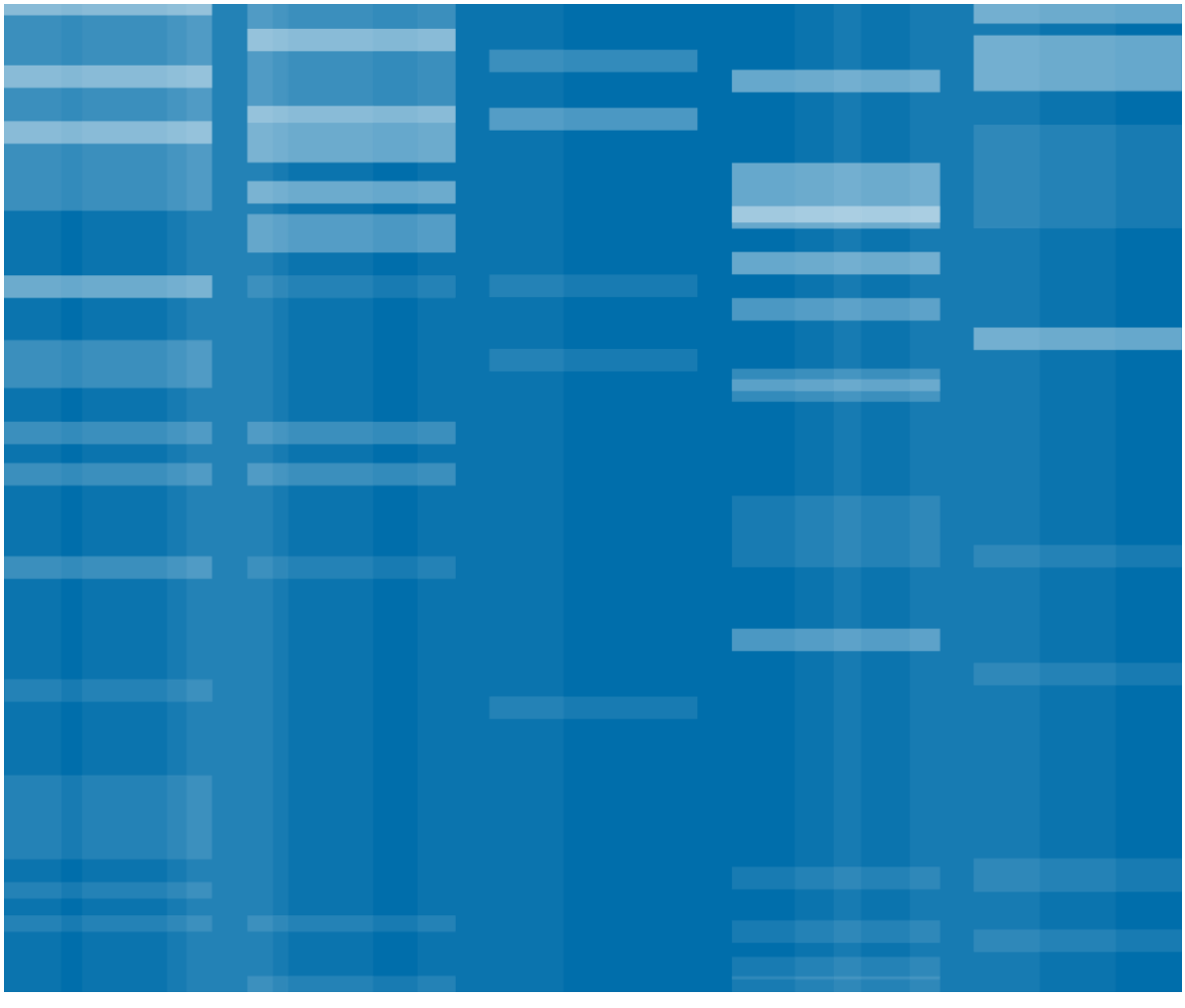
LÆGEMIDDELSTYRELSEN
DANISH MEDICINES AGENCY

05/2017

Annual report 2016

Clinical trials of medicines



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Keywords
Clinical trials, annual report, 2016, statistics

Language
English

Version
1.0

Version date
05/2017

Published by
Danish Medicines Agency, 19/05/2017

Electronic ISBN
978-87-92390-23-3

Contents

1
Background

Clinical trials of medicinal products are conducted to systematically collect data related to treatment with new or already authorised medicinal products. This is vital for the development of new, effective and safe medicines that benefit society.

