Sundhedsstyrelsen
Danish Health and Medicines Authority

Annual report 2013

Clinical trials of medicines in humans

Highlights

Below is a summary of some of the topics covered by the Danish Health and Medicines Authority's annual report on clinical trials of medicines in 2013.

The number of clinical trial applications increased by 14% from 2012 to 2013

In 2013, the Danish Health and Medicines Authority reviewed 294 applications for clinical trials, 35 trials more than in 2012. The number of notified trials sponsored by researchers increased from 106 to 129. This increase exceeds the rise in the number of trials sponsored by companies, which rose from 153 to 165 in the period from 2012 to 2013.

More trials were notified but with fewer subjects in 2013

The Danish Health and Medicines Authority estimates that 16,882 Danish trial subjects will participate in the 294 trials that were applied for in 2013. This is significantly fewer than in the past two years when the number of trial subjects was around 19-20,000. It is estimated that 7,748 trial subjects will participate in the 165 trials sponsored by companies, whereas 9,134 subjects will participate in the 129 notified trials sponsored by researchers. The average number of subjects per trial is 57. In 2012, the average number was 74. Thus, more trials were notified but generally with fewer participants. The report breaks down the trial subjects on number of trials and therapeutic areas.

The number of phase I trials doubled in three years

A targeted focus on attracting clinical trials in phases I and II to Denmark now seems to have an effect. The number of phase I trials doubled from 20 to 40 trials from 2011 to 2013. The number of phase II trials increased by 19 from 2012 to 2013.

Two thirds of the trials conducted in Denmark are also conducted in other European countries

The majority (177) of the 291 trials planned to take place in Denmark will be conducted in several other European countries. Whereas 90% of the commercial trials are multinational, this is only the case for 22% of the trials sponsored by researchers.

Assessment times are being met and an increasing number of trials are coordinated with other European authorities

The Danish Health and Medicines Authority met 88% of the fixed assessment times, and 25% of the applications were reviewed through the common European Voluntary Harmonisation Procedure (VHP).

The annual report presents several data on trials notified in 2013. You can also read about the application portal shared with the ethics committees as well as the recently adopted European clinical trials regulation.

Annual report:

Clinical trial applications increased by 14% in 2013 compared to 2012

Year	Number of clinical trials notified to the Danish Health and Medicines Authority		
	Sponsor, researcher	Sponsor, company	Total
2005	89	215	304
2006	107	229	336
2007	63	207	270
2008	81	194	275
2009	85	183	268
2010	84	142	226
2011	117	154	271
2012	106	153	259
2013	129	165	294

Table 1: Number of reviewed clinical trial applications submitted through 2005-2013 by type of sponsor.

In 2013, the Danish Health and Medicines Authority reviewed 294 applications for authorisation of clinical trials of medicines in humans, which is an increase of 35 trials or 14% on 2012.

165 of the trials were applied for by commercial sponsors and 129 by researchers. Generally, the company-initiated research activity has been on a downward slope over the past years. The level from 2011 and 2012 of around 150 trials per year may prove to be the bottom of a development that turned in 2013.

In 2013, the number of trials initiated by researchers increased by 23, corresponding to 22% compared with 2012. The 129 clinical trials or 44% of the notified trials were initiated by researchers, compared with 41% the year before.

Appendix 1 shows a graphical presentation of the development in the number of clinical trial applications from 2006-2013.

The therapeutic areas with the highest number of clinical trial applications appear from table 2. We still receive most clinical trial applications within the cancer field. Cancer-related trials amounted to 86 trials in 2013 and represent the therapeutic area with the highest number of clinical trial applications. This was also the case in 2011 and 2012 when 63 and 59 cancer-related trials were applied for, respectively.

The number of clinical trials within metabolism and nutrition disorders doubled from 19 in 2011 to 34 in 2012; in 2013, 22 trials were applied for and so the number was back at the same level as in 2011.

Within nervous system disorders 26 clinical trials were applied for, which is 13 more than in 2012. The group of trials related to cardiac disorders shows a similar increase from 9 trials in 2012 to 20 in 2013.

Within the therapeutic area surgical and medical procedures 16 trials were applied for in 2013, compared to 11 trials in 2012.

