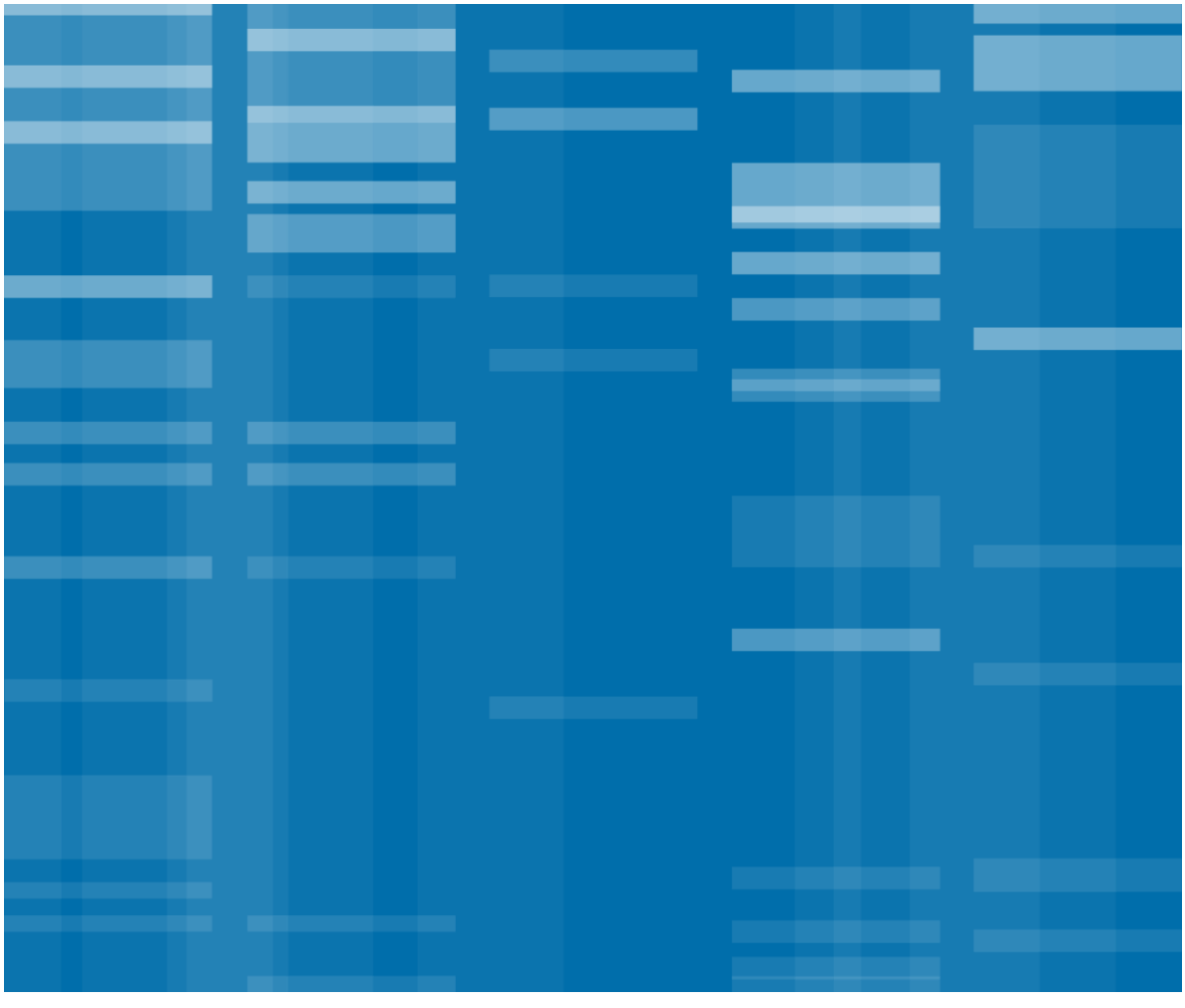
LÆGEMIDDELSTYRELSEN
DANISH MEDICINES AGENCY

07/2016

Annual report 2015

Clinical trials of medicines



Danish Medicines Agency
Axel Heides Gade 1
2300 Copenhagen S
Denmark
dkma.dk

Keywords
Clinical trials, annual report, 2015, statistics

Language
English

Version
1.0

Version date
07/2016

Published by
Danish Medicines Agency, 05/07/2016

Electronic ISBN
978-87-92390-08-0

Contents

1
Introduction

In clinical trials, data are collected systematically from treatment with new or established medicinal products. This is vital for the development of new, effective and safe medicines for the benefit of society. Consequently, it is important that the framework for conducting clinical trials in Denmark contributes to strengthening clinical pharmaceutical research.

