EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

8 April 2013
EMA/INS/GCP/676319/2012
Compliance and Inspection

Clinical trials submitted in marketing-authorisation applications to the European Medicines Agency

Overview of patient recruitment and the geographical location of investigator sites

Containing data from 2005 to 2011

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

An agency of the European Union

Table of contents

1. List of abbreviations

BE	Bioequivalence trials
CHMP	Committee for Medicinal Products for Human Use
CIS	Commonwealth of Independent States
CRO	Contract research organisation
DCP	Decentralised procedure
FDA	U.S. Food and Drug Administration
GCP	Good clinical practice
IEC	Independent ethics committee
IRB	Institutional Review Board
EEA	European Economic Area
EFTA	The European Free Trade Association
EMA	European Medicines Agency
EU	European Union
FYRM	Former Yugoslav Republic of Macedonia
MAA	Marketing-authorisation application
MAH	Marketing-authorisation holder
MRP	Mutual-recognition procedure
NCA	National competent authority
PTL	Product team leader
ROW	Rest of the world

2. Introduction

The revisions to the pharmaceutical legislation which came into force in 2005 increased emphasis on the ethical standards required of clinical trials conducted in third countries and included in marketing-authorisation applications (MAAs) submitted in the EU. There is growing concern both among regulators and in public debate about how well these trials are conducted from an ethical and scientific/organisational standpoint, including good clinical practice (GCP) compliance and about the available framework for the supervision of these trials. Information is required in each MAA regarding the location of conduct and ethical standards applied in respect of clinical trials conducted in third countries.

Information on the geographic origins of patients recruited in the pivotal trials included in MAAs submitted to the centralised procedure has been collected since 2005.

This report provides an overview of the distribution of the number of patients, investigator sites and pivotal clinical trials included in MAAs submitted to the European Medicines Agency ('the Agency'), on the number of sites subject to inspection and the geographic location of these inspections.

This report was first published in 2009 with the data from MAAs submitted between 2005 and 2008. The second report, containing data up to 2009, was published in 2010 and this is the third report adding data from MAAs submitted in 2010 and 2011.

3. Scope

The information presented in this report covers the period from January 2005 to December 2011 and relates mainly to new applications (485), line extensions (95) and variations where new clinical trial information was provided (97). Summary of the number of MAAs evaluated per year for this purpose is provided in **Table 1**.

Table 1. Number of applications per year reviewed during the preparation of this report.

	2005	2006	2007	2008	2009	2010	2011	Total
New applications	39	60	68	77	103	70	68	485
Line extensions	3	8	17	13	22	17	15	95
Type-II variations	2	5	4	12	19	30	25	97
	44	**73**	**89**	**102**	**144**	**117**	**108**	**677**

It should be noted that generic applications are included as part of the new applications. Although they do not add much to the number of patients, since these applications are mainly based on small bioequivalence trials, they do provide information on the locations where these trials are conducted.

The data provide a clear picture of where the pivotal trials have been carried out, but care needs to be taken when interpreting this information. The following therefore need to be taken into account:

- only those trials identified by the applicant as pivotal at the time of the MAA are included;
- supportive trials are not included - which means Phase I, most Phase II, and some Phase III trials; post authorisation Phase IV trials are only included where they have been used in line extensions or some variations;
- many products never come to market so the clinical trials on those products do not appear in these data;
- the data are recorded against the year in which the MAA was submitted. The patients would actually have entered the trials in preceding years (probably 1-5 years earlier in many cases), so the picture is one of a historical situation. Patient recruitment patterns that are happening now in 2013 will only appear in MAAs of 2014-2020;
- the number of trials and MAAs in any year is small in absolute terms so the overall picture can be changed by the addition of data from a small additional number of MAAs;
- the data collection period (2005-2011) is short and the major trends are undoubtedly taking place over a longer term. The widespread information on increases in clinical trials in Asia has probably not yet been fully reflected in the MAAs or involves trials that will not all be included in MAAs submitted to the Agency or these trials are not all pivotal trials.

Information on GCP inspections in relation to the centralised procedure and GCP inspections of bioequivalence trials (BE) recorded in EudraCT (up to December 2011) relating to generic applications is also provided.

4. Methods and results

4.1. The GCP validation process for MAAs

During the validation phase, prior to the start of the assessment phase of a centralized MAA, the Agency's Compliance and Inspection Sector performs a GCP validation of all new application/line extensions received and some variations when new clinical trial information is provided. It should be noted that since mid-2011 the validation of variations is performed by product team leaders (PTLs) in the Agency's Quality and Safety and Efficacy sectors instead of the Compliance and Inspection Sector and therefore the clinical trial information from these variations is not reflected in this report anymore from that date onwards. An overview of the regulatory framework for the GCP information provided in the dossier is given in **Annex 1**.

As part of this GCP validation, and in the context of the information contained in this report, the following information of the MAA dossier is reviewed:

- Module 1.9, Statement on ethical standards for third country trials, to ensure that this statement is provided as required by Directive 2001/83/EC[1]. This statement is applicable for all new applications (including extension applications), and other relevant post-authorisation regulatory procedures (e.g. variations) for which clinical trial reports are submitted. The validation process checks that this statement comes together with a listing of all trials (protocol number) and third countries involved as required in the Notice to Applicants[2].
- Module 2.5, Clinical Overview, to ensure that a statement regarding GCP compliance in relation to the clinical development programme is included in the clinical overview, as required in the Notice to Applicant, and to obtain an overview of the main pivotal trials included in the application.
- Module 5, Clinical Study Reports, the following information for the pivotal clinical trials is checked:
  - Title page, to ensure there the applicant provides a statement indicating whether the study was performed in compliance with GCP.
  - Section 5 about ethics, to ensure that the applicant provided information that:
    - the clinical trial was reviewed by an Independent Ethics Committee (IEC);
    - the study was conducted in accordance with the ethical principles equivalent to those of Directive 2001/20/EC[3];
    - the method of informed consent in the context of the patient population involved.
  - Section 9.6 Data Quality Assurance, to have a better knowledge of the quality assurance system implemented by the company in terms of monitoring, data management and audits.
  - Appendices:
    - 16.1.1 Protocol and protocol amendments;
    - 16.1.3 List of IECs or International Review Boards (IRBs) and representative written information for patient and sample consent forms;
    - 16.1.5 Signature of principal or coordinating investigator(s);
    - 16.1.4 List and description of investigators and other important participants in the study, including the number of patients recruited per site (it is from this information that this report is compiled);
    - 16.1.8 Audit certificates (if available).

[1] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (Consolidated version: 21/07/2011).
[2] EudraLex - Volume 2 - Pharmaceutical Legislation Notice to applicants and regulatory guidelines medicinal products for human use.
[3] Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (Official Journal L 121, 1/5/2001 p. 34 - 44).

A list of inspection(s) conducted or planned by other regulatory authorities, related to the product and trial sites involved, should also be available, preferably attached to the Application cover letter as indicated in Question 29 of the EMA Pre-Submission Procedural Advice[4].

The modules referred to are those of the Common Technical Dossier (Volume 2B[5] of the Notice to Applicants).

4.2. Information on the location of clinical trials and patient recruitment

It should be noted that the information from five clinical trials included in five different MAAs which contributed very large numbers of patients have been excluded from the graphs and summary tables as their inclusion would obscure the underlying trends:

- Two applications submitted in 2005 for two vaccines where 36,274 and 38,546 patients, respectively, were recruited in the USA.
- One application submitted in 2005 for a vaccine where 23,422 patients were recruited in Finland
- One application submitted in 2007 for a product for the prevention of atherothrombotic events where 45,852 patients were recruited in China.
- One application submitted in 2011 for a vaccine for prophylaxis where 27,583 and 19,492 patients recruited in Germany and Finland, respectively.

The information provided in this section is presented by region. The information by country is available in **Annex 2** (except for the number of clinical trials that is also provided by country in this section and in **Annex 2**), distinguishing the following regions:

- EU/EEA/EFTA[6] countries with the information split by:
  - EU-15/EEA: the member states of the European Union prior to the accession of the ten new countries on 1 May 2004, plus EEA countries (Norway, Iceland and Liechtenstein);
  - EU-10: 2004 accession countries (Cyprus, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, Slovakia and Slovenia);
  - EU-2: 2007 accession countries (Bulgaria and Romania);
  - EFTA countries: Switzerland.
- North America:
  - USA;
  - Canada.
- Rest of the World (ROW):
  - Africa;
  - Middle East/Asia/Pacific;
  - Australia/New Zealand;
  - Central/South America;
  - CIS (Commonwealth of Independent States i.e. Russia, Ukraine, Georgia etc.);
  - Eastern Europe (non EU) (e.g. Croatia, Serbia etc.).

[4] Human Medicines - EMA Pre-Submission Procedural Advice
[5] Notice to Applicants, Volume 2B, incorporating the Common Technical Document (CTD) (May 2008)
[6] European Union/European Economic Area/The European Free Trade Association

4.2.1. Number of patients

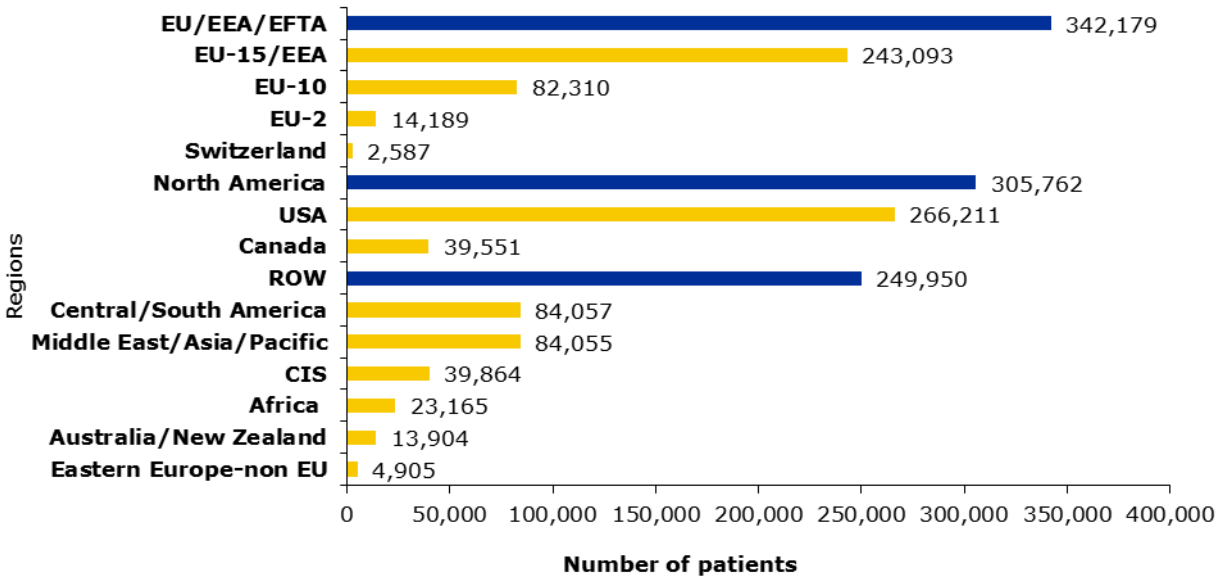
The total number of patients per country and per year is provided in **Annex 2**. A summary of this information per region is provided in Table 2. Most of the patients recruited in the pivotal trials included in the MAAs from 2005 to 2011 come from EU/EEA/EFTA (38.1%) and North America (34.1%). The regions Central/South America and Middle East/Asia/Pacific follow, both with 9.4%. Smaller numbers were recruited in the CIS region (4.4%), Africa (2.6%), Australia-New Zealand (1.5%) and Eastern Europe-non EU (0.5%).