Appendix 2 shows the distribution of all clinical trial applications by therapeutic area (blue bars).

MedDRA[1] therapeutic area code	Number of clinical trials
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	86
Nervous system disorders	26
Metabolism and nutrition disorders	22
Cardiac disorders	20
Surgical and medical procedures	16

Table 2: Top 5 therapeutic areas measured by number of clinical trial applications in 2013.

[1] Medical Dictionary of Regulatory Activities

More trials but fewer trial subjects

More trials were notified but generally with fewer participants. It is estimated that 16,882 Danish trial subjects will participate in the 294 trials that were applied for in 2013. 7,748 trial subjects will participate in trials sponsored by companies, whereas 9,134 subjects will participate in trials sponsored by researchers. In 2011 and 2012, 19-20,000 trial subjects participated in the notified trials.

The average number of subjects per trial is 57. In 2011 and 2012, the average number was 76 and 74, respectively. Thus, more trials were notified, but the average number of trial subjects per trial has decreased by approximately 20. One of the reasons is that the primary increase in the number of trials is within the cancer field where the number of patients per trial is generally low because they are conducted for low prevalence diseases in Denmark.

As illustrated in Figure 1, the number of trial subjects varies – the lowest number of subjects is two, the highest is 800. 67 (23%) of the clinical trials planned in Denmark have ten or fewer trial subjects. Compared to 2012, the number of trials with less than ten trial subjects has increased by 35. In five trials, the number of Danish trial subjects exceeds 500, representing 19% of all trial subjects in Denmark.

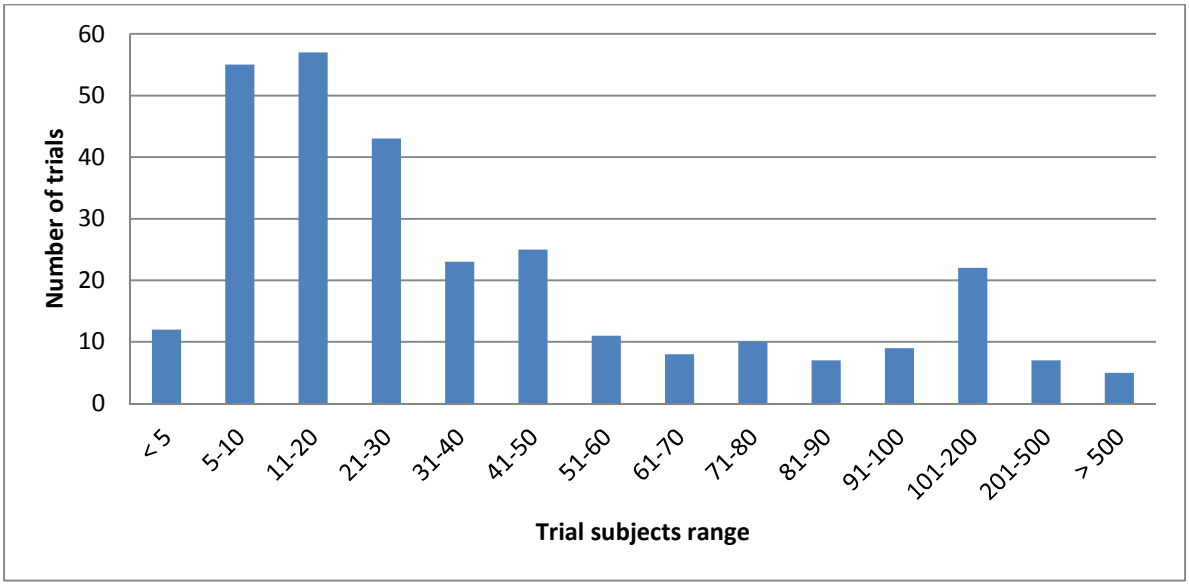


Figure 1: Bar chart of the number of trials in trial subject ranges.

Most trial subjects in trials dealing with cardiac diseases

The therapeutic areas with the highest number of clinical trial subjects appear from table 3. Appendix 2 shows the distribution of trial subjects on therapeutic areas (red bars).