A clinical trial must meet a number of ethical and scientific standards to ensure that trial subjects are protected in the best possible way. To make sure that clinical trials comply with these standards, all trials must be authorised by both the Danish Medicines Agency and the research ethics committee system.

In Denmark, clinical trial applications are assessed by Clinical Trials, a unit of the Medicines Licensing & Availability division. Clinical Trials also monitors all ongoing trials on the basis of amendment notifications, reported adverse reactions and annual safety reports.

This annual report presents the most important 2015 figures from Clinical Trials.

2
Summary

Increase in the number of clinical trial applications in 2015 on 2014

In 2015, the Danish Medicines Agency received 329 applications for authorisation of clinical trials of medicines in humans, which is an increase of 15.8% on 2014. Commercial sponsors applied for 190 trials and researchers (non-commercial sponsors) for 139. The increase in the number of applications is the result of a rise in commercial trials (17.3%) and non-commercial trials (13.9%), which means that the distribution of applications from commercial and non-commercial applicants is at the same level as in 2014, 57.8% and 42.2% respectively.

The majority of clinical trial applications are authorised

In 2015, the Danish Medicines Agency authorised 314 applications for authorisation of clinical trials of medicines in humans, corresponding to 95.4% of all clinical trials applied for in 2015. Only four applications were rejected, corresponding to 1.2%, and 11 were withdrawn. Two thirds of the clinical trials were authorised after the Danish Medicines Agency had given grounds for non-acceptance.

Increase in national non-commercial applications

The number of national trials increased as a result of an increase in the number of non-commercial trials of 22%. However, the share of national trials is at the same level as in 2014 and accounts for 37.1% of the total number of applications. The number of multinational trials also increased due to an increase in the number of commercial trials of 13%.

Marked increase in phase I trials

The number of commercial phase I trials rose from 16 applications in 2014 to 32 applications in 2015, or an increase of 100%.

More trial subjects expected to participate in trials in 2015 compared with 2014

In 2015, 19,616 Danish trial subjects are expected to participate in 329 trials. This is an increase of around 6,000 compared to 2014 (13,743). This is a larger increase than what could be expected from the increased number of applications in 2015.

Cancer-related clinical trials still the dominant area in 2015

The cancer field (neoplasms benign, malignant and unspecified (incl cysts and polyps)) continues to be the most frequent therapeutic area, and the therapeutic area expected to have the highest number of trial subjects in 2015.

3
Significant increase in the number of clinical trial applications in 2015 on 2014

In 2015, the Danish Medicines Agency received 329 applications for authorisation of clinical trials of medicines in humans, which is an increase of 15.8% on 2014.

Commercial sponsors applied for 190 trials and researchers (non-commercial sponsors) for 139.

Number of clinical trials notified to the Danish Medicines Agency			
Year	Commercial sponsor	Non-commercial sponsor	Total
2005	215	89	304
2006	229	107	336
2007	207	63	270
2008	194	81	275
2009	183	85	268
2010	142	84	226
2011	154	117	271
2012	153	106	259
2013	165	129	294
2014	162	122	284
2015	190	139	329

Table 1: Number of clinical trial applications received from 2005 to 2015, by type of sponsor.

It is positive to see a significant increase in the number of new applications for authorisation of clinical trials of medicines in humans in 2015 compared with 2014, considering the marginal fall in the number of applications in 2014 on 2013. This led

to a concern about a downward trend in the number of clinical trial applications in Denmark. With the 2015 figures, this concern proved unfounded, and the development from 2010 has now been reversed. In addition, the number of clinical trial applications is almost at the same level as in 2006, which was the peak year.

The number of applications from non-commercial sponsors rose by 17, or 13.9% relative to 2014. In the same period, the number of applications from commercial sponsors rose by 28, or 17.3%. The percentage distribution of applications from commercial and non-commercial sponsors, respectively, in 2015 (57.8% and 42.2%) is comparable to the figures from 2014 (57% and 43%).

Appendix 1 shows a graphical presentation of the development in the number of clinical trial applications by type of sponsor from 2006 to 2015.

4
Increase in non-commercial national clinical trial applications in 2015 on 2014

Among the 329 clinical trial applications, 207 trials are conducted simultaneously in Denmark and other European countries (multinational trials), whereas just over one third of the trials (122) are conducted in Denmark only (national). The percentage distribution of applications from multinational and national sponsors, respectively, in 2015 (63% and 37%) is comparable to the figures from 2014 (65% and 35%).