Table 2. Number of patients in pivotal trials submitted in MAAs to the Agency per region and year. The data are shown as three "global regions" – EU/EEA/EFTA, North America and ROW (Rest of the World). These 3 global regions are also shown split into their component sub-regions

	2005		2006		2007		2008		2009		2010		2011		Total	
	Σ	%	Σ	%	Σ	%	Σ	%	Σ	%	Σ	%	Σ	%	Σ	%
EU/EEA/EFTA	**32,090**	**37.0**	**49,960**	**44.2**	**55,667**	**44.1**	**42,024**	**28.6**	**51,628**	**42.1**	**66,220**	**41.6**	**44,590**	**31.2**	**342,179**	**38.1**
EU-15/EEA	27,822	32.1	30,714	27.2	42,894	34.0	27,561	18.7	33,711	27.5	52,680	33.1	27,711	19.4	243,093	27.1
EU-10	3,412	3.9	16,601	14.7	11,016	8.7	11,706	8.0	14,768	12.0	11,358	7.1	13,449	9.4	82,310	9.2
EU-2	656	0.8	2,146	1.9	1,251	1.0	2,447	1.7	2,628	2.1	1,792	1.1	3,269	2.3	14,189	1.6
Switzerland	200	2.1	499	0.4	506	0.4	310	0.2	521	0.4	390	0.2	161	0.1	2,587	0.3
North America	**37,117**	**42.8**	**33,389**	**29.6**	**41,810**	**33.2**	**55,165**	**37.5**	**42,269**	**34.5**	**51,025**	**32.0**	**44,987**	**31.5**	**305,762**	**34.1**
Canada	3,477	4.0	3,919	3.5	6,231	4.9	4,454	3.0	9,581	7.8	6,811	4.3	5,078	3.6	39,551	4.4
USA	33,640	38.8	29,470	26.1	35,579	28.2	50,711	34.5	32,688	26.7	44,214	27.7	39,909	27.9	266,211	29.6
ROW	**17,585**	**20.3**	**29,637**	**26.2**	**28,628**	**22.7**	**49,948**	**33.9**	**28,663**	**23.4**	**42,105**	**26.4**	**53,384**	**37.3**	**249,950**	**27.8**
Africa	523	0.6	1,938	1.7	2,061	1.6	9,962	6.8	3,431	2.8	2,952	1.	2,298	1.6	23,165	2.6
Middle East/ Asia/Pacific	1,694	2.0	9,925	8.8	7,801	6.2	17,458	11.9	9,627	7.9	19,307	12.1	18,243	12.8	84,055	9.4
Australia/New Zealand	1,560	1.8	1,892	1.7	2,663	2.1	1,219	0.8	1,344	1.1	3,321	2.1	1,905	1.3	13,904	1.5
CIS	664	0.8	6,939	6.1	2,731	2.2	6,677	4.5	5,653	4.6	6,463	4.1	10,737	7.5	39,864	4.4
Eastern Europe-non EU	69	0.1	862	0.8	1,202	1.0	1,370	0.9	539	0.4	121	0.1	742	0.5	4,905	0.5
Central/South America	13,075	15.1	8,081	7.2	12,170	9.7	13,262	9.0	8,069	6.6	9,941	6.2	19,459	13.6	84,057	9.4
total	**86,792**	**100**	**112,986**	**100**	**126,105**	**100**	**147,137**	**100**	**122,560**	**100**	**159,350**	**100**	**142,961**	**100**	**897,891**	**100**

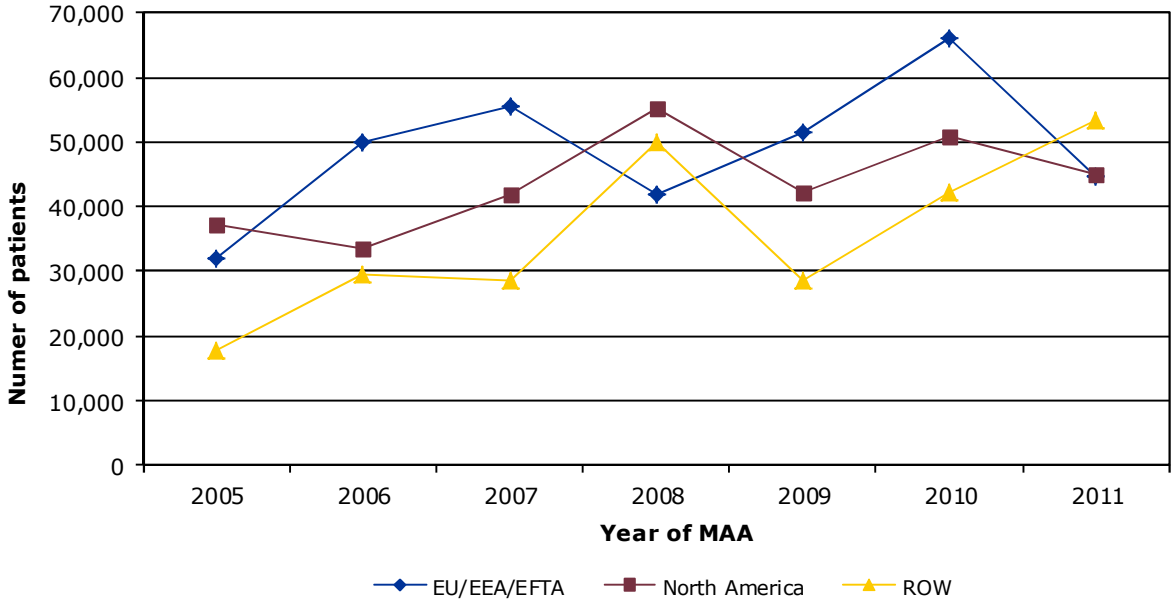
An overview of the situation in the three main regions and corresponding sub-regions in terms of total numbers of patients is shown in **Figure 1**.

Figure 1. Number of patients in pivotal trials submitted in MAAs to the Agency per region/sub-region during the period 2005-2011. The data are shown as three "global regions" – EU/EEA/EFTA, North America and ROW (Rest of the World) and then split into its component sub-regions.



An overview of the trend per year in the three main regions is shown in **Figure 2**.

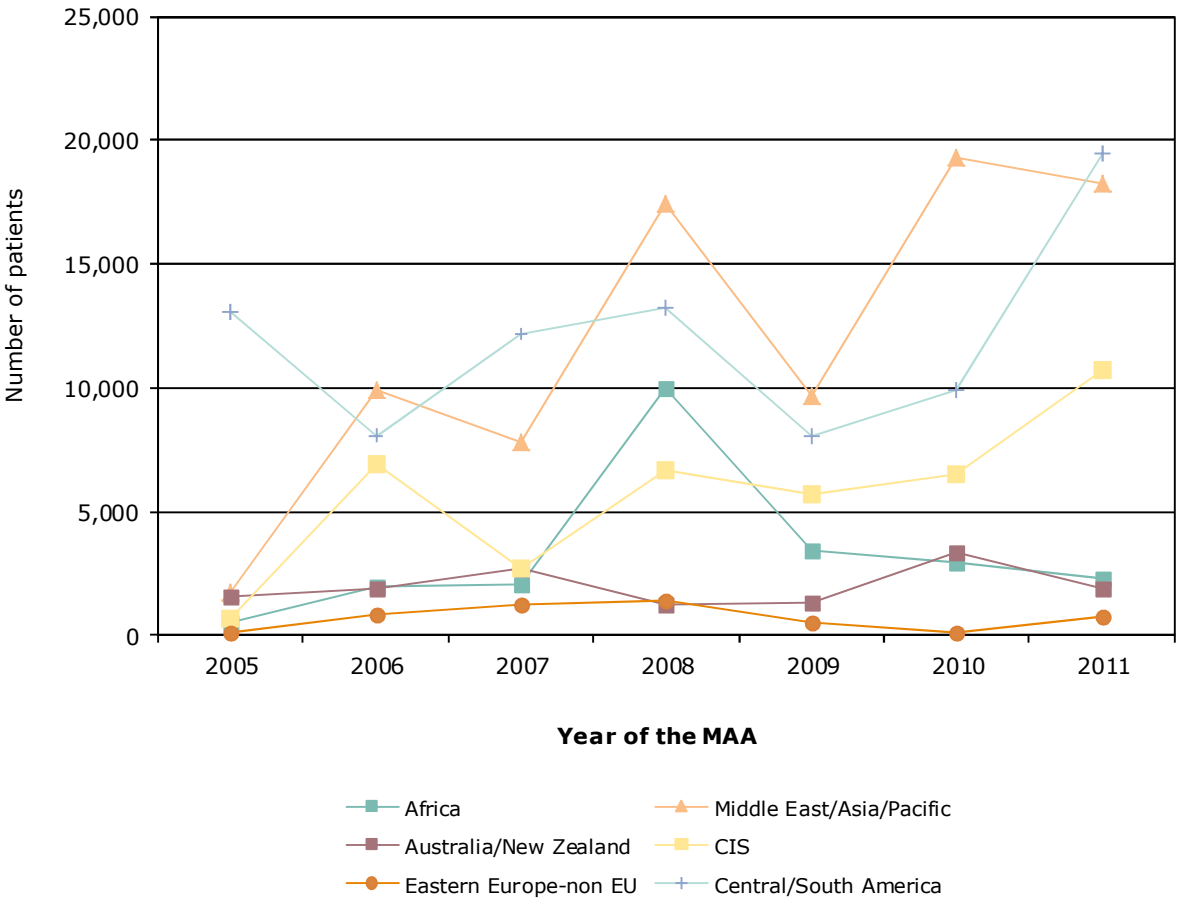
Figure 2. Number of patients in pivotal trials submitted in MAAs to the Agency per region and year. The data are shown as three "global regions" – EU/EEA/EFTA, North America and ROW.



It should be noted that the addition of small numbers of applications may alter this picture significantly.

The trend in the sub-regions of the ROW area per year is shown in **Figure 3**:

Figure 3. Number of patients in pivotal trials submitted in MAAs to the Agency in the sub-regions of ROW region per year.



