human monographs. Instead, heavy metal testing will be performed with atomic absorption spectrometry (AAS) and inductively coupled plasma (ICP) spectrometry. DB Lab, a GMP contract laboratory, has extensive experience in providing these analyses to the pharmaceutical industry.

- Currently, we are dealing with a change of methods that have been applied for over 100 years. I consider this an improvement for our clients, as the ICP is a more specific and sensitive analysis, says Michael Wamberg, Sales Manager at DB Lab. An ICP analysis still requires many individual assessments where the real asset is our extensive experience.

He points to the fact that the changes that currently apply to the European Pharmacopoeia will also apply to the US pharmacopoeia as of January 1st 2018. The conversion of methods has implications which clients need to take into account during drug manufacturing.

- ICH Q3D 'guideline for elemental impurities' applies to tests for heavy metals on the final product. When it comes to API and excipients, manufacturers can either perform the test to eliminate any potential risk or perform a risk assessment. This puts a new demand on the subcontractor of the raw materials who now has to supply their customers with documentation regarding the heavy metals, Michael Wamberg explains.

Michael Wamberg, Sales Manager at DB Lab



Ulrika Rosdahl, Sales & Business Development at DB Lab

ICP screening by classification

His colleague Ulrika Rosdahl, Sales & Business Development at DB Lab carries on,

- Whereas AAS is a technique that handles one metal at a time, ICP can perform a total screening of all the metals that the product contains. ICH Q3D has classified the metals according to their toxicity: Class 1, 2A, 2B, 3 and 'other elements'.

We can do a quantitative or a qualitative screening based on the classification as well as on individual metals. Having both ICP-OES and ICP-MS, we can accommodate sample material of both high and low concentrations.

Method validation required

Ulrika Rosdahl acknowledges that some drug manufacturers have already enclosed the new requirements regarding heavy metal testing by purchasing ICP equipment of their own. In these cases, DB Lab remains a qualified partner in the process.

- At DB Lab, we have a range of specialist chemists who offer their expertise regarding ICP when it comes to method optimisation and validation, she says and ends:

- This is what we are really good at, namely tailoring our services specifically to the needs of our client at all times.

About testing for heavy metals

- As of January 1st 2017, the heavy metals tests described in the European Pharmacopoeia chapter 2.4.8 were deleted from all human monographs, affecting 753 monographs and the same will apply to the US Pharmacopoeia from January 1st 2018.
- AAS and ICP-OES/ICP-MS are the techniques that are now in use for heavy metals testing.

About DB Lab

- DB Lab is a qualified contract laboratory providing chemical and microbiological analyses after Good Manufacturing Practice (GMP) standards with a long-standing experience regarding ICP analyses.
- DB Lab is working with pharmaceutical clients all over Europe, primarily the Nordic countries.
- The company has more than 20 years of experience with GMP analyses, a staff of 42 employees, and is located in Odense.
- www.dblab.dk

DB Lab more than a lab

Clinical trials in Denmark – 2016 at a glance

In total 286 applications for new clinical trials were submitted with the Danish Medicines Agency in 2016. This was a slightly lower number compared to 2015. Cancer trials remain a major driver of trial activity.

By Charlotte Strøm, MD PhD Journalist

Systematic investigations in humans are undertaken in order to collect data about new or already licensed medicinal products, and the clinical trials must comply with certain scientific and ethical standards. In order to meet these requirements, in Denmark, all clinical trials must be approved upfront by the regional ethical committee and the Danish Medicines Agency (DKMA). The level of clinical trial activity in Denmark is reported by the DKMA annually.

With the DKMA the clinical trial activity is registered according to the sponsor: commercial or non-commercial. The total number of clinical trial applications submitted with the DKMA in 2016 was 286, which was slightly less than the number submitted in 2015. Historically, the global financial crisis did not leave the business area untouched.

There was a remarkable drop in commercial clinical trials from 2006- 2010. Clinical trials with non-commercial sponsors have been on the rise or steady since 2010.

The vast majority, 67%, of clinical trials undertaken in Denmark in 2016 was part of multinational trials, and the number of Danish study subjects appeared to be on the rise. The DKMA annual report showed a 16% increase in the number of Danish patients participating in clinical trials in 2016 (21.965 study subjects) compared to 2015 (18.922 study subjects); this was an ongoing trend since 2014 (13.088 study subjects). According to the DKMA this increase was due to initiation of large scale phase IV trials that typically enroll large numbers(> 500) of study subjects.