Among the 122 national trials, 89% (109) of the trials are conducted by non-commercial sponsors, and only 11% (13) are conducted by commercial sponsors. Among the 207 multinational trials, 85.5% (177) of the trials are conducted by commercial sponsors, and 14.5% (30) are conducted by non-commercial sponsors.

Table 2 shows that the increase in the total number of clinical trial applications in 2015 is the result of an increase in commercial multinational trials and non-commercial national trials. This is a positive development, especially for non-commercial national trials, which decreased from 2013 to 2014 and which caused a concern for a negative trend in relation to national clinical trials. This development

turned in 2015, which shows an increase in non-commercial national trials of 22% on 2014.

The continued large share of commercial multinational applications in 2015 once again underlines the observation from previous annual reports of how important it is that the Danish authorities continue to participate actively in influencing the European development in the clinical trial area.

Distribution of multinational and national trials by type of sponsor						
	Multinational trials			**National trials**		
	Commer-cial	Non-commercial	All trials	Commer-cial	Non-commercial	All trials
2011	144	26	170	10	91	101
2012	144	16	160	9	90	99
2013	148	29	177	17	100	117
2014	152	32	184	10	90	100
2015	177	30	207	13	109	122

Table 2: Distribution of multinational and national trials by type of sponsor from 2011 to 2015.

5
Increase in commercial phase I and phase III clinical trial applications in 2015 on 2014

Figure 1 shows the distribution of applications according to trial phase and type of sponsor from 2011 to 2015. It appears from the figure that the increase in the number of applications from 2014 to 2015 is mainly attributable to a rise in the number of commercial phase I and phase III applications. The number of

commercial phase I trials rose by 16 applications, which is an increase of 100%. The number of commercial phase III trials rose by 19 applications, which is an increase of 20.4%.

The number of clinical trial applications in phases II and IV (both non-commercial and commercial trials) are comparable with data from 2013, and the same applies to non-commercial phase I and phase III trials.

The significant increase in commercial phase I applications may be attributable to the National Experimental Therapy Partnership (NEXT). NEXT is a public-private partnership with an ambition to establish Denmark as a country of choice for the pharmaceutical industry for carrying out early-stage clinical trials of new medicinal products in patients. The objective in 2015 was at least four clinical trials under the auspices of NEXT; an objective which was met by far with the initiation of 42 trials[1].

[1] The figures are provided by NEXT, see News on NEXT's website
The news article is from November 2015 (in Danish only).

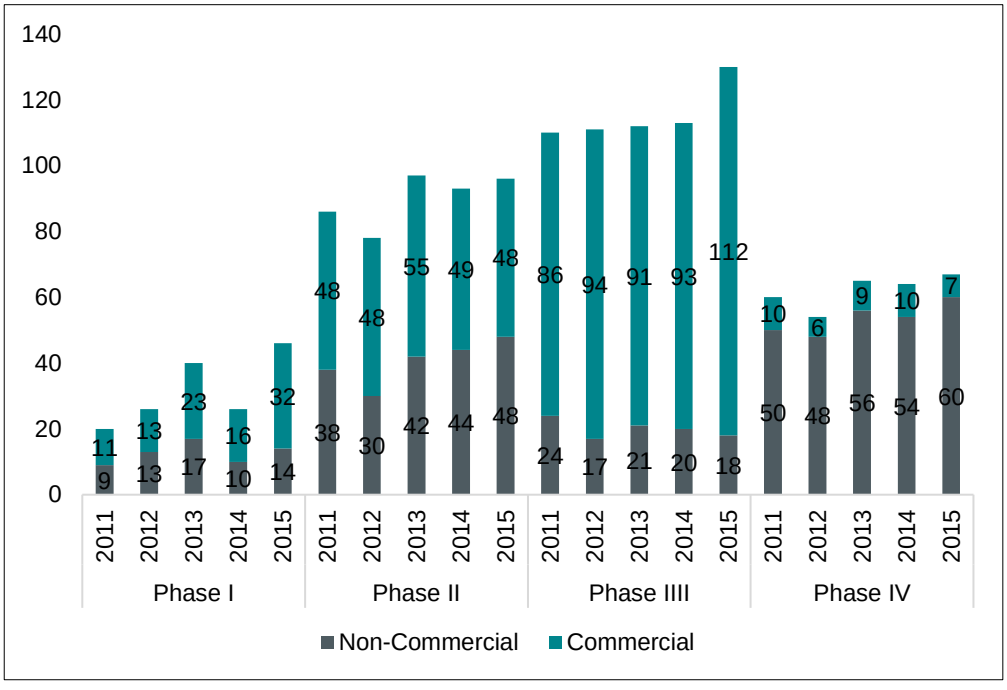


Figure 1: Distribution of clinical trial applications according to trial phase and type of sponsor.