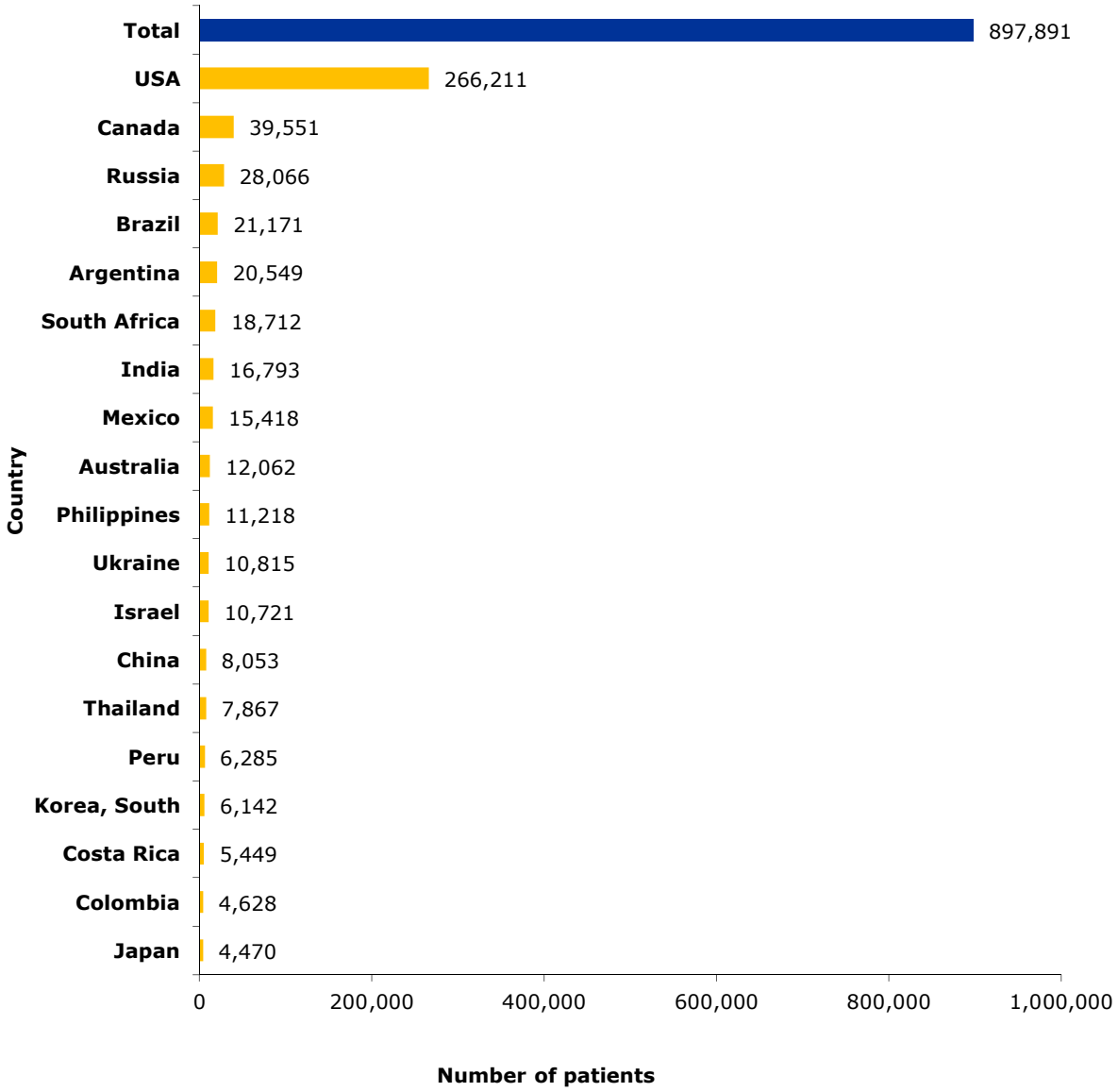
The detailed information on patient recruitment per country and per year can be found in **Annex 2**. A summary of the overall situation during the period 2005-2011 referring mainly to countries recruiting 0.5% or more of the total is:

- EU/EEA/EFTA: the major contributors are Germany (6.8%), Poland (3.9%), France (3%), Finland (2.9%), Italy (2.3%), Spain (2.2%) and UK (2.1%). They are followed in order by Czech Republic, the Netherlands, Belgium and Hungary contributing between 2% and 1.5% of the total number of patients and then Sweden, Denmark, Austria and Lithuania contributing between 1.4% and 0.5%, by descending order;
- Non-EU Eastern European countries: the major contributor is Croatia with a 0.3% of the total number of patients;
- CIS (Commonwealth of Independent States): the major contributor is Russia with 3.1%, followed by Ukraine (1.2%);
- North America: USA is the major contributor with 29.6% while Canada contributes 4.4%;

- Australia-New Zealand: this area provides 1.5%, mainly from Australia (1.3%);
- Central/South America: the major contributor is Brazil (2.4%) followed by Argentina (2.3%), Mexico (1.7%), Peru (0.7%), Costa Rica (0.6%) and Colombia (0.5%);
- Middle East/Asia/Pacific: the major contributors are India (1.9%), Philippines (1.2%), Israel (1.2%), China (0.9%), Thailand (0.9%), Chinese Taipei (0.8%), South Korea (0.7%) and Japan (0.5%);
- Africa: South-Africa is the major contributor with 2.1% of the patients. All the other countries of Africa together represent 0.5% of the patients.

The total number of patients in MAA submitted to the Agency during the 2005-2011 period in those third countries contributing at least 0.5% of the patients is shown in **Figure 4**.

Figure 4. Third countries with at least 0.5% of patients in the pivotal trials included in the MAA submitted to the Agency during the 2005-2011 period.



4.2.2. Number of investigator sites

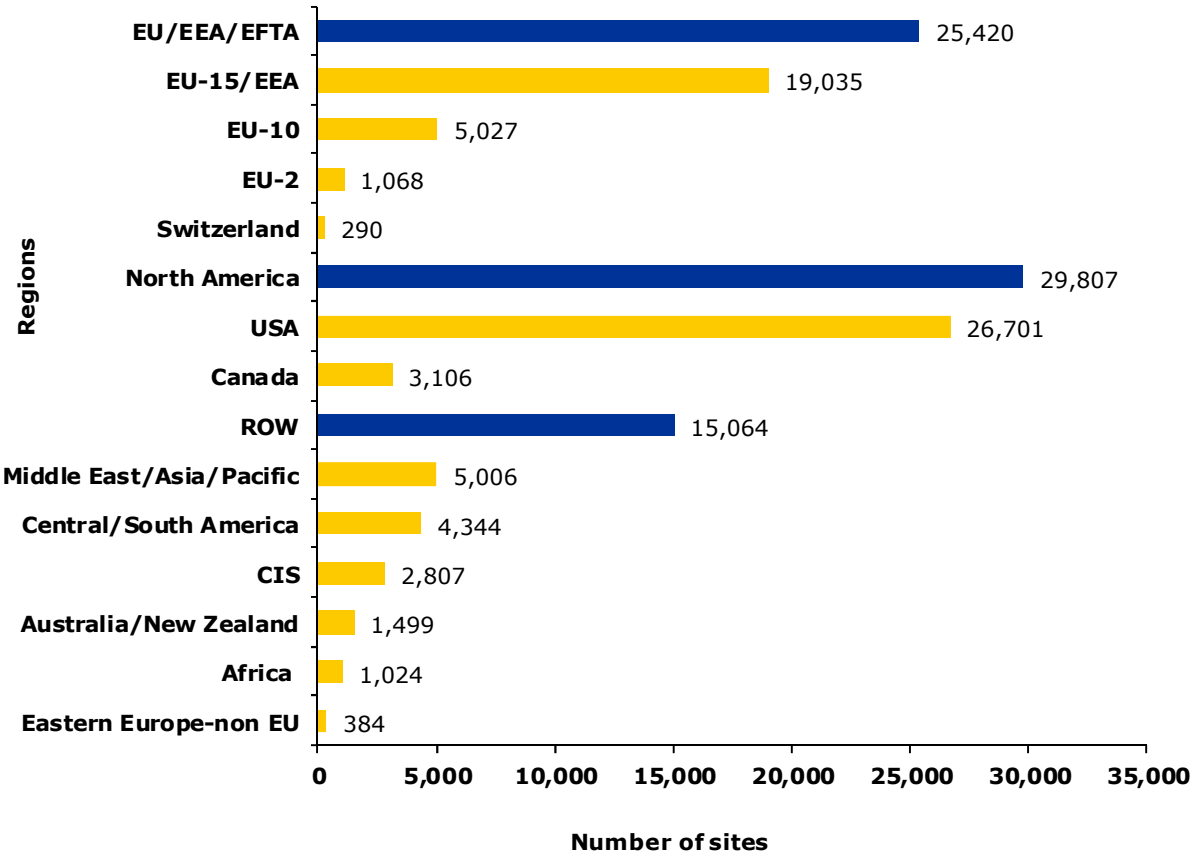
The total number of investigator sites per country is also provided in **Annex 2**. A summary of this information per region is provided in **Table 3**. The highest numbers of sites were located in North America (42.4 %) and EU/EEA/EFTA (36.2 %), followed by Middle East/Asia/Pacific (6.6%) and Central/South America (6.0%) and smaller numbers in the rest of the ROW region.

Table 3. The number of investigator sites involved in pivotal clinical trials submitted in MAAs to the Agency per region and year. The data are shown as three "global regions" – EU/EEA/EFTA, North America and ROW (Rest of the World). These 3 global regions are also shown split into their component sub-regions

No. sites	2005		2006		2007		2008		2009		2010		2011		Total	
	Σ	%	Σ	%	Σ	%	Σ	%	Σ	%	Σ	%	Σ	%	Σ	%
EU/EEA/EFTA	**1,974**	**35.2**	**3,567**	**37.7**	**3,441**	**37.0**	**3,373**	**34.2**	**3,708**	**37.9**	**4,809**	**36.1**	**4,548**	**35.2**	**25,420**	**36.2**
EU-15/EEA	1,676	29.9	2,759	29.1	2,648	28.5	2,431	24.6	2,730	27.9	3,668	27.5	3,123	24.2	19,035	27.1
EU-10	224	4.0	638	6.7	639	6.9	734	7.4	758	7.7	894	6.7	1,140	8.8	5,027	7.2
EU-2	52	0.9	126	1.3	110	1.2	177	1.8	170	1.7	177	1.3	256	2.0	1,068	1.5
Switzerland	22	0.4	44	0.5	44	0.5	31	0.3	50	0.5	70	0.5	29	0.2	290	0.4
North America	**3,042**	**54.3**	**4,168**	**44.0**	**4,150**	**44.7**	**4,182**	**42.3**	**3,820**	**39.0**	**5,701**	**42.8**	**4,744**	**36.7**	**29,807**	**42.4**
Canada	282	5.0	392	4.1	361	3.9	398	4.0	621	6.3	528	4.0	524	4.1	3,106	4.4
USA	2,760	49.2	3,776	39.9	3,789	40.8	3,784	38.3	3,199	32.7	5,173	38.8	4,220	32.6	26,701	38.0
ROW	**589**	**10.5**	**1,737**	**18.3**	**1,699**	**18.3**	**2,320**	**23.5**	**2,264**	**23.1**	**2,819**	**21.1**	**3,636**	**28.1**	**15,064**	**21.4**
Africa	59	1.1	140	1.5	141	1.5	216	2.2	151	1.5	171	1.3	146	1.1	1,024	1.5
Middle East/Asia/Pacific	119	2.1	551	5.8	417	4.5	682	6.9	808	8.3	1,024	7.7	1,405	10.9	5,006	7.1
Australia/New Zealand	118	2.1	229	2.4	220	2.4	175	1.8	177	1.8	311	2.3	269	2.1	1,499	2.1
CIS	72	1.3	320	3.4	226	2.4	498	5.0	450	4.6	434	3.3	807	6.2	2,807	4.0
Eastern Europe - non EU	8	0.1	29	0.3	51	0.5	73	0.7	54	0.6	62	0.5	107	0.8	384	0.5
Central/South America	213	3.8	468	4.9	644	6.9	676	6.8	624	6.4	817	6.1	902	7.0	4,344	6.2
total	**5,605**	**100**	**9,472**	**100**	**9,290**	**100**	**9,875**	**100**	**9,792**	**100**	**13,329**	**100**	**12,928**	**100**	**70,291**	**100**