MedDRA therapeutic area code	Number of trial subjects
Cardiac disorders	3,541
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2,025
Nervous system disorders	1,453
Surgical and medical procedures	1,362
Infections and infestations	1,254

Table 3: Top 5 therapeutic areas measured by number of trial subjects.

Two thirds of the trials conducted in Denmark are also conducted in other European countries

The majority (177) of the 294 trials notified in Denmark will also include trial subjects in other European countries.

Among the 165 commercial trials, 148 (90%) are multinational. 17 trials (10%) are conducted in Denmark only, an increase of eight trials compared with 2012.

Among the 129 trials sponsored by researchers, 29 (22%) are multinational. 100 (78%) trials sponsored by researchers are conducted in Denmark only.

The share of Danish trial subjects participating in multinational trials is 9% on average, and the number of subjects varies considerably from two to 600 trial subjects. The proportion of Danish trial subjects ranges from 1% to 76%.

The large share of multinational trials in Denmark underlines the importance for Danish authorities to participate in and shape the European development of the area and contribute constructively to the harmonisation between the European countries.

	Multinational trials			National trials		
	2011	**2012**	**2013**	**2011**	**2012**	**2013**
All trials	170	160	177	101	99	117
Sponsor, company	144	144	148	10	9	17
Sponsor, researcher	26	16	29	91	90	100

Table 4: Distribution of multinational and national trials by type of sponsor in 2011, 2012 and 2013.

Distribution of trials by phase

Figure 2 shows the number of applications according to type of sponsor and clinical trial phase in 2011, 2012 and 2013.

The increase in the number of notified trials from 2012 to 2013 are mainly phase I, II and IV trials. The number of phase III studies notified in 2013 (112) is in line with the numbers notified in 2012 (111) and 2011 (110).

A targeted focus on attracting clinical trials in phases I and II to Denmark now seems to have an effect. The number of phase I trials doubled from 20 to 40 trials from 2011 to 2013. The number of phase II trials increased by 19 from 2012 to 2013.