It is positive to see an increase in phase I and phase III trials. Commercial phase I trials are usually trials of new medicinal products administered to humans for the first or second time. In recent years, we have also seen that integrated protocols have become more common in development trials. These trials require further assessment because more documentation must be submitted to guarantee the safety of the trial subjects (see international guidelines).

6
More trial subjects expected to participate in clinical trials in 2015 compared with 2014

In 2015, 19,616 Danish trial subjects are expected to participate in 329 trials. This is an increase of around 6,000 compared to 2014 (13,743). This is an increase of 42.7% on 2014. And 26.9% more than what could be expected on the basis of the increase in the number of trials in 2015[2]. Thus, the increase in the number of trial subjects is not only attributable to the increase in the number of trials.

The higher number of trial subjects in 2015 on 2014 is a break with the downward trend in the number of trial subjects that started in 2011.

Figure 2 shows the number of clinical trials in trial subject ranges in both 2014 and 2015. When we compare the number of trial subjects for the two years, it appears that the number of trials in the trial subject ranges of 101-200, 201-500 and more than 500 increased by five trials from 2014 to 2015. This is the primary reason for the increase in the expected number of trial subjects in 2015. The lowest number of trial subjects in 2015 was one, as in 2014, the highest 1,200.

[2] Calculated on the basis of the increase in trials multiplied by the average number of trial subjects per trial in 2014.

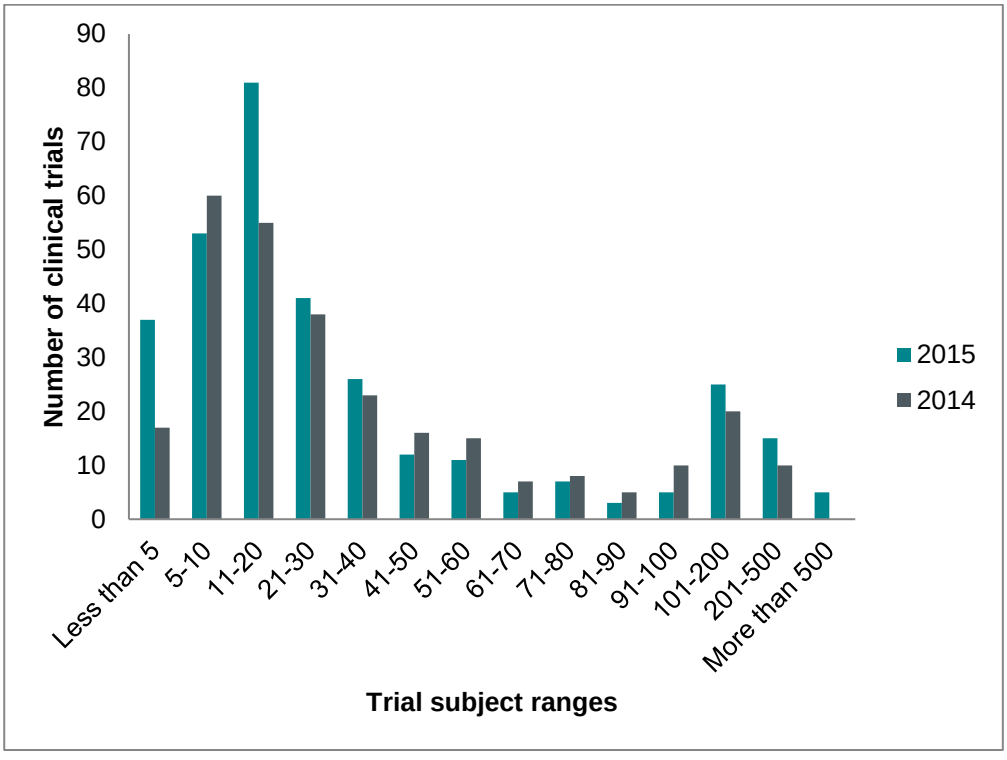


Figure 2: Bar chart of the number of trials in trial subject ranges.