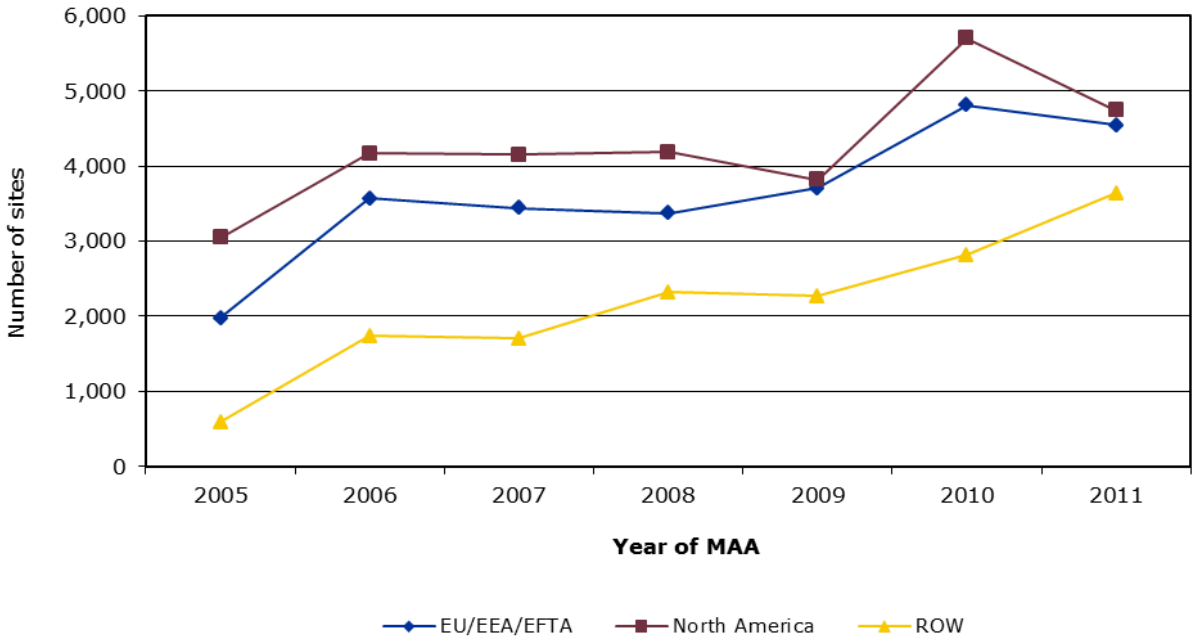
An overview of the situation in the three main regions and corresponding sub-regions in terms of absolute numbers of investigator sites is shown in **Figure 5.**

Figure 5. Number of investigator sites in pivotal trials submitted in MAAs to the Agency per region during the period 2005-2011. The data are shown as three "global regions" – EU/EEA/EFTA, North America and ROW (Rest of the World) and then split into its component sub-regions



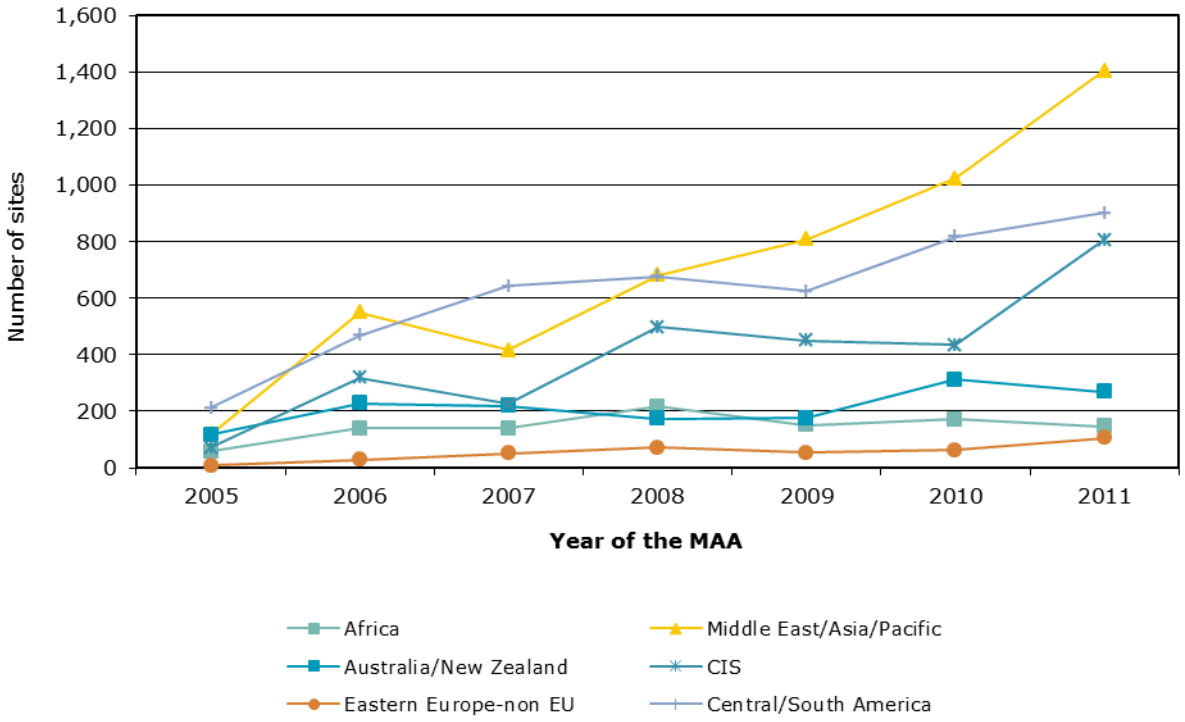
An overview of the trend per year is shown in **Figure 6**. In North America the trend is very similar to the EU/EEA/EFTA situation; however, the number of sites is higher than in Europe over all years, except in 2009 with similar numbers, as opposed to the number of patients (**Figure 2**), which is less except in 2005, 2008 and very similar in 2010 (slightly higher in North America). The trend of these two regions shows an increase in 2006 and in 2010. There has been stability from 2007 to 2009 and a decrease in 2011. In the rest of the world region (ROW) the trend is similar to the trend observed for the number of patients except in 2009 whereas the number of sites remains stable and the number of patients decreases.

Figure 6. The number of investigator sites involved in pivotal clinical trials submitted in MAAs to the Agency per region and year. The data are shown as three "global regions" – EU/EEA/EFTA, North America and ROW (Rest of the World)



The trend per year in the sub-regions of the ROW area, as shown in **Figure 7,** is very similar to the number of patients (**Figure 3**) with the exception of Central/South America in 2006 (with a decrease of sites but increase of patients) and Middle East/Asia Pacific in 2009 and 2011 (with an increase of number of sites but with a decrease in the number of patients). The trend in 2010 and in 2011 is a general increase of both the number of sites and number of patients with the exception of Africa (with an increase in the number of sites but decrease of patients), CIS (with a decrease of the sites but increase of patients) and Eastern Europe-non EU (with small increase of sites, but decrease of the patients).

Figure 7. The number of investigator sites involved in pivotal clinical trials submitted in MAAs to the Agency in the sub-regions of ROW region per year



4.2.3. Number of clinical trials

The overview of this information is provided only per country in **Figures 8** and **9**, as the data, if cumulated per region, result in multiple counting of the same trial.

Figure 8. The number of pivotal clinical trials in MAA submitted to the Agency performed in each country of the North America and EU/EEA/EFTA regions in the 2005-2011 period

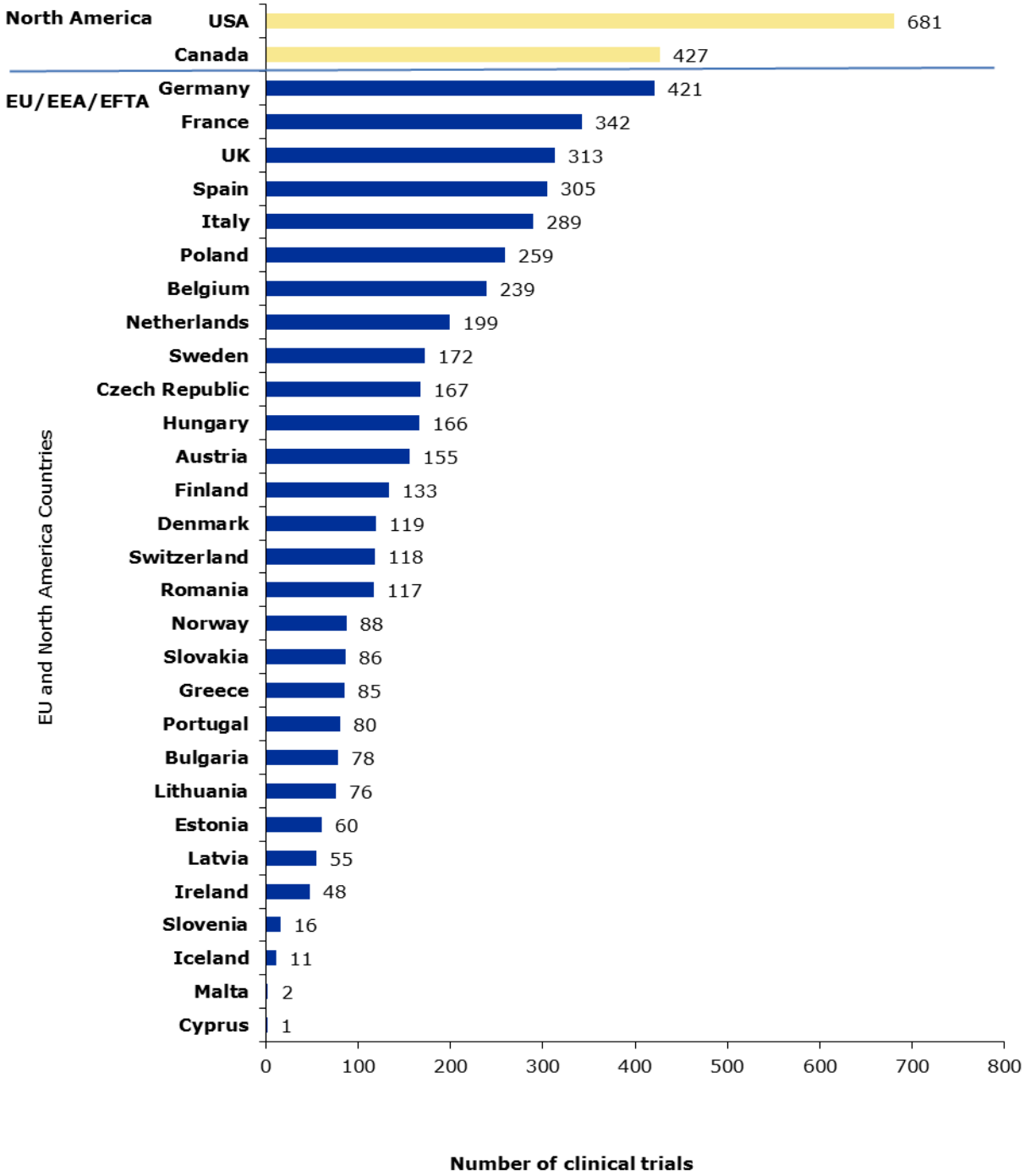
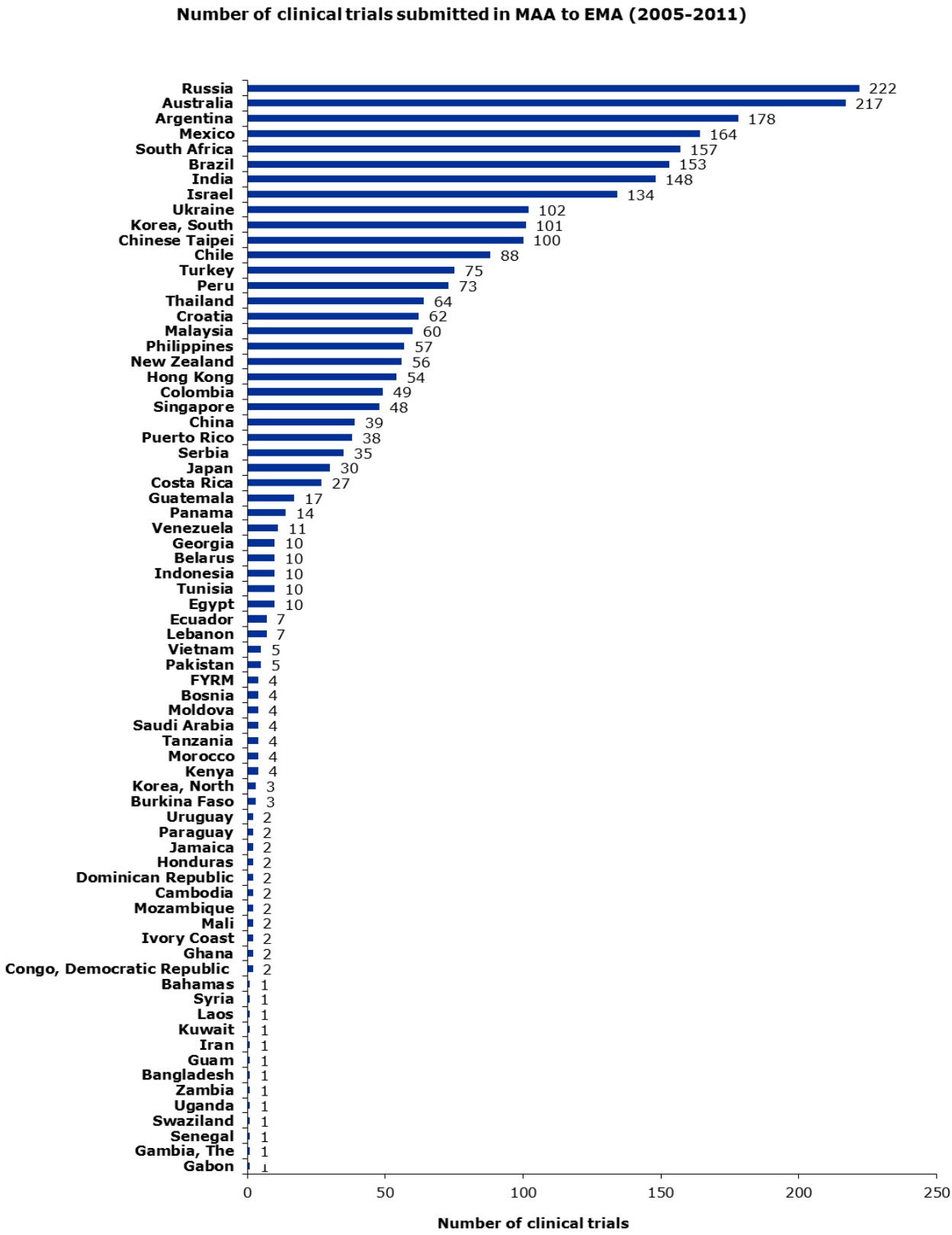