Type of trials conducted

The commercial clinical trials were typically phase I and phase III trials, although both type's commercial phase I (31%) and phase III (17%) declined heavily in 2016 compared to 2015.

The annual report showed a rise (29%) in non-commercial phase II clinical trials compared to 2015, and a decline in non-commercial phase IV trials. The report stated that DKMA anticipates an increased focus on assigning the label phase II, and not IV, to clinical trials investigating new indications of already licensed medicinal products to be the reason to this change. ▶

The total number of clinical trial applications submitted to the Danish Medicines Agency

Year	Commercial	Non-commercial	Total
2012	153	106	**259**
2013	165	129	**294**
2014	162	122	**284**
2015	190	139	**329**
2016	158	128	**286**

Source: Danish Medicines Agency Annual report on clinical trials, 2016.
https://laegemiddelstyrelsen.dk/da/nyheder/2017/kliniske-forsoeg-med-laegemidler-aarsrapport-2016

▶ Cancer trials remained a key driver of clinical trial activity. This therapeutic area accounted for 99 (35%) of the new clinical trial applications that were submitted with the DKMA in 2016, albeit not reflected in the number of study subjects. The 99 trials only accounted for 18% of the total number of Danish study subjects in 2016. Clinical trials within neurology, genetic diseases, and metabolic disorders each gave rise to 7% of the total number of clinical trials.

Geographically, by far the Capitol Region of Denmark attracted the majority (56%) of clinical trials in 2016, followed by the Central Denmark Region (18%), and the Region of Southern Denmark (16%). ■

Four phases of clinical trials in humans

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

By Charlotte Strøm, MD PhD Journalist

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

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

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

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

Prepare for the future legal framework for clinical trials in Europe

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

Lillan Rejkjær, Managing Partner and Head Regulatory & Medical Development

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

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

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

More than words

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

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

Aim for the MAA

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

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

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

About IWA Consulting

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

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

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

CLINICAL TRIALS

Clinical trial activity improves health care, employment, and learning

A report based on questionnaires among health care professionals (HCP) documents the local effects of industry initiated clinical trial activity on education, improved care, research activities, and jobs.

By Charlotte Strøm, MD PhD Journalist

When a medicinal product is investigated in Sweden, Estonia, and Slovakia, or elsewhere on the globe, it will – if the data attributes licensing – be available as well to Danish patients in due time. However, clinical trial activity initiated by the industry implies distinct local benefits in the health care system that should be taken into account when estimating the added value of this activity. In January 2017 The Danish Association of the Pharmaceutical Industry (Lif), the NEXT Partnership, and Invest in Denmark released a report provided by Copenhagen Economics quantifying the value of industry initiated clinical trials in Denmark.

The report puts into numbers the effects that may appear difficult to quantify properly, such as the learnings and knowledge sharing among HCP from working with a clinical trial. More than 53% of respondents agreed that they felt working with clinical trials had improved their clinical skills, and 61% responded that their knowledge had been shared with colleagues.

The motivation among health care professionals to join clinical trials as investigators covers a professional interest in being part of the most recent pharmaceutical development as well as an interest in strengthening the scientific network. Moreover, clinical trials tend to implicate clinical improvements at participating hospitals e.g. by changes made to daily clinical practice, treatment guidelines, changes made to national guidelines etc. Furthermore, the respondents pointed to a trend that clinical trial activity subsequently resulted in increased scientific activity taking place at the institution, i.e. attracting more clinical trials or other research activities, publication of scientific results directly or indirectly related to the clinical trial etc. ▶

Thomas Kongstad Petersen, Chair of the NEXT Partnership and Vice President at LEO Pharma

▶ Clinical trials initiated by the life science industry tend to attract millions in investments, improving capacity and qualifications with the staff. Investments made by the pharmaceutical industry in the Danish health care system in 2015, were estimated to be around 37 million EUR. Moreover, the industry initiated clinical trials also create jobs and improve the gross national product.

Are there any downsides to the industry initiated trials in the public health care system?