7 Cancer-related clinical trials still the dominant area in 2015

Table 3 shows that the cancer field (neoplasms benign, malignant and unspecified (incl cysts and polyps)) continues to be the most frequent therapeutic area among clinical trial applications, which has been the case for the past five years. The number of applications related to cancer increased from 80 applications in 2014 to 101 in 2015. The number of applications related to cancer is four times higher than the four second-most occurring therapeutic areas. Compared with 2014, investigations, congenital, familial and genetic disorders as well as metabolism and nutrition disorders are no longer in top five of the most frequent therapeutic areas

within clinical trials. However, nervous system disorders are back on the list. Appendix 2 shows a comparison between notified trials by therapeutic area for 2014 and 2015. Note that an individual trial may be conducted in several therapeutic areas.

Notified trials by therapeutic area	
MedDRA[3] therapeutic area code	**Number of trials**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	101
Nervous system disorders	24
Respiratory, thoracic and mediastinal disorders	22
Infections and infestations	21
Surgical and medical procedures	21

Table 3: Top 5 therapeutic areas measured by the number of clinical trial applications in 2015.

When looking at the number of trial subjects by therapeutic area, it also appears that cancer-related trials are the dominant area. Table 4 shows the top 5 therapeutic areas with the highest number of clinical trial subjects. Compared with data from 2014, the primary reason for the expected increase in the number of trial subjects is an increase within almost all therapeutic areas. However, it should be noted that there is a major decline in the number of expected trial subjects within investigations, reproductive system and breast disorders as well as vascular disorders. This is in line with the fall in the number of clinical trials applied for within these therapeutic areas.

[3] Medical Dictionary of Regulatory Activities

Top 5 therapeutic areas measured by number of trial subjects.	
MedDRA[4] therapeutic area code	**Number of trial subjects**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3,053
Surgical and medical procedures	2,787
Cardiac disorders	1,975
Infections and infestations	1,872
Gastrointestinal disorders	1,255

Table 4: Top 5 therapeutic areas measured by number of trial subjects.

8 Increase in the share of clinical trials coordinated by the Central Denmark Region

Figure 3 shows the distribution of clinical trial applications according to which regional ethics committee received the application for approval. The Capital Region of Denmark coordinates the majority of clinical trials (54.7%) in 2015, which was also the case in 2014. However, this share is somewhat lower than in 2014 (62%). The reason is that the number of clinical trials coordinated by the Capital Region of Denmark in 2015 did not increase significantly compared with 2014, despite the higher number of clinical trials. In return, there is an increase of 32 trials coordinated by the Central Denmark Region in 2015 on 2014. This is an increase of 74.4%, which means that the Central Denmark Region coordinates 22.8% of all clinical trials. The other regions coordinate more or less the same number of applications as

[4] Medical Dictionary of Regulatory Activities

in 2014. Region of Southern Denmark received 40 applications (44 in 2014), North Denmark Region and Region Zealand both received 14 (12 and 9, respectively, in 2014).