Figure 9. The number of pivotal clinical trials in MAA submitted to the Agency performed in each country of the ROW region in the 2005-2011 period.



It should be noted that those countries with more than 100 clinical trials during the whole period are:

- North America: Canada and USA;
- EU/EEA/EFTA: Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Hungary, Italy, Netherlands, Poland, Romania, Spain, Sweden, Switzerland and UK;
- ROW: Argentina, Australia, Brazil, Mexico, Israel, India, South Africa, South Korea, Ukraine and Russia.

4.2.4. Number of patients in relation to the number of investigator sites

The trend per year regarding the number of patients per investigator site is shown in **Figure 10**. It should be noted that in the ROW area the average number of patients per site over the whole period 2005-2011 is higher than in the other regions, with the exception of 2009 when EU/EEA/EFTA is slightly higher. The average per region, all years combined, is shown in Figure 11 with around 17 patients per site in the ROW, 13 patients per site in the EU/EEA/EFTA and 10 patients per site in North America regions.

Figure 10. Average number of patients per site in pivotal trials submitted in MAAs to the Agency per region and year. The data are shown as three "global regions" – EU/EEA/EFTA, North America and ROW (Rest of the World).

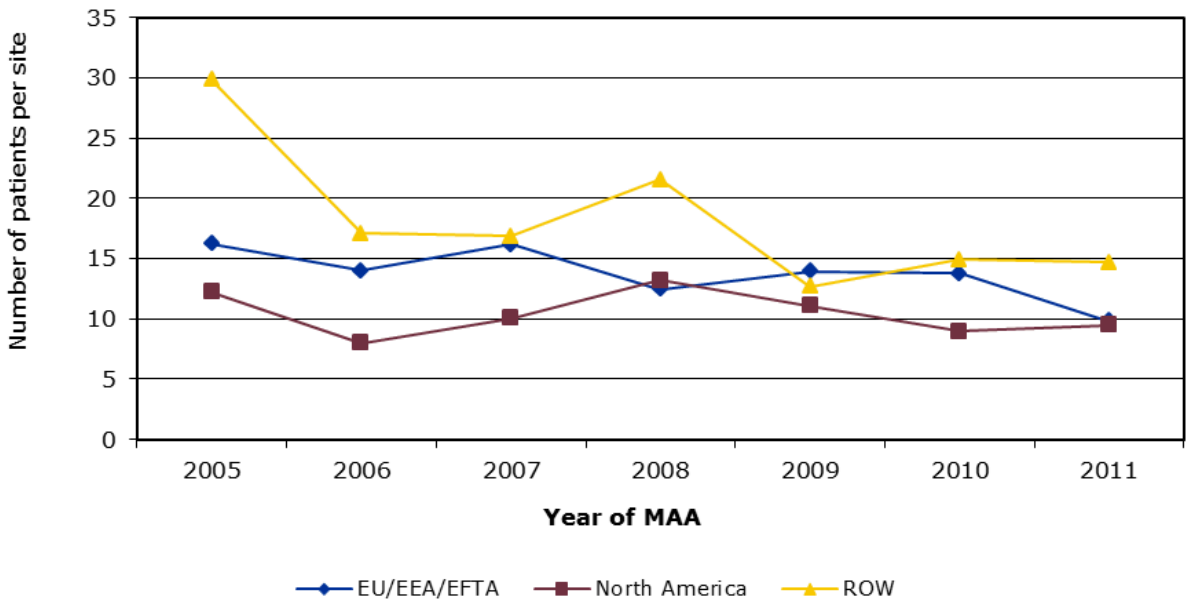
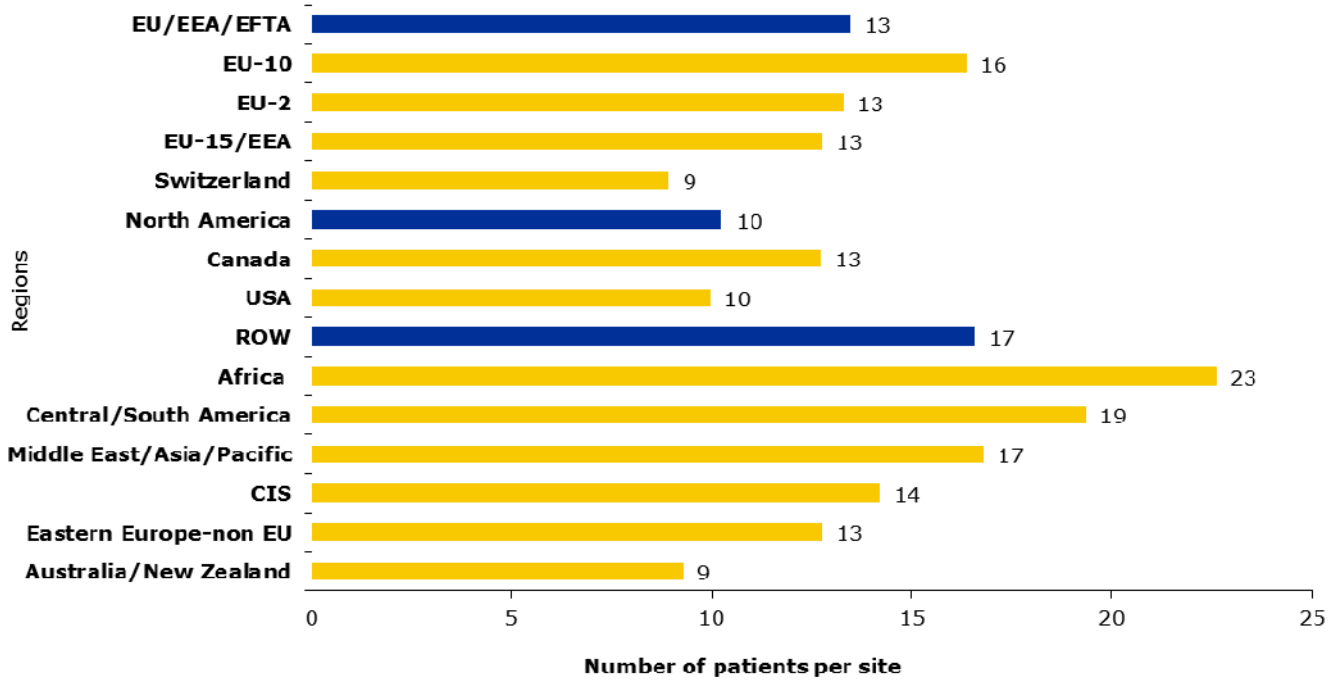


Figure 11. Average number of patients per trial site(s) in pivotal trials submitted in MAAs to the Agency per region during the period 2005-2011. The data are shown as three "global regions" – EU/EEA/EFTA, North America and ROW (Rest of the World) and then split into their component sub-regions



4.2.5. Number of patients in relation to the number of clinical trials

An overview of this information per country is provided in **Figure 12** and **Figure 13.** It should be noted that only those countries with 20 or more clinical trials have been included in both figures.

Figure 12. The average number of patients recruited per pivotal clinical trial per country in MAAs submitted to the Agency in each country of the North America and EU/EEA/EFTA region (excluding those countries with less than 20 clinical trials) in the 2005-2011 period