-For the patients, the health care system, and for society, it is hard to find any downsides. The HCP learn more from working with clinical trials, and the capacity and quality of the health care system increases because the industry pays for the time, medicine, and equipment used during the clinical trials, says Thomas Kongstad Petersen, Chair of the NEXT Partnership and Vice President at LEO Pharma. He agrees, however, that locally – and bedside – it may be a challenge for the individual physician and nurse, who are doing the practical assignments, related to the industry initiated trials.

-One side of the story is that the industry pays the hospitals to conduct the trials, but if this does not materialize into more head counts then it definitely puts a strain on the staff that will have even more chores and assignments to fill into a day that was busy already. Clearly this is unsustainable, Thomas Kongstad Petersen explains.

He envisions that the NEXT Partnership demonstrates how it can be done, as NEXT has helped build clinical trial competences and manpower at the partnering departments.

-I believe it is essential that the hospitals prioritize clinical research. Clinical trials take human resources, professional commitment, and engagement among the staff to contribute to a trial. It's possible to encourage and stimulate that through more part-time research positions, education in clinical trial conduct, and possibly by setting goals for clinical trial activity that are aligned with goals measuring patient treatment and care at the hospitals, Thomas Kongstad Petersen concludes. ■

"The report puts into numbers the effects that may appear difficult to quantify properly, such as the learnings and knowledge sharing among HCP from working with a clinical trial."

Ida Sofie Jensen, CEO at Lif

Raised application fees and overhead costs put strain on clinical trial budgets

Clinical trials already engage a large proportion of budgets in pharmaceutical companies. Remarkable increases in fees with the Danish Medicines Agency and overhead costs at hospitals may jeopardize the current level of activity.

By Charlotte Strøm, MD PhD Journalist

Through an executive order the Danish Medicines Agency (DKMA) raised the fees to be paid to the agency for applications on clinical trials of medicinal products as of 01 July 2017. The fees apply to all, irrespective of the origin of the trial sponsor.

During the public hearing prior to the decision made by the Minister of Health, Ellen Trane Nørby, several stakeholders raised their concerns on the remarkable raise in the fees. An application involving new medicinal products from 01 July 2017 costs 6.087 EUR, applications involving already marketed products cost 3.066 EUR. Additionally, as a new item, an annual fee of 1.711 EUR applies to every trial for every ongoing year. Amendments to the protocol cost 635 EUR. Overall, the fees have been raised considerably.

Henrik Bendixen, Chief Adviser at the DKMA explains on the increase of fees:

-A national audit earlier stressed that the fees of clinical trial applications and other fees subject to The Danish Medicines Act with the DKMA must be closely related to the actual costs of assessing them. Hence, we improved the registration tools, allowing us to assess the actual time consumption, and ended up with this new level of fees.

He points to the reflection of the real cost.

-Some fees have been raised quite a lot, others have been lowered. But overall the level of the fees now reflects the real cost of assessing the applications, Henrik Bendixen says.

The fees relate to the administration costs of assessing and approval of clinical trial applications and continuously conduct inspections at clinical sites, manufacturing facilities etc. The revenues of fees related to clinical trials represent 6% of the total turnover of the DKMA according to Henrik Bendixen.

Risk of fewer trials

Critics of the raise of fees at DKMA claim that the increase in costs may jeopardize the activity on clinical trials. The Danish Medical Association worries on the raised fees particularly concerning the investigator initiated trials.

In the association's hearing response to the executive order, it says: "A lot non-commercial research is taking place partly unpaid in the physician's spare time, and rarely the grants cover all studies. With the proposed increase in fees, it will be difficult – if not impossible – for medical doctors to initiate trials on their own in areas such as medicine interaction or adverse effect studies, because there is no money to pay for the fees."

The Danish Association of the Pharmaceutical Industry (Lif) also raised concern regarding the increase in fees.

-The fees related to approval of, and ongoing control with clinical trials ought not to be above the average level of fees in countries for comparison, when the EU act on clinical trials is issued. This is expected to happen in 2019, says Ida Sofie Jensen, CEO at Lif.

Lif has compared the level of fees with the National Competent Authorities in 17 European countries. The key concern with the numbers is that the fees in Denmark are now in the high end.