A clinical trial of medicinal products must comply with a number of ethical and scientific standards to secure the best possible protection of trial subjects. To make sure that clinical trials of medicinal products comply with these standards, all trials planned to be conducted in Denmark must be authorised by both the Danish Medicines Agency and the system of research ethics committees.

At the Danish Medicines Agency, clinical trial applications are assessed by the Clinical Trials unit of the Medicines Licensing 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 2016 figures from Clinical Trials.

2
Summary

The number of clinical trial applications varies from month to month, but also from year to year. In 2016, we saw a fall in the number of clinical trial applications compared with 2015. However, over a number of years (2013 to 2016), the number of clinical trial applications has remained stable at around 300 applications.

In 2016, the Danish Medicines Agency received 286 applications for authorisation of clinical trials of medicines in humans. 281 of these applications were authorised, corresponding to 98% of all trials applied for in 2016. Only two applications were rejected and three were withdrawn. Two thirds of the clinical trials were authorised after the Danish Medicines Agency had given grounds for non-acceptance, which is comparable to 2015.

In 2016, we saw an increasing number of amendment notifications regarding ongoing trials. The Danish Medicines Agency processed 803 amendments in 2016 compared with 699 in 2015, which is an increase of 15%.

The percentage distribution of applications from commercial and non-commercial sponsors in 2016 (55% and 45%, respectively) is comparable to the figures from 2015. The same applies to the percentage distribution of applications from multinational and national sponsors in 2016 (62% and 38%, respectively).

If we look at the relationship between the various phases of a clinical trial of medicinal products and the number of applications, we saw a decline in 2016 in clinical trial applications in phases I, III and IV, but an increase in the number of phase II trials applied for.

The cancer field continued to be the most frequent therapeutic area among clinical trial applications. In 2016, the number of applications related to cancer is at the same level as in 2015.

Despite the fall in the number of clinical trial applications in 2016, we saw an increase of around 3,000 in the planned number of trial subjects on the Danish sites for trials authorised in 2016. This equals an increase of 16% on 2015.

3
Number of clinical trial applications on a stable level since 2013

In 2015, we saw a significant increase in the number of clinical trial applications in Denmark compared with 2014. This increase did not continue in 2016 and the number of clinical trial applications is now at the same level as in 2014. Overall, the number of clinical trial applications has remained stable at around 300 applications per year since 2013.

In 2016, the Danish Medicines Agency received 286 applications for authorisation of clinical trials of medicines in humans, which is a decline of 13% on 2015.

Commercial sponsors applied for 158 trials and researchers (non-commercial sponsors) for 128 trials.

Number of clinical trials submitted to the Danish Medicines Agency			
Year	Commercial sponsor	Non-commercial sponsor	Total
2012	153	106	259
2013	165	129	294
2014	162	122	284
2015	190	139	329
2016	158	128	286

Table 1: Number of clinical trial applications received from 2012 to 2016, by type of sponsor.

The number of applications from non-commercial sponsors dropped by 11, or 8% relative to 2015. In the same period, the number of applications from commercial sponsors declined somewhat more than the number of applications from non-commercial sponsors; we received 32 fewer applications than in 2015, a drop of 17%. The percentage distribution of applications from commercial and non-commercial sponsors in 2016 (55% and 45%, respectively) is comparable to the figures from 2015 (58% and 42%).

Figure 1 shows a graphical presentation of the development in the total number of clinical trial applications by type of sponsor from 2006 to 2016.