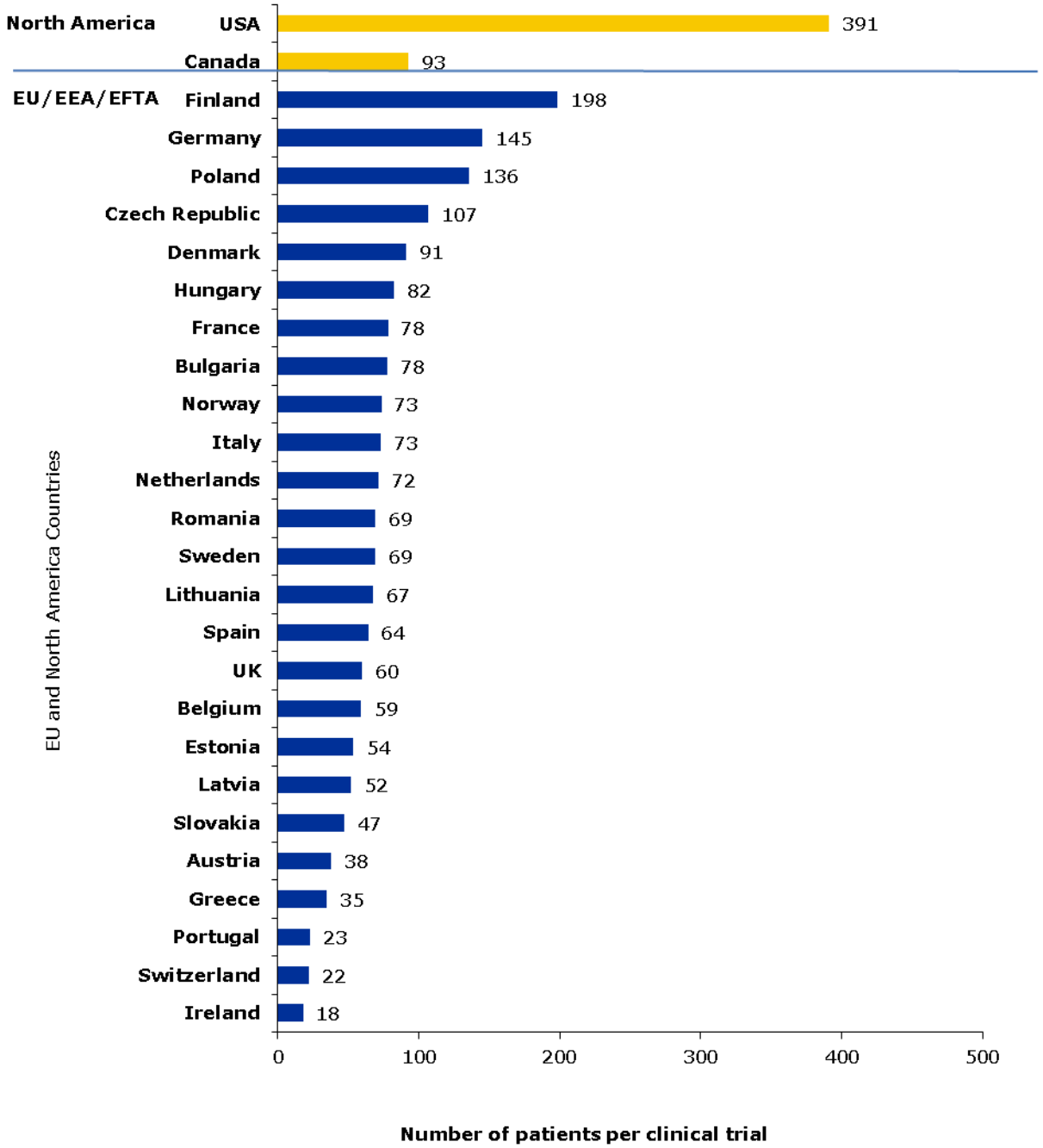
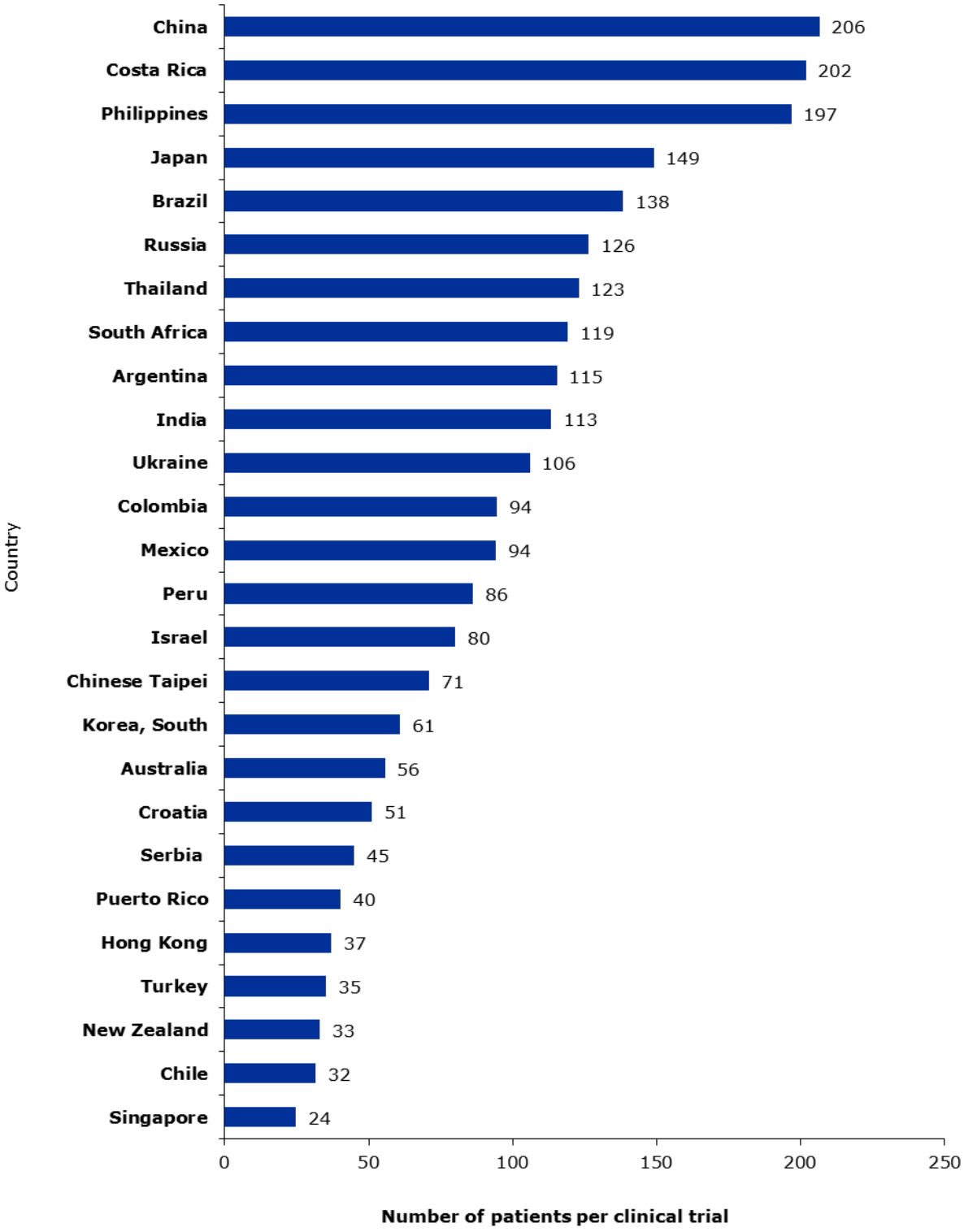


Figure 13. The average number of patients recruited per pivotal clinical trial per country in MAAs submitted to the Agency in each country of the ROW region (excluding those countries with less than 20 clinical trials) in the 2005-2011 period



4.3. Additional information on GCP inspections

4.3.1. GCP inspections in relation to the centralised procedure

The total number of GCP inspections requested by the CHMP per country and per year from 1997 to December 2011 can be found in **Annex 3**. An overview is shown in **Table 4**, split by the 3 main regions, EU/EEA/EFTA, North America and the rest of the world-ROW (Africa, Middle East/Asia/Pacific, Central/South America, CIS, and non EU/ Eastern Europe).

This report contains information from more than 1340 trials from around 677 MAAs submitted since 2005. GCP inspections have been requested for 357 sites (out of 70,291 investigator sites counted as part of the pivotal trials in these MAAs) from 1997 up to 2011, giving an idea of the very small sample of sites that are, or can be, inspected. Even considering that some sites are counted several times as many perform more than one trial, the number of sites is very large with respect to the number of inspections requested. The requests for inspection also include a number of sponsors, CROs and laboratories. The key to the process is therefore to test, by sampling, the processes and systems for different regions/regulatory frameworks, companies, therapeutic areas, population types (pediatric, adult, elderly, in-patient/out-patient), orphan product, commercial or academic sponsor, etc., rather than validating sites per se.

Not all MAAs are subject to a GCP inspection. Data on pivotal trials from 117 MAAs in 2010 are presented in this report of which 21 were subject to GCP inspection at the time of the MAA. For 2011 data from 108 MAAs are presented of which 24 were subject to GCP inspection at the time of the MAA. The numbers of inspections are, ultimately, limited by the available resources from the Member State inspectorates who also need to inspect the ongoing trials in their territories and MAAs to the MRP/DCP and national procedures. Further expansion of inspections will require an increase in the available inspection resources. Inspections in third countries are particularly time consuming given the travel time (including often significant local travel time in the site country), need to research local requirements, slower progress on-site due to translation issues etc.

Some of the trials, sites or sponsors have been inspected, by the NCA inspectorates, in the EU during the ongoing conduct of clinical trials, as part of their responsibility to supervise the conduct of clinical trials ongoing in their national territories. This type of inspection only takes place at sites in the EU. In the US the FDA inspects almost all NDAs, again mainly pivotal trials, and again a small sample of all sites involved. Inspection in the ROW region is mainly dependent on US FDA and EU activities – it is therefore important that local supervision in every country is supported and strengthened, through capacity building, networking, and information exchange and by taking advantage of opportunities for joint or observed inspections. For this reason the current collaboration with the FDA through the EMA-FDA GCP initiative[7] is very important. The initiative is carried out under the scope of the confidentiality arrangement between the European Commission, the Agency and the FDA[8], which has laid the foundation for a more efficient use of limited resources, improved inspection coverage and better understanding of each agency's inspection procedures (more details can be found in the report on the pilot EMA-FDA GCP initiative[9]).

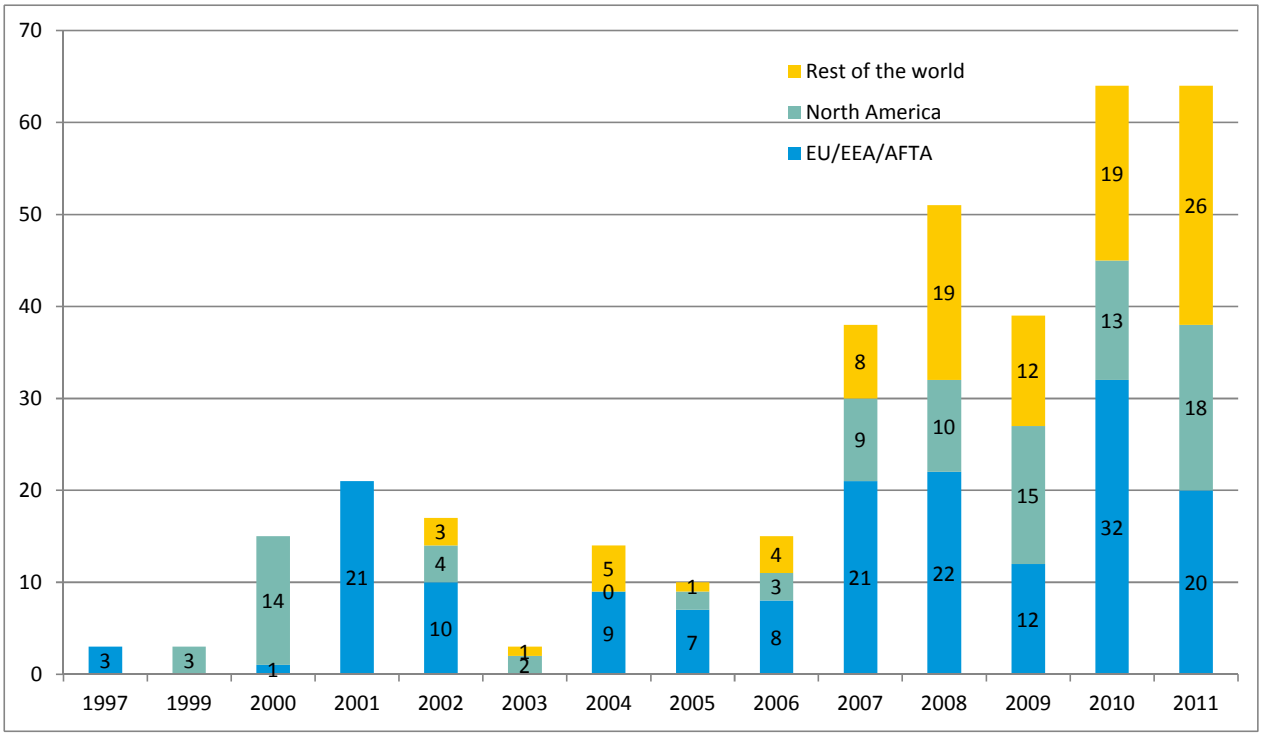
[7] EMA-FDA GCP Initiative
[8] Confidentiality arrangements between the European Commission and the FDA
[9] Report on the pilot EMA-FDA GCP initiative

Table 4. GCP inspections per year and by region requested by the CHMP

	1997	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
EU/EEA/AFTA	3	0	1	21	10	0	9	7	8	21	22	12	32	20
North America	0	3	14	0	4	2	0	2	3	9	10	15	13	18
Rest of the world	0	0	0	0	3	1	5	1	4	8	19	12	19	26
total	3	3	15	21	17	3	14	10	15	38	51	39	64	64

Since 1997, 166 (46.5%) inspections have been requested for sites in the EU/EEA/EFTA region, 93 (26.05%) have been requested for sites in North America and 98 (27.45%) in the rest of the world. Since 1997 up to 2011 the number of inspections in the ROW region have increased since 2006 (4) and more considerably in 2008, 2010 and 2011 (19, 19 and 26). An overview of these results can be found in Figure 14.