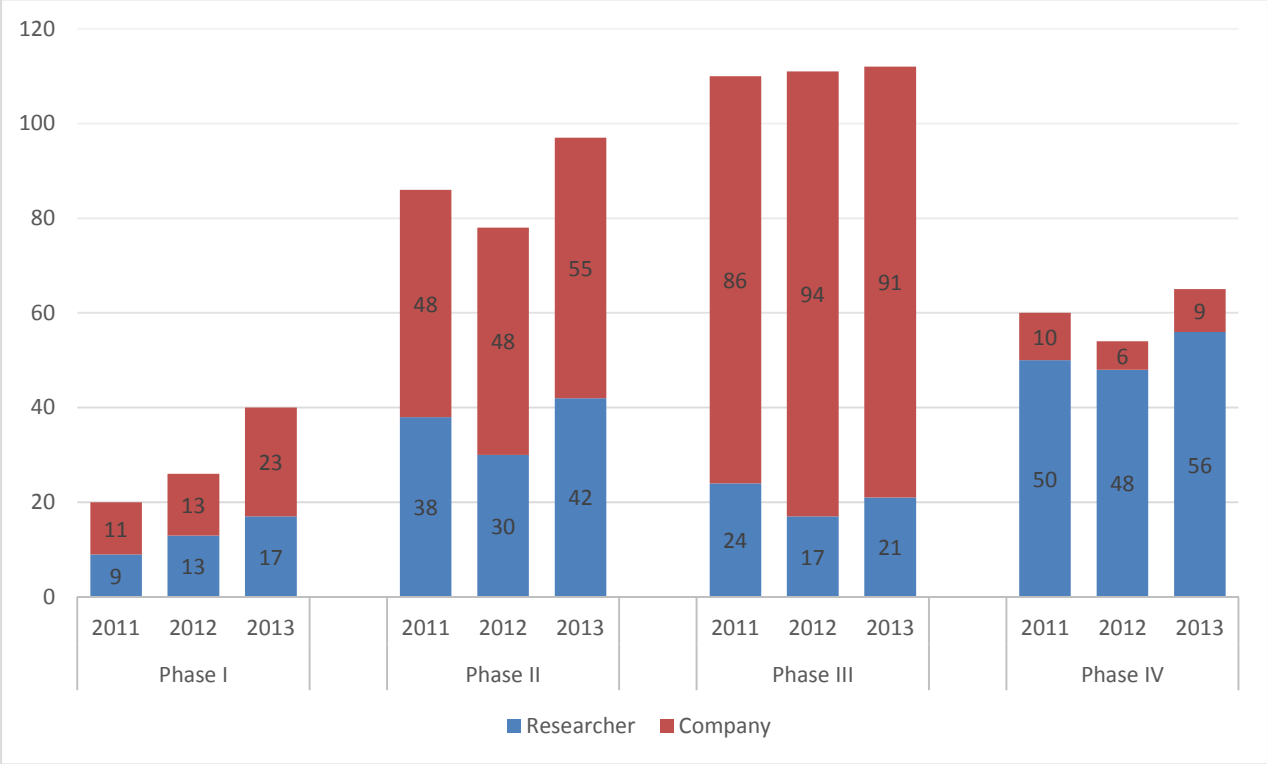


Figure 2: Distribution of clinical trial applications according to trial phase and type of sponsor.

More than half of the clinical trials of medicines are coordinated by the Capital Region of Denmark

Figure 3 shows the distribution of clinical trial applications according to which regional ethics committee has received the application for approval. The regional distribution of clinical trial applications in 2013 is broadly in line with 2012.

The coordinating investigator's affiliation determines which ethics committee is to approve the clinical trial, and it appears that 166 (56%) of the clinical trials of medicines are coordinated from a hospital located in the Capital Region of Denmark. 66 trials (22%) are to be coordinated from the Central Denmark Region, and 37 trials (13%) from the Region of Southern Denmark. 11 trials (4%) are to be coordinated from the North Denmark Region, 4 trials (1%) from Region Zealand.

Furthermore, 100 (60%) of the company-sponsored trials are coordinated from the Capital Region of Denmark. The Central Denmark Region coordinates 37 company-sponsored trials, whereas the Region of Southern Denmark coordinates 17. The North Denmark Region has 4 company-sponsored trials, and Region Zealand coordinates 2 company-sponsored trials.

In this connection it is important to bear in mind that an authorised clinical trial of medicinal products which is coordinated from the Capital Region of Denmark may be conducted at clinical departments (sites) in hospitals of other Danish regions. Consequently, the figure does not point to trends for the overall clinical research activity with medicines in a specific region.