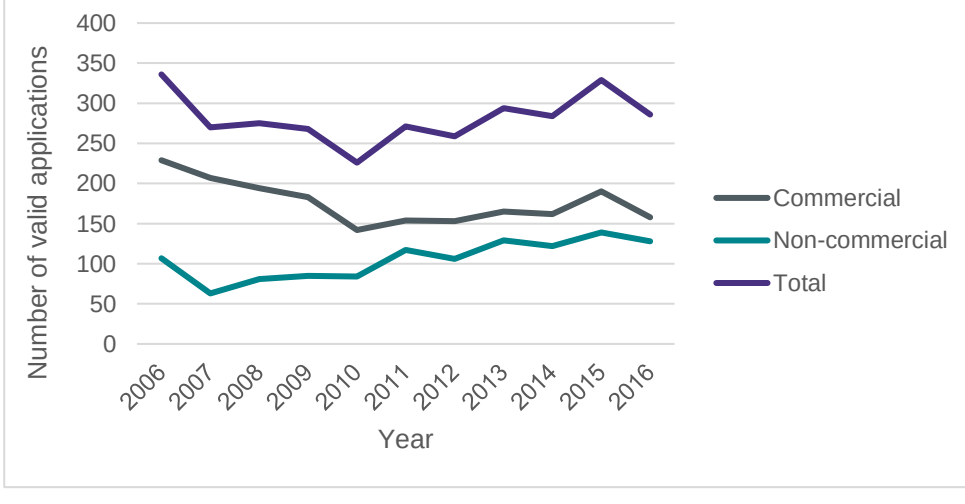

Figure 1: Development in the number of clinical trial applications from 2006 to 2016

In contrast to the decline in the number of applications for new trials, we saw an increasing number of amendment notifications regarding ongoing trials. The Danish Medicines Agency processed 803 amendments in 2016 compared with 699 in 2015, which is an increase of 15%.

4
Distribution of multinational and national trials unchanged

In 2016, the number of both multinational and national trials dropped. However, the distribution of clinical trial applications from multinational and national sponsors is still comparable to both 2014 and 2015.

Among the 286 clinical trial applications, 177 trials are conducted both in Denmark and other countries (multinational trials), whereas just over one third of the trials (109) are conducted in Denmark only (national). The percentage distribution of applications from multinational and national sponsors in 2016 (62% and 38%, respectively) is comparable to the figures from 2015 (63% and 37%).

Distribution of multinational and national trials by type of sponsor						
	Multinational trials			**National trials**		
	Commer-cial	Non-commercial	All trials	Commercial	Non-commercial	All trials
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
2016	151	26	177	7	102	109

Table 2: Distribution of multinational and national trials by type of sponsor from 2012 to 2016.

Among the 109 national trials, 94% (102) of the trials are conducted by non-commercial sponsors, and only 6% (7) are conducted by commercial sponsors. Among the 177 multinational trials, 85% (151) of the trials are conducted by commercial sponsors, and 15% (26) are conducted by non-commercial sponsors.

5
Increase in non-commercial phase II trials

The number of commercial phase I and phase III clinical trial applications is falling. But the number of non-commercial phase II clinical trial applications is increasing.

Figure 2 shows the distribution of applications according to trial phase, type of sponsor and number of applications from 2012 to 2016.

In 2015, we saw an increase of 100% on 2014 in the number of commercial phase I trials applied for. This increase did not continue in 2016 as we saw a decline of 31% (10) in the number of commercial phase I trials applied for, compared with 2015. Commercial phase III applications also fell (17% (19)) compared with 2015.

Non-commercial applications for authorisation to conduct a phase II clinical trial increased by 29% (14) compared with 2015. In return, we saw a fall of 37% (22) in phase IV applications. The reason for this may be that in 2016 the Danish Medicines Agency focused on whether phase IV trials should be considered as phase II trials if new indications for a marketed product are investigated.