Figure 14. GCP Inspections per year and by region requested by the CHMP.



The total GCP inspections per 3rd country (North America + ROW) are shown in **Table 5**. According to this data the country with highest number of sites inspected is USA (21.57%) followed by Canada (4.48%), India (4.48%), Russia (3.08%) and Argentina (2.24%).

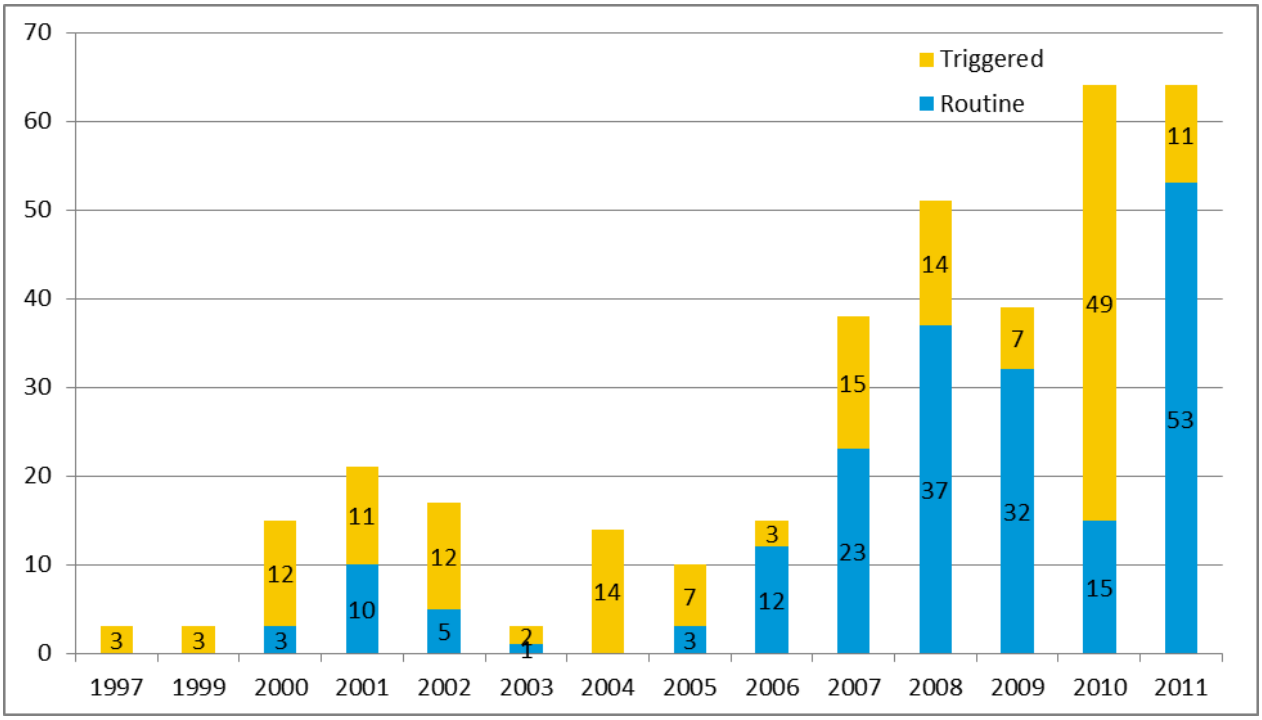
Table 5. GCP inspections conducted in third countries at the request of the CHMP per region and per country

	Number of third-country inspections in 2010	Number of third-country inspections in 2011	Total	% of all inspections
North America	**13**	**18**	**93**	**26.05%**
Canada	4	0	16	4.48%
USA	9	18	77	21.57%
Eastern Europe – non EU	**1**	**3**	**6**	**1.68%**
Bosnia	0	0	1	0.28%
Croatia	1	0	2	0.56%
Serbia	0	3	3	0.84%
CIS	**1**	**4**	**15**	**4.20%**
Russia	1	2	11	3.08%
Ukraine	0	2	4	1.12%
Central/South America	**5**	**7**	**23**	**6.44%**
Argentina	4	2	8	2.24%
Brazil	0	2	4	1.12%
Chile	0	0	1	0.28%
Colombia	0	0	1	0.28%
Costa Rica	1	0	2	0.56%
Mexico	0	2	5	1.40%
Peru	0	1	2	0.56%
Middle East/Asia/ Pacific	**9**	**8**	**42**	**11.76%**
Australia	2	0	2	0.56%
China	0	2	6	1.68%
India	5	2	16	4.48%
Korea (south)	1	0	2	0.56%
Malaysia	0	1	2	0.56%
Philippines	0	2	6	1.68%
Chinese Taipei	0	0	1	0.28%
Thailand	1	1	5	1.40%
Turkey	0	0	2	0.56%
Africa	**3**	**4**	**12**	**3.36%**
Ghana	0	0	1	0.28%
Kenya	2	1	3	0.84%
Morocco	0	0	1	0.28%
South Africa	0	3	6	1.68%
Zambia	1	0	1	0.28%
Total	**64**	**64**	**191**	**53.50%**

It should be noted that the countries with sites inspected in the ROW region as outlined in the above table are almost the same as those with at least 0.5% of patients in the pivotal trials included in the MAA submitted to the Agency (**Figure 4**) with the exceptions of Israel and Japan. Sites from these countries will be subject to inspections in 2012 where possible.

The increase in inspections since 2006 follows the implementation of a formal system of routine GCP inspection. An overview of this information can be found in **Figure 15.** In the case of the ROW region inspections, the 27.45% of inspections carried out is split between routine inspections (54.8%) and of triggered (45.2%).

Figure 15. GCP Inspections requested by the CHMP per year and type of inspection (routine/triggered)



4.3.2. Inspections recorded in EudraCT (up to December 2011) related to generic product applications (DCP/MRP as well as centralised MAAs)

An overview of inspections carried out on bioequivalence (BE) trials in generic applications per region and respective sub-regions based on the information recorded in EudraCT (up to December 2011) is given in **Table 6**. It should be noted that the numbers given in this table depend on the data entered into EudraCT by the NCAs, which is incomplete in some cases.

In the EU/EEA/EFTA states, the BE trials make up only a small number of trial inspections (4.6 %), while in Asia, Africa, North America and CIS-Eastern Europe this was about half of the trial inspections (66, 30, 30 and 12 %, respectively). There were no BE trial inspections reported in South America.

Table 6. List of inspections, retrieved from EudraCT, highlighting inspections carried out on bioequivalence (BE) trials

List of inspections (retrieved from EudraCT) of bioequivalence (BE) studies			
Region in which inspections were carried out:	No. of inspections related to BE trials	% of total no. of inspections	total no. of inspections
EU/EEA/EFTA (without EU-10 + EU-2)	121	4	2779
EU-10 + EU-2	15	10.0	139
North America	30	30	97
CIS and Eastern Europe	2	12	25
Asia	67	68	98
Africa	3	30	10
South America	0	0.0	9
Totals	236	7.43	3175
Top 5 countries where BE trial inspections have been carried out:			
India	63	82%	76
Italy	60	37%	161
Canada	28	63%	44
Germany	18	2%	649
United Kingdom	11	0%	1166

5. Conclusions

From this report and subject to its limitations, as indicated in section 2, the following general points can be concluded:

- 61.9% of the patients in pivotal trials submitted in MAAs to the Agency during the observation period from January 2005 to December 2011 were from third countries, comprising 27.8% from the ROW region (Africa, Middle East/Asia/Pacific, Australia/New Zealand, Central/South America, CIS, Eastern Europe-non EU), and 34.1% from North America.
- 9.4% of patients in pivotal trials submitted in MAAs to the Agency during the observational period from January 2005 to December 2011 were included in trials in Middle East/Asia/Pacific.
- 9.4% of patients in pivotal trials submitted in MAAs to the Agency during the observational period from January 2005 to December 2011 were included in trials in Central/South America.
- 10.8% of patients in the EU/EEU/EFTA region come from the EU-10 and EU-2 countries, which make a significant contribution to the European figures.
- The contribution of certain third countries from the ROW area (27.8% of patients), in terms of numbers of patients included in pivotal trials submitted in MAAs to the Agency during the observational period January 2005 to December 2011, are as follow:
  - Africa: South Africa (2.08%);
  - Middle East/Asia/Pacific: India (1.87%), Philippines (1.25%), Israel (1.19%), China (0.9%), Thailand (0.88%), South Korea (0.68%), Chinese Taipei (0.78%), Japan (0.5%);
  - Australia/New Zealand: Australia (1.34%);
  - Central/South America: Brazil (2.36%), Argentina (2.29%), Mexico (1.72%), Peru (0.7%), Costa Rica (0.61%), Colombia (0.52%);
  - CIS: Russia (3.13%) and Ukraine (1.20%);
  - Eastern Europe (non EU): Croatia (0.35%).
- Those countries with more than 100 pivotal clinical trials included in MAAs to the Agency, during the whole period are:
  - North America: USA and Canada;
  - EU/EEA/EFTA: Germany, France, UK, Spain, Italy, Poland, Belgium, Netherlands, Sweden, Czech Republic, Hungary, Austria, Finland, Denmark, Switzerland and Romania;
  - ROW: Russia, Australia, Argentina, Mexico, South Africa, South Africa, Brazil, India, Israel, Ukraine, South Korea and Chinese Taipei.
- The average number of patients per site in the ROW area (17) over the whole period 2005-2011 is higher than in the other regions (13 and 10 patients per site in the EU/EEA/EFTA and North America regions, respectively).
- The minimum average number of patients per clinical trial is considerable higher in North America followed by ROW and EU/EEA/EFTA over the whole period 2005-2011. If we consider a cut-off point of 125 patients per trial, considering only those countries with a minimum of 20 clinical trials, the most relevant countries observed are USA, China, Costa Rica, Finland, Philippines, Japan, Germany, Panama, Brazil, Poland and Russia.