Need for evaluation

When executing the order, the Minister of Health, Ellen Trane Nørby, suggested that the raised fees will be subject to evaluation after some time. Ida Sofie Jensen comments on this point:

-It makes sense to ensure that the fees for clinical trials are not an independent barrier obstructing the attraction of clinical trials to Denmark. We tend to agree with the Minister of Health that the new level of fees should be thoroughly evaluated in due time. Once the damage is done, and Denmark gets the reputation of being expensive, it can be difficult and take a long time to recover from.

Thomas Kongstad Petersen, Chair of the Board at the NEXT (National Experimental Therapy) Partnership and Vice President at LEO Pharma dares to put an actual estimate on this risk.

-For sure this will have an impact. The fees were fairly low, I admit to that and more realistic fees are fair, however, the increase we see here is out of the ordinary, and likely to have a prohibitive effect, he says and carries on, ▸

"A national audit report stressed that tax money cannot be used in support of private companies"

-I'm afraid we will see the impact quite soon, within six months or so.

Overhead costs increased

He stresses that not only has the DKMA raised the fees for clinical trial applications considerably over the summer, the Capital Region of Denmark in early 2016 also raised the overhead cost on all research activity performed with external sponsors at the region's hospitals.

The overhead cost is a fee in percentage of the revenue, generated by the trial, in order to cover indirect costs.

-Previously, the overhead across the regions varied, from a few percent to 5%. Within the Capital Region of Denmark, the overhead was increased to 15% in 2016 overnight, he says.

But there is more to come. Based on a national audit report, the Danish regions that own the hospitals have decided to synchronize the level of overhead across the country. This decision came into act in the spring of 2017, and the overhead for any research conducted on behalf of external partners was raised to 18%. The overhead is to cover indirect costs such as administration, management, finance and control, facility management, purchases of IT etc.

A national audit report stressed that tax money cannot be used in support of private companies. Hence, any type for research that is conducted at the public hospitals for external parties must be self-financed to comply with the law. According to Jeppe Hedegaard Munck, team leader at Economic Affairs, Danish Regions, that is why the overhead has been applied and set to a fixed rate of 18 % across the country. Jeppe Hedegaard Munck explains further:

-The national audit found that the hospitals and regions did not in an adequately way separate the budget for research from the regular budget for patient treatment. This means that potentially money allocated to patient treatment, against the law, has been used for conducting research for private companies.

-However, the national audit did not conclude that this was the case, as hospitals to some extent already charged a sufficient payment to cover both direct and indirect costs. This is also why the application of overhead of 18% will not imply that the costs of research projects will rise by 18%, says Jeppe Hedegaard Munck.

Overhead in most European countries

The work group at Danish Regions has investigated the level of overhead in Europe and found that overhead is commonly applied in most other countries; some places even more than 18% is charged according to Jeppe Hedegaard Munck.

Overlooking the continent from a pharma headquarter office in Boston, Chicago, Paris, or Zürich during the planning of large scale global clinical trials involving millions of Euros, the overhead of 18% may need some explaining, including the fact that it is legally required at Danish hospitals.

Whether the fixed national overhead rate of 18% for external research at hospitals will dampen the clinical trial activity in Denmark remains to be seen. However, in part this tends to go against the Life Science Growth Team's 17 recommendations for the government on a stronger life science sector. The report was presented in March 2017, stressing the strengthening of clinical research as the first recommendation.

-Altogether, the increased costs of overhead at hospitals and increased fees with the DKMA appear to be counterproductive. The pharmaceutical companies are hardly counting pennies; however, it would be unwise to make the mistake to assume that price is not at all an issue. It is, Thomas Kongstad Petersen concludes. ■

FACTS

- On 01 July 2017, an executive order on fees for applications concerning clinical trials came into act. The executive order covers the determination of fees for applications regarding clinical trials submitted with the Danish Medicines Agency (DKMA).
- Read more about the fees for clinical trials with the DKMA at https://laegemiddelstyrelsen.dk/en/licensing/clinical-trials/fees/
- The overhead is to cover indirect costs such as administration, facility management, IT etc.
- The Capital Region of Denmark issued new rules on determination of overhead costs in 2016 applied to research performed at the region's hospitals with external partners. The overhead was subsequently set to 15%.
- The hospitals owners, the regions of Denmark, have altogether in 2017 decided to set the overhead to a fixed rate of 18% for research activities performed in collaboration with external partners.