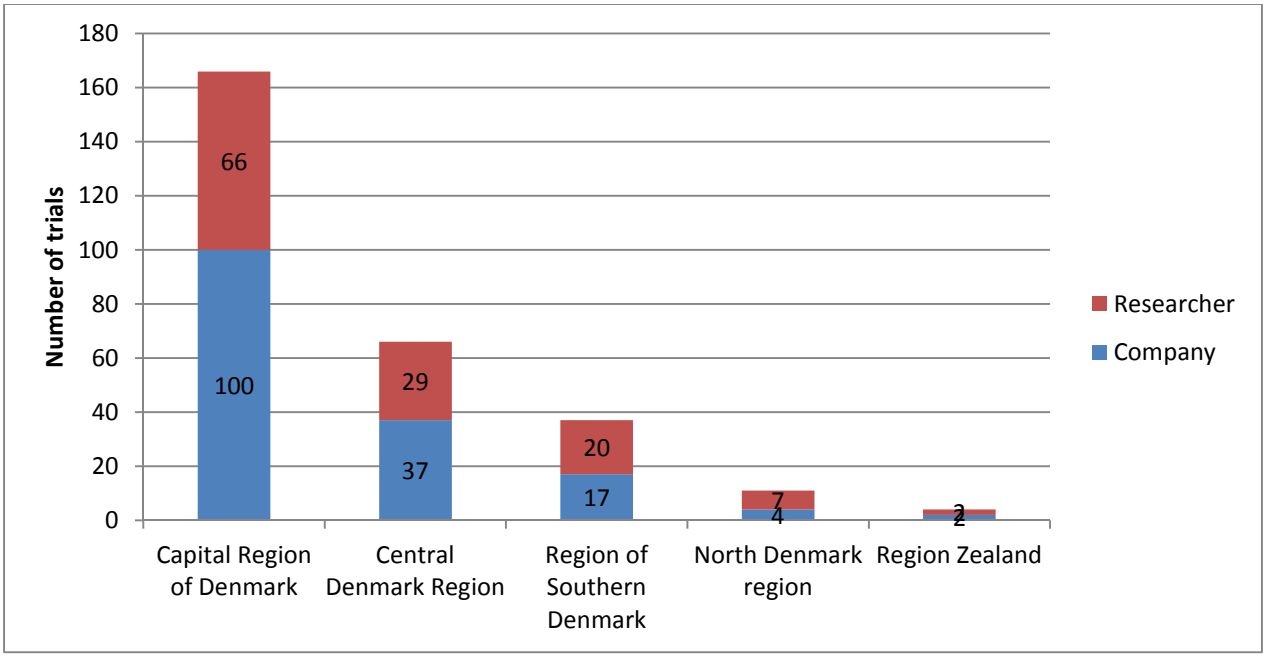


Figure 3: Distribution of clinical trial applications according to type of sponsor and regional affiliation of the ethics committee with which the application has been filed.

The assessment by the Danish Health and Medicines Authority

The work with clinical trials is organised in the Clinical Trials Unit under the Medicines Assessment & Clinical Trials Division. The Clinical Trials Unit has nine full-time and nine part-time employees. The unit reviews clinical trial applications and monitors all ongoing trials based on notified amendments, reported adverse reactions and annual safety reports.

The Danish Health and Medicines Authority received 306 applications and reviewed 294. 291 trials were authorised in 2013. We refused two trials and one clinical trial application is still being assessed.

Continued increase in the use of VHP

Since 2009 it has been possible to obtain a coordinated assessment of an application for a clinical trial that is to take place in more than three European countries through the Voluntary Harmonisation Procedure (VHP). As appears from Figure 4, the number of cases being reviewed through this procedure continues to increase. Denmark participated in 44 cases, which implies that 25% of the authorisations for the conduct of multinational clinical trials in Denmark have been coordinated with the other European regulatory authorities in the countries where the trials are planned to take place. In 2012, this share amounted to 15%. Denmark's share of the total number of European VHP cases is 27%. Denmark acted as reference member state in 1 case in 2011, 2 cases in 2012 and 5 cases in 2013.

The procedure is offered by the European working group CTFG, Clinical Trials Facilitation Group, which was formed by the Heads of Medicines Agencies i 2004 with the purpose of coordinating and seeking harmonisation of decisions and administrative procedures related to the GCP Directive 2001/20/EC, which came into force in 2004. You can find more information about the procedure on our website Voluntary Harmonisation Procedure