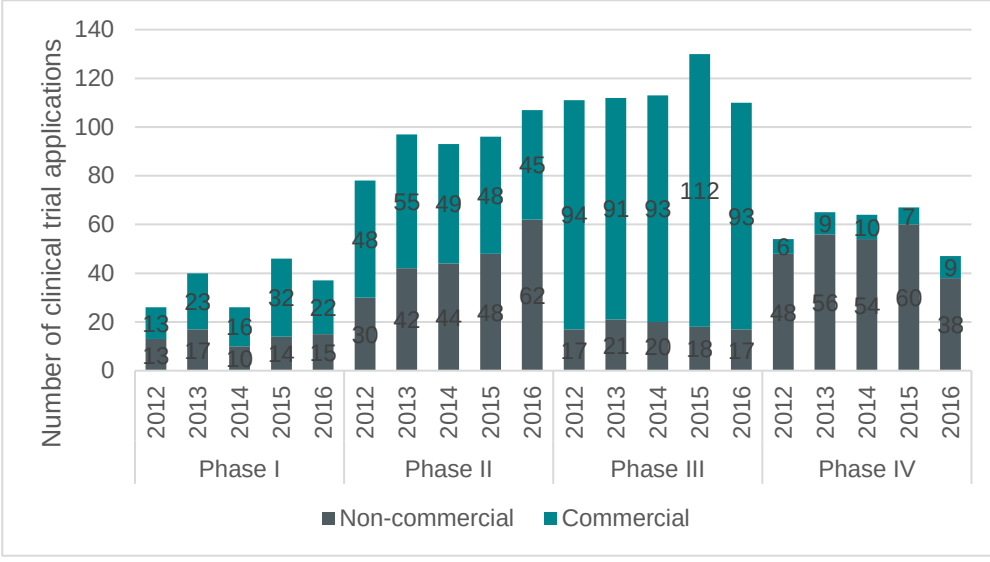

Figure 2: Distribution of clinical trial applications according to trial phase and type of sponsor.

6
The expected number of planned trial subjects continues to increase

In 2016, 21,965 Danish trial subjects were expected to participate in the 281 clinical trials authorised in 2016. This is an increase of around 3,000 compared to 2015 (18,922), corresponding to 16%. Figure 3 shows an increase in the number of expected Danish trial subjects that have participated in clinical trials since 2014. This increase is related to non-commercial trials. This is mainly due to large phase IV trials (>500 trial subjects) that are planning to include more trial subjects.

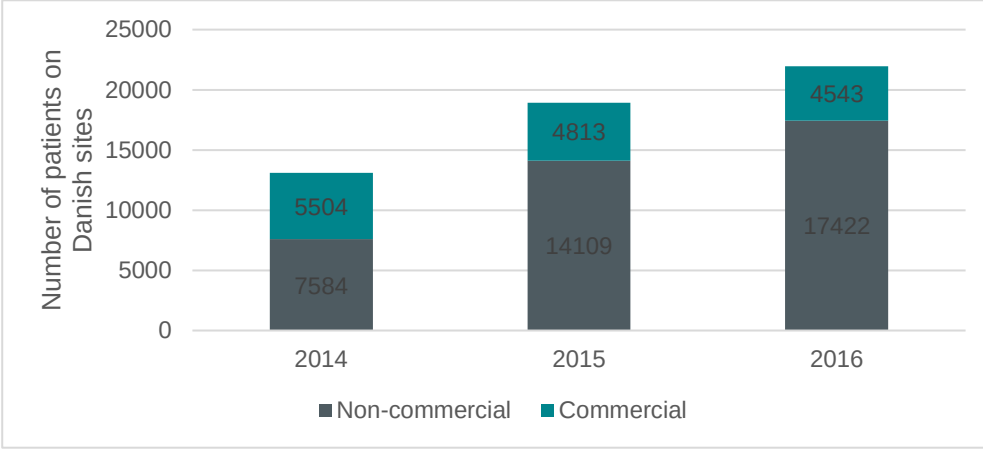

Figure 3: Expected number of included patients on Danish sites in 2016 by type of sponsor.

7
The number of clinical trial applications related to cancer still the dominant area

Once again, the cancer field continues to be the most frequent therapeutic area among clinical trial applications (see table 3). The number of applications related to cancer in 2016 (99) is largely unchanged compared to 2015 (101). The number of applications related to cancer is five times higher than the second-most occurring therapeutic areas. This means that applications related to cancer account for 35% of all clinical trial applications in 2016. However, the planned number of included patients in the cancer field does not account for an equivalent share as 18% of the total number of planned trial subjects in Denmark are patients within the cancer field. See the appendix for the distribution of the planned number of trial subjects in Denmark, by therapeutic area.