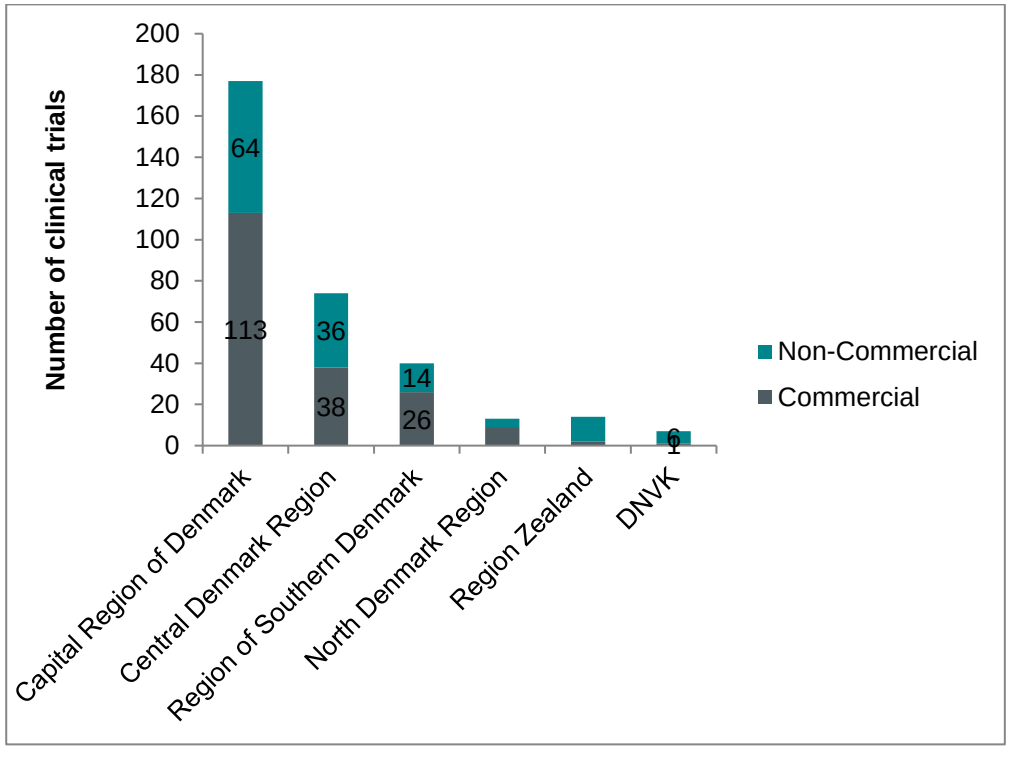


Figure 3: Distribution of clinical trial applications according to type of sponsor and regional affiliation of the ethics committee with which the application has been filed.

9 Assessment by the Danish Medicines Agency

The work with clinical trials is organised in the Clinical Trials unit under Medicines Licensing & Availability. In 2015, Clinical Trials had eight full-time employees and seven 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 Medicines Agency received 329 applications in 2015. 314 authorisations were granted, corresponding to 95.4% of all trials applied for in 2015, four applications were rejected and 11 were withdrawn.

The Danish Medicines Agency gives grounds for non-acceptance and requests corrections to the documentation of the majority (66.6%) of the clinical trial applications in 2015. This should be seen in the light of the Danish Medicines Agency's intention to give sponsors advice to ensure that clinical trials comply with applicable requirements.

9.1.1 Stable use of Voluntary Harmonisation Procedure (VHP)

Since 2009, it has been possible to obtain a coordinated assessment of an application for a clinical trial that is to be conducted in more than three European countries through the Voluntary Harmonisation Procedure (VHP). Figure 4 shows that the number of cases reviewed through this procedure in Europe increased from 2014 to 2015. In 2015, 218 clinical trials were applied for through VHP, which is an increase of 45 trials (26%).

In 2015, Denmark participated in 50 VHP cases, which means that Denmark participates in 23% of the total number of European VHP cases. Unfortunately, this is a decline on 2014. Denmark acted as reference member state in 1 case in 2011, 2 cases in 2012, 5 cases in 2013, 1 case in 2014 and 6 cases in 2015. In four of the cases from 2015, the sponsor asked us to act as reference member state.

The procedure is offered by the European working group Clinical Trials Facilitation Group (CTFG). CTFG was formed by the Heads of Medicines Agencies in 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. Read more about the procedure.

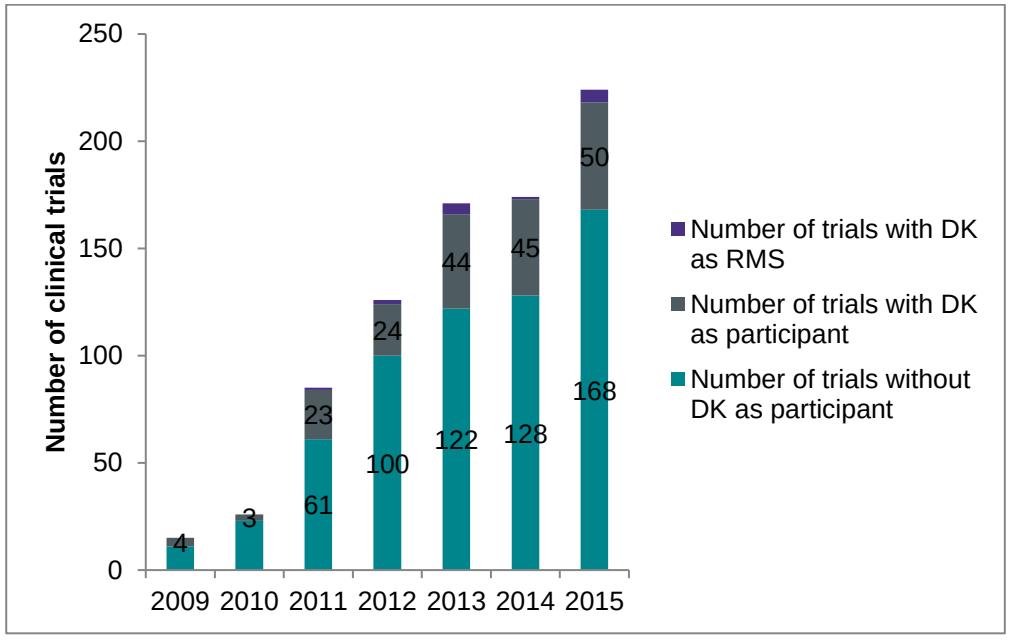


Figure 4: Number of cases reviewed through the Voluntary Harmonisation Procedure

9.1.2 Assessment times

The maximum time for assessment is 60 calendar days[5] as set out in the executive order on clinical trials of medicinal products in humans. If the Danish Medicines Agency gives grounds for non-acceptance, the sponsor can 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 Medicines Agency has received a valid application.