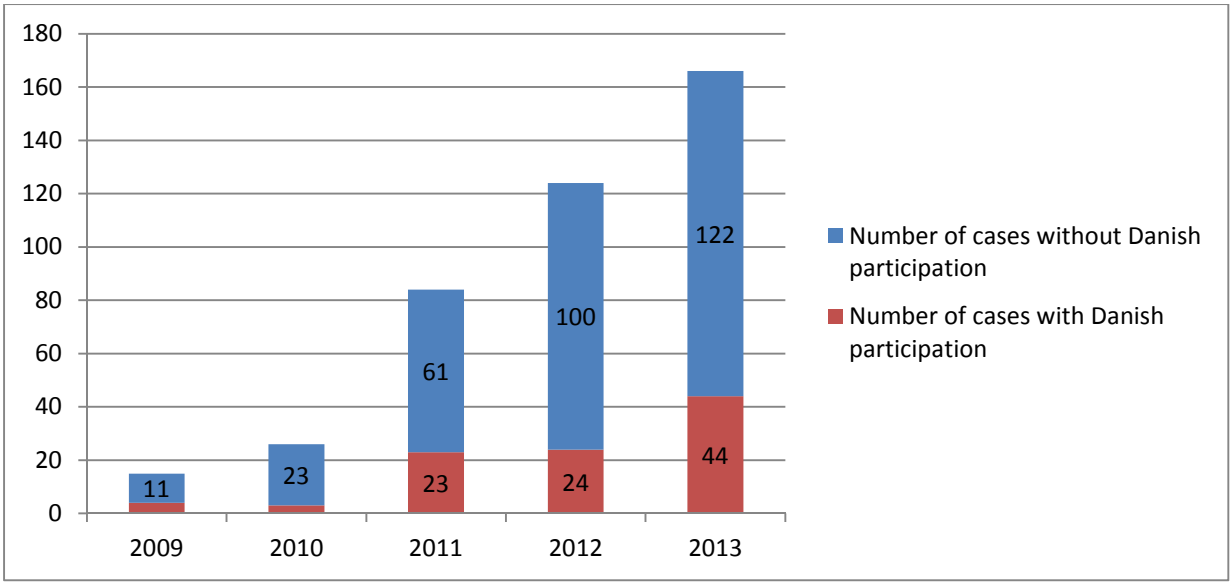


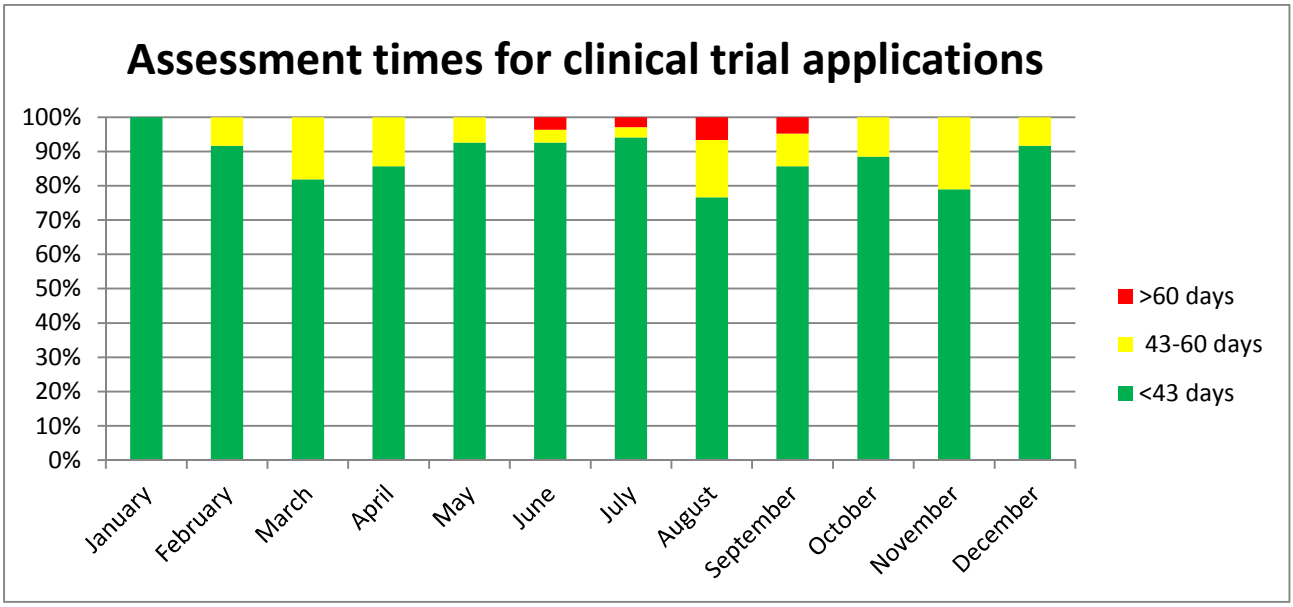
Figure 4: Number of cases reviewed through the Voluntary Harmonisation Procedure (VHP)

Assessment times

The maximum time allowed for assessment is 60 calendar days[2] as set out in the executive order on clinical trials of medicinal products in humans. In case the Danish Health and Medicines Authority gives grounds for non-acceptance, the sponsor has the opportunity to amend the application once. To ensure that the sponsor has the required time to amend the application, it has been agreed with the pharmaceutical industry that the sponsor is to receive a reply within 42 calendar days, starting on the day the Danish Health and Medicines Authority has received a duly completed application.

In 2013, 88% of all applications were reviewed within 42 calendar days. 10% were reviewed within 60 calendar days, which is the time limit laid down in Directive 2001/20 EC on review of clinical trial applications. The remaining 2% were replied to after more than 60 calendar days.