Notified trials by therapeutic area	
MedDRA[1] therapeutic area code	**Number of trials**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	99
Neurological disorders	20
Congenital, familial and genetic disorders	19
Metabolism and nutrition disorders	18
Surgical and medical procedures	16
Cardiac disorders	15
Respiratory, thoracic and mediastinal disorders	13
Musculoskeletal and connective tissue disorders	13
Gastrointestinal disorders	10
Investigations (including pharmacokinetics)	9

Table 3: Top 10 therapeutic areas measured by the number of clinical trial applications in 2016.

8
Distribution of trials coordinated by the regional research ethics committees

Figure 4 shows the distribution of clinical trial applications according to which regional research ethics committee received the application for authorisation to conduct the clinical trial. The Capital Region of Denmark coordinated the majority of clinical trials (56%) in 2016, which was also the case in 2015.

[1] Medical Dictionary of Regulatory Activities

The Capital Region of Denmark and the Central Denmark Region are mostly impacted by the fall in the number of clinical trial applications in 2016 compared with 2015. They received 17 and 22 fewer clinical trial applications, respectively, in 2016 compared with 2015. In return, the regional research ethics committee of the Region of Southern Denmark saw a 13% (5) increase in the number of applications in 2016 on 2015, despite the fall in the total number of clinical trial applications.

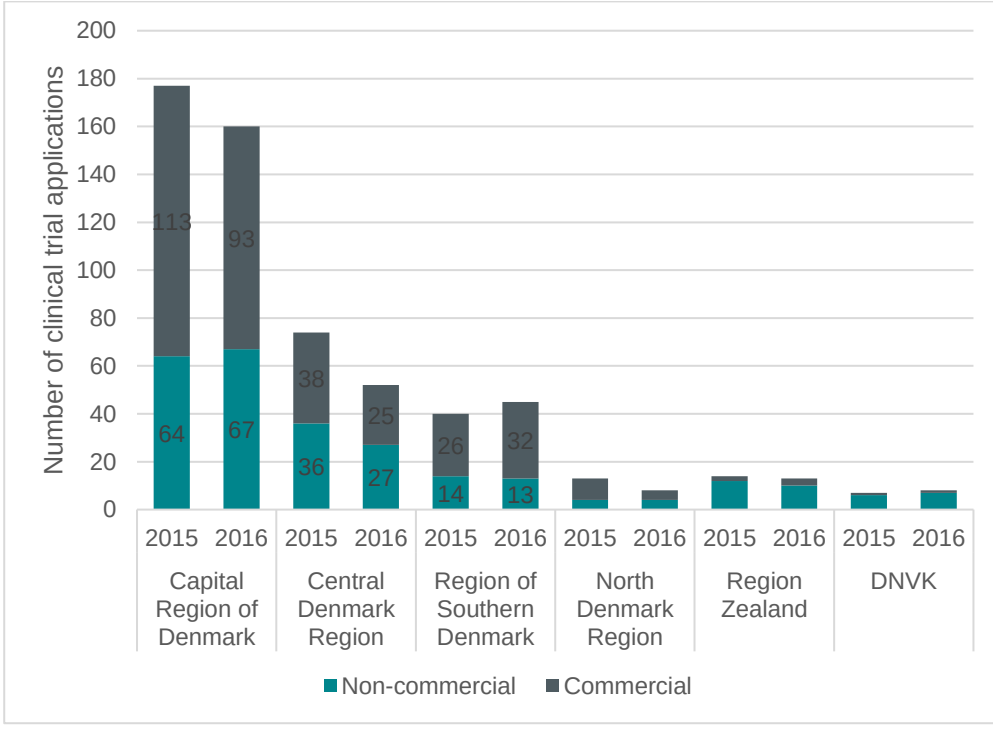

Figure 4: Distribution of the number of clinical trial applications in 2015 and 2016, according to type of sponsor and regional research ethics committee.