In 2015, 80.3% of all applicants received a reply within 42 calendar days. 19.6% received a reply within 60 calendar days and the remaining <1% received replies after more than 60 calendar days. Our assessment times are published regularly on

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

our website. In 2013 and 2014, 88% and 91.1%, respectively, of all applications were replied to within 42 calendar days.

In the light of the resources allocated and the fact that clinical trial applications are becoming more complex (see section 6), the assessment times are considered satisfactory.

Figure 5: Assessment time intervals as a percentage of the total number of applications per month.

10
Other activities in 2015

10.1.1 Preparations for Regulation 536/2014 require national and European cooperation – IT project

New legislation on clinical trials of medicines was adopted in Europe in 2014. Regulation 536/2014 was published on 28 May 2014, and in December 2015 the European Medicines Agency Management Board endorsed a revised time frame. As a result, the regulation is expected to become applicable in October 2018.

The new rules imply complex changes of the European regulatory authorities' authorisation and supervision of clinical trials of medicinal products, and we participate in the preparatory work, both nationally and in Europe.

The development of the European database and portal are a condition for applying the rules of the regulation and conditional upon an audit of the system which is approved by the European Medicines Agency Management Board.

In Denmark, the regulation requires that the Danish Medicines Agency and the medicinal research ethics committees, unlike today, coordinate their assessments and decisions of clinical trials of medicinal products.

The European database and portal are expected to support the collaboration between member states, but the national process required for the coordination and completion of the assessment phase is not expected to be supported by the common European system. Consequently, a pre-analysis project has been initiated to map out the opportunities for IT support of the new, national business processes in connection with the authorisation of clinical trials.

The Danish Medicines Agency participates in the European collaboration and is a member of the European Medicines Agency's working groups concerning the development of the new European database and portal and is also involved in the testing of the system.

In addition, the Danish Medicines Agency participates in the European Commission's Ad Hoc group, which prepares guidelines on the interpretation of the regulation, and in the Clinical Trials Facilitation Group (CTFG), which focuses on operational changes in the member states.

10.1.2 Common application portal with the research ethics committees, DKMAnet

We plan to launch a new version of DKMAnet for clinical trials shortly.

We have received input from our present users and the new version of DKMAnet will indicate more clearly the information retrieved from EudraCT and the information to be provided by the applicant. It will be possible to submit the annual safety report

with the same substance to several ethics committees, and trials assessed under the Voluntary Harmonisation Procedure (VHP) can also be submitted.

It will not become mandatory to use DKMAnet for clinical trials until an updated executive order on clinical trials is submitted for consultation, which awaits the operating reliability of DKMAnet.

10.1.3 New legislation on clinical trials of medicinal products has been prepared

The adoption of the new European regulation on clinical trials implies changes to the clinical trial rules throughout the EU, and consequently a new national act on clinical trials has been prepared. The new national legislation describes the Danish rules that will apply when the new regulation becomes effective. The act comes into force when the EU regulation becomes effective, most likely in October 2018. However, the present Danish Medicines Act and the Danish act on research ethics committees have been amended at 1 July 2016 and specify that the sponsor, monitor and the Danish Medicines Agency's GCP inspectors have direct access to trial subjects' patient records.