Our assessment times are published regularly on our website. In 2012, 98% of all applications were replied to within 42 calendar days. In light of the increase in the number of applications and the resources allocated in 2013, the assessment times are considered satisfactory.



[2] The deadline is extended by 30 calendar days for the review of applications for trials with medicinal products for gene therapy and somatic cell therapy as well as medicinal products containing genetically modified organisms. For these medicinal products, the deadline of 90 days may be extended by a further 90 days in cases where public boards or the like are consulted.

Other activities in 2013

We continue our close work with our stakeholders

The clinical research area has many stakeholders, both national and European, and we prioritise interaction highly.

The Danish Health and Medicines Authority meets regularly with: The secretariats of the national and regional ethics committees, the Organization of Danish Medical Societies and the Danish Medical Association, the GCP units, the pharmaceutical industry's committee for clinical research and gene therapy committee (Danish Environmental Protection Agency, Danish Working Environment Authority and the Danish Health and Medicines Authority). In addition, a series of general and specific training activities are conducted.

On a European level, the Clinical Trials Unit participates in three European working groups: The EU Commission's Ad Hoc group, the Clinical Trials Facilitation Group (CTFG) formed by the Heads of Medicines Agency as well as a working group on IT support of new European legislation on clinical trials.

Common application portal with the ethics committees launched in the spring of 2014

In 2013, a new version of the Danish Health and Medicines Authority's extranet DKMAnet was launched; it is a common application portal for the ethics committees and the Danish Health and Medicines Authority. The portal was launched to company users in the spring of 2014 and will be offered to researchers in the course of 2014.

In the long term, the plan is to introduce format requirements so that material related to clinical trials on medicinal products is only received via DKMAnet. We encourage Danish and foreign companies to use the new portal so that any adjustments of procedures can be prepared.

The project is financed by the Danish Ministry of Health and is integrated with the patient recruitment platform on sundhed.dk

New regulation on clinical trials of medicinal products adopted in 2014

The Danish Health and Medicines Authority participated in the negotiations in the Council for the European Commission's proposal for new European legislation on clinical trials of medicinal products, which was adopted in the spring of 2014.

The main objective of the regulation is to promote the number of clinical trials in the EU, including trials with the same medicinal product in several EU countries; the regulation was adopted to harmonise the rules for authorisation as well as the overall conduct and monitoring of clinical trials throughout the EU.

The regulation sticks to central principles from the applicable Directive 2001/20/EC on good clinical practice in connection with the conduct of clinical trials. As a general principle, a clinical trial can only be conducted

provided that the trial subject's rights, safety and welfare are protected and if data from the trial are reliable and robust. Moreover, a number of quality standards for the various trial phases and for the handling of data are also continued.

The regulation also comprises significant changes to the existing system for clinical trials. For example, the introduction of a new model for submission of applications as well as European and national collaboration between member states about the authorisation of trials. Clinical trial applications must be submitted to a common EU portal with an accompanying database so that any information about trials in the EU is accessible in one place. Where trials are to be conducted in several countries, the relevant countries' authorities will collaborate on the authorisation, and the national drug regulatory authority and ethics committees will work closely together. The European Commission and the European Medicines Agency provide technical support to the common assessment.

Other changes include specific provisions on clinical trials in emergencies, risk-based requirements to the application material, shorter assessment times and simplified rules on safety reporting during the trial period.

Moreover, the regulation sets stricter requirements for public access to data related to clinical trials.

The Danish Health and Medicines Authority now participates in European and national working groups to prepare the coming into force of the regulation.

Campaign about Reference Safety Information

When conducting clinical trials of medicinal products, suspected unexpected serious adverse reactions (SUSAR) must be reported on an ongoing basis to the Danish Health and Medicines Authority (read more). In connection with the assessment of applications, we have in 2013 focused on the Reference Safety Information, which is the list of expected adverse reactions, that is adverse reactions which should not be reported to the Danish Health and Medicines Authority. We have focused on the Reference Safety Information, the contents of the document and the wish to use the same document for a period of one year. This is to ensure agreement between the sponsor, the investigator and the authorities on the expected adverse reactions and thus which adverse reactions need to be reported as unexpected reactions. The Clinical Trials Facilitation Group has made a common document about the Reference Safety Information; read more in the news item from 2013.