9
Assessment by the Danish Medicines Agency

9.1 Clinical trials of medicines in humans

The work with clinical trials is organised in the Clinical Trials unit under the Medicines Licensing division. The unit reviews clinical trial applications and monitors all ongoing trials based on amendment notifications, reported adverse reactions and annual safety reports.

In 2016, the Danish Medicines Agency received 286 applications for authorisation of clinical trials of medicines in humans. 281 of these applications were authorised, corresponding to 98% of all trials applied for in 2016. Only two applications were rejected and three were withdrawn before the assessment was completed. As regards the 281 authorised clinical trials, the Danish Medicines Agency gave grounds for non-acceptance and requested corrections to the documentation of the majority (65%) of the clinical trial applications. The high share of authorised clinical trials should be seen in the light of the Danish Medicines Agency's strategy to provide the best possible advice to applicants before and after the submission of an application to ensure that clinical trials comply with applicable requirements.

9.2 Clinical trials of medicines in animals

The Clinical Trials unit also assesses clinical trials in animals, and for the first time the number of applications for clinical trials of veterinary medicinal products is included in the annual report. In 2016, the number of applications for clinical trials in animals doubled compared with 2015. We received 16 applications for clinical trials in animals compared with 8 applications in 2015. All of the 16 applications for clinical trials of medicines in animals were authorised.

9.3 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). The procedure is offered by the European 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.

Figure 5 shows that the number of cases reviewed through this procedure in Europe dropped from 2015 to 2016. In 2016, 209 clinical trials were applied for through VHP, which is a small drop of 9 trials (4%) on 2015. Denmark participated in 39 VHP cases, which means that Denmark participated in 19% of the total number of European VHP cases. Since 2014, we have seen a slight fall in the number of VHP cases we participate in. Denmark acted as reference member state in 15 cases from 2011 to 2015, which means that Denmark assumed a leading role in the assessment of the VHP application.