10.1.4 Notes

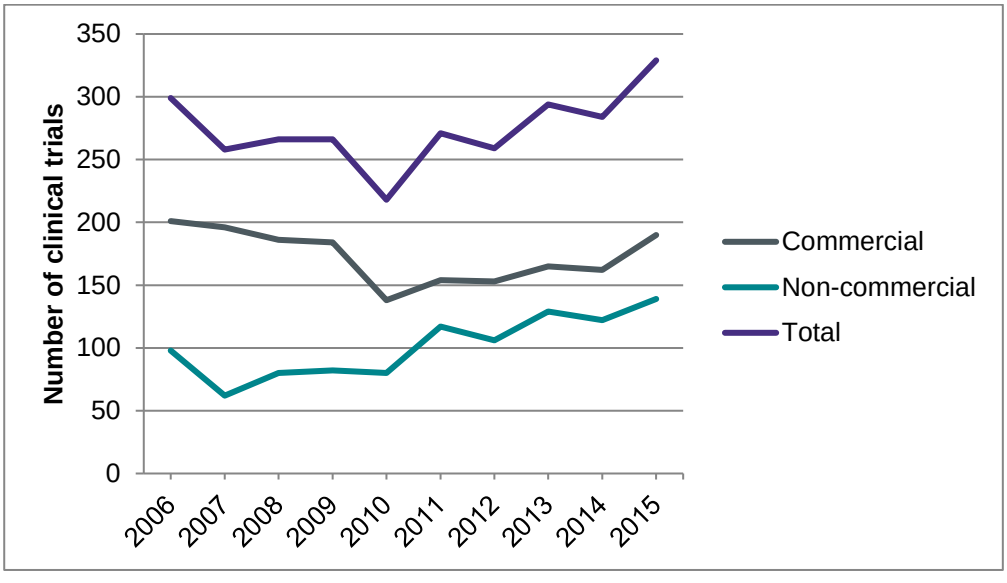
This report is primarily based on data from EudraCT, the common European database, which was established with the implementation of Directive 2001/20/EC in 2004. Data was extracted in May 2016 and represents a snapshot of the data and data quality of EudraCT.

The annual report presents data on all trials applied for to the Danish Medicines Agency by way of a full application in 2015 and therefore comprises trials assessed in 2016.

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

11
Appendices

Appendix 1: Development in the number of clinical trials in Denmark by type of sponsor from 2006 to 2015.



Appendix 2: Number of trials applied for by therapeutic area from 2013 to 2015

	Number of clinical trials applied for		
MedDRA code (SOC)	2015	2014	2013
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	101	80	86
Nervous system disorders	24	15	21
Respiratory, thoracic and mediastinal disorders	22	15	14
Infections and infestations	21	13	16
Surgical and medical procedures	21	21	20
Metabolism and nutrition disorders	18	18	22
Musculoskeletal and connective tissue disorders	18	12	14
Congenital, familial and genetic disorders	17	19	8
Gastrointestinal disorders	14	11	11
Cardiac disorders	12	16	20
Skin and subcutaneous tissue disorders	12	7	7
Investigations	11	22	11
Injury, poisoning and procedural complications	10	9	8
Renal and urinary disorders	9	6	14
Immune system disorder	6	1	4
Endocrine disorders	5	6	4
Eye disorders	5	2	5
General disorders and administration site conditions	5	3	5
Psychiatric disorders	5	1	2
Hepatobiliary disorders	3	3	3
Blood and lymphatic system disorders	2	3	4
Reproductive system and breast disorders	2	8	4
Pregnancy, puerperium and perinatal conditions	0	1	5
Skeletal malformation NOS	0	0	0
Social circumstances	0	1	0
Vascular disorders	0	7	5
Total number of authorised trials in Denmark	343	300	313

Appendix 3: Number of trial subjects by therapeutic area from 2013 to 2015

	Number of patients in Denmark		
MedDRA code (SOC)	2015	2014	2013
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3053	2914	2025
Surgical and medical procedures	2787	2445	1362
Cardiac disorders	1975	1142	3541
Infections and infestations	1872	788	1254
Gastrointestinal disorders	1255	257	533
Respiratory, thoracic and mediastinal disorders	1107	568	378
Musculoskeletal and connective tissue disorders	1075	804	1073
Injury, poisoning and procedural complications	1050	472	347
Nervous system disorders	950	772	1453
Metabolism and nutrition disorders	947	1023	1199
Immune system disorders	864	18	139
General disorders and administration site conditions	506	74	252
Renal and urinary disorders	472	166	721
Psychiatric disorders	340	120	90
Investigations	271	922	648
Blood and lymphatic system disorders	212	210	138
Skin and subcutaneous tissue disorders	201	131	117
Endocrine disorders	194	144	106
Congenital, familial and genetic disorders	147	293	376
Eye disorders	111	15	125
Reproductive system and breast disorders	52	539	340
Hepatobiliary disorders	40	206	87
Pregnancy, puerperium and perinatal conditions	0	24	269
Skeletal malformation NOS	0	0	0
Social circumstances	0	30	0
Vascular disorders	0	359	295
Total number of patients	19,481	14,436	16,868