SUSAR project

From January to August, the Danish Health and Medicines Authority received 293 SUSARs. Approximately 48% of the SUSARs did not meet the requirements for SUSAR reporting and should not have been reported. Consequently, we invited the Danish Association of the Pharmaceutical Industry to a meeting about this issue. The purpose was to create awareness about this and in the long term to ensure optimisation of the resources for SUSAR reporting at the investigator, the sponsor and the Danish Health and Medicines Authority.

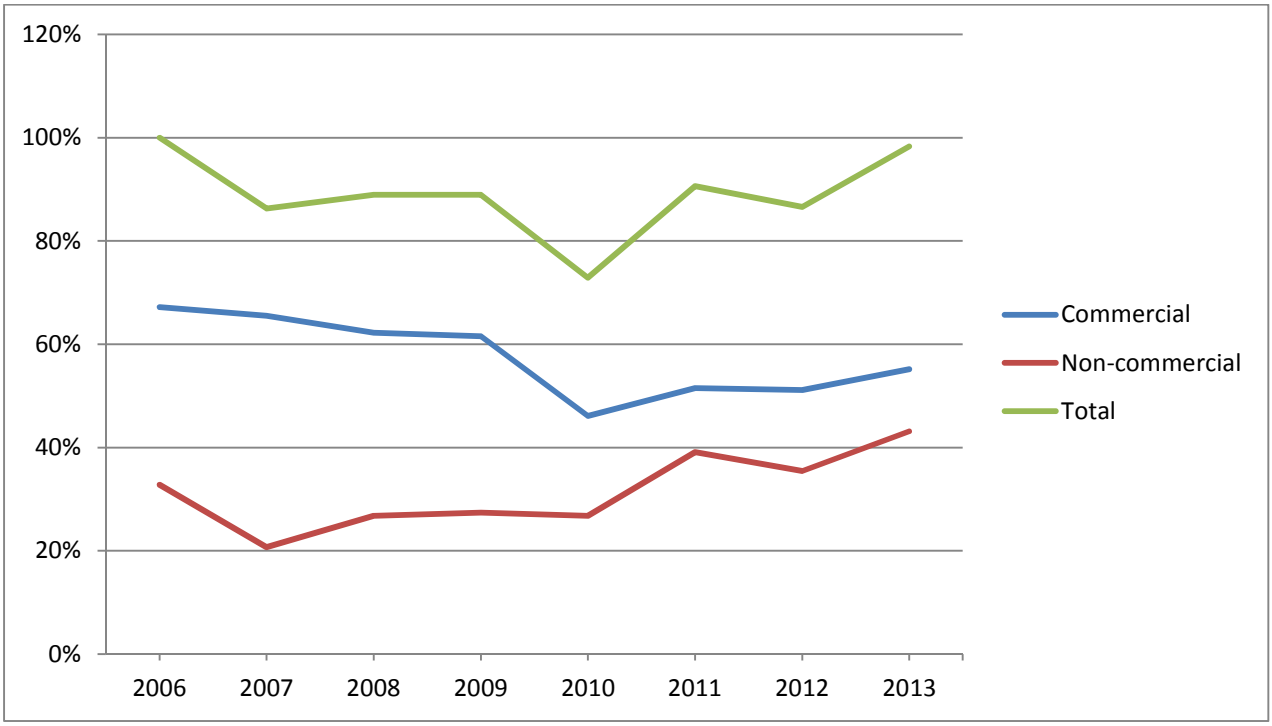
Notes

This report is primarily based on data from EudraCT, the common European database, which was established with the implementation of Directive 2001/20/EC in 2004. Data was extracted in February 2013 and represents a snapshot of the data and data quality of EudraCT. It is therefore likely that newer searches would return a slightly different result.

The annual report presents data on all trials applied for to the Danish Health and Medicines Authority in 2013 and are not corrected for the trials that have been withdrawn or refused.

The annual report concerns trials notified in 2013 and does not reflect the overall medicines development research activity in Denmark as many trials are conducted over several years.

Appendix 1: The development in the number of clinical trials in Denmark distributed according to type of sponsor in the period 2006 to 2013.



Appendix 2: Distribution of the number of trials and number of trial subjects on therapeutic area.