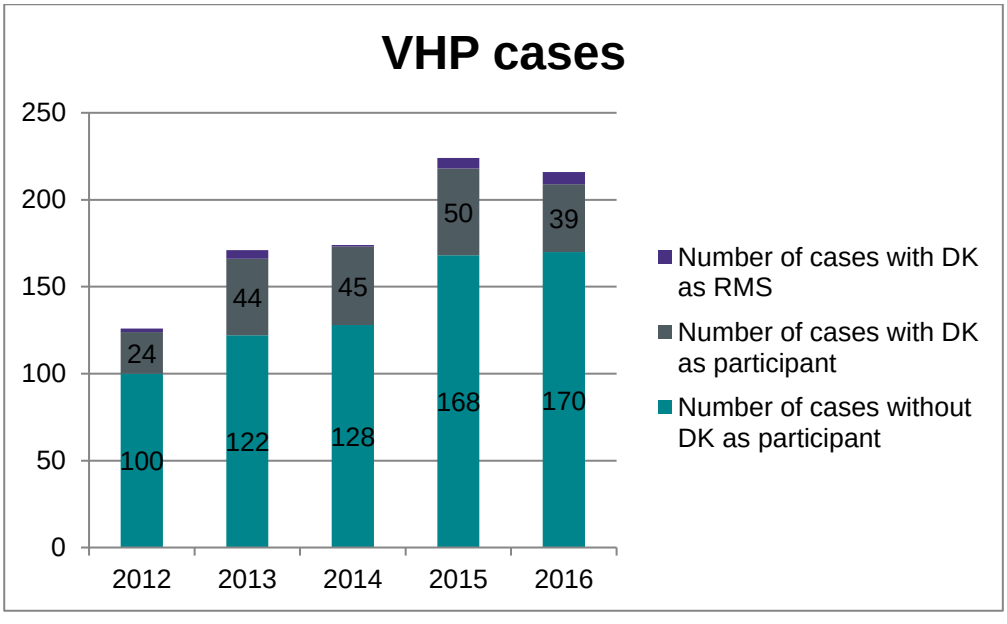

Figure 5: Number of cases reviewed through the Voluntary Harmonisation Procedure

Amendments to trials conducted under this procedure are also assessed through VHP. Figure 6 shows that the number of amendments reviewed through this procedure in Europe increased from 2012 to 2016. In 2016, 452 amendments were applied for through VHP. Denmark participated in 124 VHP amendments, which means that Denmark participated in 27% of the total number of VHP amendments. From 2012 to 2015, Denmark acted as reference member state in 18 amendments. In 2016, Denmark acted as reference member state in 15 amendments. Thus, the handling of amendments under VHP accounts for a larger part of assessments than previously.

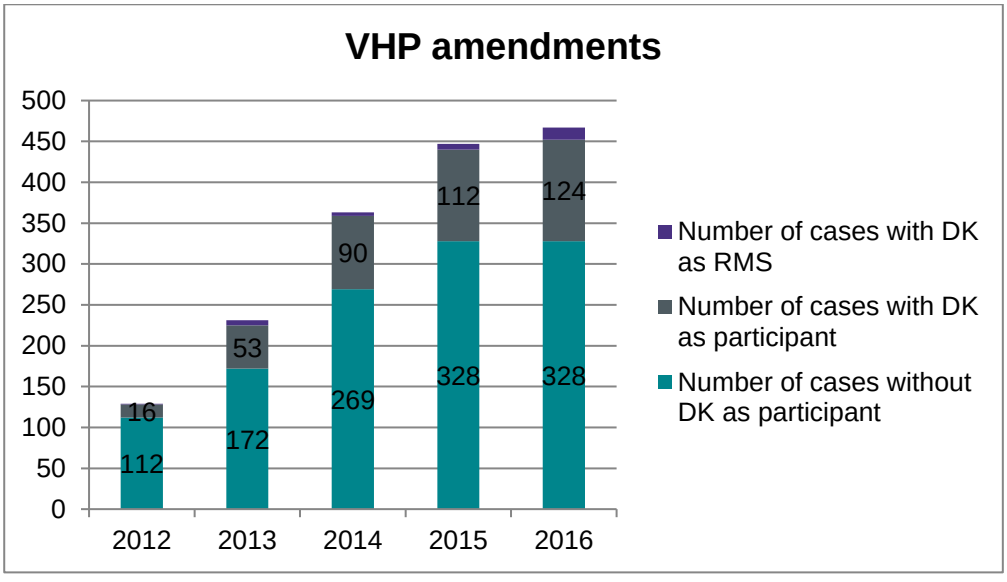

Figure 6: Number of amendments reviewed through the Voluntary Harmonisation Procedure

The VHP-plus procedure was introduced in 2016. This procedure allows the participation of the research ethics committees in VHP in some EU countries. In 2016, Denmark started to offer VHP-plus, which improves the cooperation between the National Committee on Health Research Ethics and the Danish Medicines Agency on the preparations for the clinical trials regulation. VHP-plus in Denmark is offered for clinical trials involving children and/or advanced therapies (ATMP). At present, Denmark has participated in 3 VHP-plus clinical trials. Read more about the VHP procedures on our website and on the CTFG's website

9.4 Assessment times

The maximum time for assessment is 60 calendar days[2] 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 first reply (including grounds for non-acceptance, an

[2] The deadline is extended by 30 calendar days for the review of applications for trials involving 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.

authorisation with terms attached or an authorisation) within 42 calendar days, starting on the day the Danish Medicines Agency has received a valid application.

I 2016, 92% of all applicants received a first reply within 42 calendar days, and the remaining applications for clinical trials of medicinal products received a first reply within 60 calendar days. We publish our assessment times regularly on our website. In 2014 and 2015, 91% and 80% of all sponsors of clinical trial applications received a first reply within 42 calendar days.

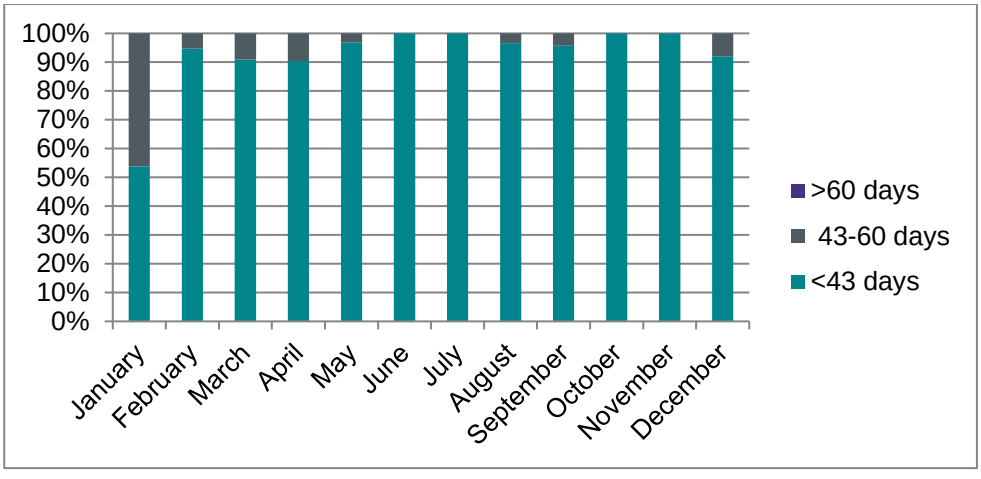

Figure 7: Assessment time intervals (first reply) as a percentage of the total number of applications per month.

10
Other activities in 2016

10.1 Preparations for regulation 536/2014

A new EU regulation on clinical trials will become effective in October 2018, amending the rules on clinical trials throughout the EU. In Denmark, we have come a long way implementing the new regulation compared with other EU countries.

To prepare for the implementation of regulation 536/2014, the Danish Medicines Agency, the secretariat of the National Committee on Health Research Ethics and the Danish Ministry of

Health have contributed to the preparatory work of the Danish Parliament's adoption of a new act on clinical trials of medicinal products, which implies that new medicinal research ethics committees must be established, among other things.

The new EU regulation does not describe the national collaboration on clinical trials, and consequently the Danish Parliament has adopted a new Danish act on clinical trials of medicinal products which lays down the Danish rules that will apply when the new regulation becomes effective.

The act comes into force when the EU regulation becomes effective.

The application of the EU regulation requires the development of an EU portal and database (EUPD) for clinical trials in the EU. The European Medicines Agency (EMA) is responsible for the development of the EUPD and the Danish Medicines Agency contributes actively to the groups of experts set up by the EMA.

The implementation of the new EU regulation implies significant changes to procedures and processes of the national competent authorities. Consequently, the Danish Medicines Agency and the secretariat of the National Committee on Health Research Ethics have made a preliminary IT analysis to identify any needs for IT support of the new national procedures.

10.2 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 April 2017 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 2016 and therefore comprises trials assessed in 2017.

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

11
Appendix

MedDRA code (SOC)	2016
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3,877
Neurological disorders	620
Congenital, familial and genetic disorders	239
Metabolism and nutrition disorders	1,440
Surgical and medical procedures	7,875
Cardiac disorders	2,701
Respiratory, thoracic and mediastinal disorders	788
Musculoskeletal and connective tissue disorders	150
Gastrointestinal disorders	320
Investigations (including pharmacokinetics)	449
Infections and infestations	644
Skin and subcutaneous tissue disorders	197
Injury, poisoning and procedural complications	286
Renal and urinary disorders	189
Reproductive system and breast disorders	328
Eye disorders	82
Psychiatric disorders	526
Immune system disorders	130
Hepatobiliary disorders	70
Haematological disorders	52
Endocrine disorders	60
General disorders and administration site conditions	12
Vascular disorders	10
Pregnancy, puerperium and perinatal conditions	0
Skeletal malformation	0
Social circumstances	0

Appendix 1: Distribution of the planned number of trial subjects in Denmark in clinical trials of medicinal products, valid and authorised in 2016, by therapeutic area.