- Around 47.22% (34 out of 72) of the countries in the ROW region have more than 81 patients (the average in the EU/EEA/EFTA region) enrolled per clinical trial.
- There is an increase of GCP inspections in third countries conducted at the request of CHMP since the implementation of the GCP inspection policy in 2006 with a significant increase in routine inspections. The countries with highest number of requested inspections are USA (21.57%) followed by India (4.48%), Canada (4.48%), Russia (3.08%), Argentina (2.24%), China (1.68%), Philippines (1.68%), South Africa (1.68%), Mexico (1.40%), Thailand (1.40%), Ukraine (1.12%), and Brazil (1.12%). Most of these countries are also those that contribute with at least 0.5% of patients in the pivotal trials included in the MAA submitted to the Agency (see **Figure 4**).
- A total of 357 sites inspected out of 70,291 indicates that a very small sample of sites is, or can be, inspected. Further increase in inspections will require not only additional GCP inspection resources from the Member States but also to promote international collaboration to improve the inspection coverage and capacity building activities to support and strength local supervision in every country.
- The third countries with more BE studies inspected were in India and Canada based on information recorded in EudraCT. Italy, Germany and United Kingdom were the countries in the EU with most inspection of BE trial sites. Similar pattern is observed in the BE studies included in the generic applications submitted to the Agency.

Annex 1 – Regulatory framework

1- REGULATION (EC) No. 726/2004 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency

Preamble

"Whereas:

(16) There is also a need to provide for the ethical requirements of Directive 2001/20/EC of 4 April 2001 of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (1) to apply to medicinal products authorised by the Community. In particular, with respect to clinical trials conducted outside the Community on medicinal products destined to be authorised within the Community, at the time of the evaluation of the application for authorisation, it should be verified that these trials were conducted in accordance with the principles of good clinical practice and the ethical requirements equivalent to the provisions of the said Directive."

Article 6

"1. Each application for the authorisation of a medicinal product for human use shall specifically and completely include the particulars and documents as referred to in Articles 8(3), 10, 10a, 10b or 11 of, and Annex I to, Directive 2001/83/EC. The documents must include a statement to the effect that clinical trials carried out outside the European Union meet the ethical requirements of Directive 2001/20/EC."

Article 56.4

"The Committee for Medicinal Products for Human Use and the Committee for Medicinal Products for Veterinary Use may, if they consider it appropriate, seek guidance on important questions of a general scientific or ethical nature."

2- DIRECTIVE 2001/83/EC (as amended) OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 6 November 2001 on the Community code relating to medicinal products for human use

Article 8

"The application shall be accompanied by the following particulars and documents, submitted in accordance with Annex I:

(ib) A statement to the effect that clinical trials carried out outside the European Union meets the ethical requirements of Directive 2001/20/EC."

Annex I

Introduction and general principles

"(8) All clinical trials, conducted within the European Community, must comply with the requirements of Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (3). To be taken into account during the assessment of an application, clinical trials, conducted outside the

European Community, which relate to medicinal products intended to be used in the European Community, shall be designed, implemented and reported on what good clinical practice and ethical principles are concerned, on the basis of principles, which are equivalent to the provisions of Directive 2001/20/EC. They shall be carried out in accordance with the ethical principles that are reflected, for example, in the Declaration of Helsinki."

3- NOTICE TO APPLICANTS (Eudralex Volume 2 of the The Rules Governing Medicinal Products in the European Union)

Module 1.9 Information relating to Clinical Trials

"According to Article 8 (ib) of Directive 2001/83/EC a statement to the effect that clinical trials carried out outside the European Union meet the ethical requirements of Directive 2001/20/EC should be provided, where applicable.

This statement should indicate that "clinical trials carried out outside the European Union meet the ethical requirements of Directive 2001/20/EC" together with a listing of all trials (protocol number) and third countries involved.

The requirement applies to **all new applications** (including extension applications), and **other** relevant post-authorisation regulatory procedures (e.g. variations) for which clinical trial reports are submitted."

Module 2.5 Clinical Overview, Preamble

"In order to achieve these objectives the Clinical Overview should:

- assess the quality of the design and performance of the studies, and include a statement regarding GCP compliance;"

Module 5 Clinical Study Reports (See section 4)

4- CPMP/ICH/137/95 Note for Guidance on Structure and Content of Clinical Study Reports

Section 1 TITLE PAGE

"Statement indicating whether the study was performed in compliance with Good Clinical Practices (GCP), including the archiving of essential documents"

Section 5. ETHICS

5.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

"It should be confirmed that the study and any amendments were reviewed by an Independent Ethics Committee or Institutional Review Board. A list of all IECs or IRBs consulted should be given in appendix 16.1.3 and, if required by the regulatory authority, the name of the committee Chair should be provided."

5.2 Ethical Conduct of the Study

"It should be confirmed that the study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki."

5.3 Patient Information and Consent

"How and when informed consent was obtained in relation to patient enrolment, (e.g., at allocation, pre-screening) should be described.

Representative written information for the patient (if any) and a sample patient consent form should be provided in appendix 16.1.3."

Section 6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

"The administrative structure of the study (e.g., principal investigator, coordinating investigator, steering committee, administration, monitoring and evaluation committees, institutions, statistician, central laboratory facilities, contract research organization (C.R.O.), clinical trial supply management) should be described briefly in the body of the report."

There should be provided in appendix 16.1.4 a list of the investigators with their affiliations, their role in the study and their qualifications (curriculum vitae or equivalent), a similar list for other persons whose participation materially affected the conduct of the study should also be provided in appendix 16.1.4. In the case of large trials with many investigators the above requirements may be abbreviated to consist of general statements of qualifications for persons carrying out particular roles in the study with only the name, degree and institutional affiliation and roles of each investigator or other participant.

The listing should include:

a) Investigators

b) Any other person carrying out observations of primary or other major efficacy variables, such as a nurse, physician's assistant, clinical psychologist, clinical pharmacist, or house staff physician. It is not necessary to include in this list a person with only an occasional role, e.g., an on-call physician who dealt with a possible adverse effect or a temporary substitute for any of the above.

c) The author(s) of the report, including the responsible biostatistician(s).

Where signatures of the principal signatory investigators are required by regulatory authorities, these should be included in appendix 16.1.5 (see Annex II for a sample form). Where these are not required, the signature of the sponsor's responsible medical officer should be provided in appendix 16.1.5."

Section 9.6 Data Quality Assurance

"The quality assurance and quality control systems implemented to assure the quality of the data should be described in brief. If none were used, this should be stated. Documentation of inter-laboratory standardisation methods and quality assurance procedures if used, should be provided under appendix 16.1.10.

Any steps taken at the investigation site or centrally to ensure the use of standard terminology and the collection of accurate, consistent, complete, and reliable data, such as training sessions, monitoring of investigators by sponsor personnel, instruction manuals, data verification, cross-checking, use of a central laboratory for certain tests, centralised ECG reading, or data audits, should be described. It should be noted whether investigator meetings or other steps were taken to prepare investigators and standardise performance.

If the sponsor used an independent internal or external auditing procedure, it should be mentioned here and described in appendix 16.1.8; and audit certificates, if available, should be provided in the same appendix."

Section 16.1 Study Information

16.1.1 Protocol and protocol amendments.

16.1.3 List of IECs or IRBs (plus the name of the committee Chair if required by the regulatory authority) - representative written information for patient and sample consent forms.

16.1.4 List and description of investigators and other important participants in the study, including brief (1 page) CVs or equivalent summaries of training and experience relevant to the performance of the clinical study.

16.1.5 Signatures of principal or coordinating investigator(s) or sponsor’s responsible medical officer, depending on the regulatory authority's requirement.

16.1.8 Audit certificates (if available).

Annex 2 – Number of patients, sites and pivotal clinical trials[10] in MAAs submitted to the Agency from 2005 to 2011

	2005			2006			2007			2008			2009			2010			2011			TOTAL		
	No. CTs	No. of sites	No. Patients	No. CTs	No. of sites	No. Patients	No. CTs	No. of sites	No. Patients	No. CTs	No. of sites	No. Patients	No. CTs	No. of sites	No. Patients	No. CTs	No. of sites	No. Patients	No. CTs	No. of sites	No. Patients	No. CTs	No. of sites	No. Patients
EU/EEA/EFTA	**345**	**1,974**	**32,090**	**668**	**3,567**	**49,960**	**648**	**3,441**	**55,667**	**601**	**3,373**	**42,024**	**509**	**3,708**	**51,628**	**750**	**4,809**	**66,220**	**679**	**4,548**	**44,590**	**4,200**	**25,420**	**342,179**
EU-15/EEA	**269**	**1,676**	**27,822**	**496**	**2,759**	**30,714**	**467**	**2,648**	**42,894**	**413**	**2,431**	**27,561**	**348**	**2,730**	**33,711**	**543**	**3,668**	**52,680**	**463**	**3,123**	**27,711**	**2,999**	**19,035**	**243,093**
Austria	10	18	233	24	48	482	23	79	1,389	21	64	978	15	53	586	34	124	1,360	28	105	796	155	491	5,824
Belgium	28	145	2,526	31	82	1,136	41	158	2,956	37	158	2,453	25	101	917	45	229	2,737	32	160	1,370	239	1,033	14,095
Denmark	10	67	2,854	13	50	788	17	70	1,996	18	66	702	21	129	2,474	20	67	952	20	77	1,026	119	526	10,792
Finland	12	53	2,564	18	62	783	21	80	1,595	22	113	3,395	16	89	3,857	22	150	10,063	22	132	4,091	133	679	26,348
France	31	282	2,330	57	371	3,876	59	578	8,818	40	289	1,918	41	371	3,464	60	543	3,972	54	391	2,314	342	2,825	26,692
Germany	36	436	7,095	76	838	9,161	63	482	7,835	57	521	5,664	49	691	9,064	71	889	15,123	69	778	7,053	421	4,635	60,995
Greece	6	23	146	16	50	776	7	27	253	13	46	428	9	33	263	20	84	830	14	46	257	85	309	2,953
Iceland	3	3	740	1	1	6	2	2	6	3	3	62	1	4	49				1	1	7	11	14	870
Ireland	4	11	60	10	29	79	5	21	134	7	16	84	3	10	40	7	22	265	12	35	193	48	144	855
Italy	30	146	1,002	54	274	3,069	46	253	3,093	39	308	3,352	31	286	2,551	50	371	4,523	39	336	3,508	289	1,974	21,098
Liechtenstein																						0	0	0
Luxembourg																0	0	0				0	0	0
Netherlands	16	75	729	31	146	2,938	30	123	2,945	27	126	1,247	20	150	1,727	45	200	3,561	30	168	1,088	199	988	14,235
Norway	7	52	2,193	18	58	730	17	70	986	14	52	822	8	53	868	11	43	483	13	60	380	88	388	6,462
Portugal	10	33	166	12	30	235	17	64	466	10	42	187	11	41	322	13	43	319	7	21	108	80	274	1,803
Spain	25	118	849	54	293	2,879	46	269	4,648	41	250	2,343	40	353	3,498	56	413	3,518	43	302	1,787	305	1,998	19,522
Sweden	14	71	2,156	30	153	1,729	31	137	2,079	18	91	995	17	120	1,458	34	136	2,053	28	126	1,358	172	834	11,828
UK	27	143	2,179	51	274	2,047	42	235	3,695	46	286	2,931	41	246	2,573	55	354	2,921	51	385	2,375	313	1,923	18,721
EU-10	**55**	**224**	**3,412**	**131**	**638**	**16,601**	**141**	**639**	**11,016**	**134**	**734**	**11,706**	**123**	**758**	**14,768**	**144**	**894**	**11,358**	**160**	**1,140**	**13,449**	**888**	**5,027**	**82,310**
Cyprus																1	1	1				1	1	1
Czech Republic	10	42	869	18	79	2,565	21	85	1,368	32	174	2,243	24	150	3,069	30	315	3,365	32	379	4,332	167	1,224	17,811
Estonia	3	6	98	13	38	537	10	23	712	8	17	588	11	37	743	7	15	128	8	31	419	60	167	3,225
Hungary	13	66	813	22	108	2,131	33	121	1,817	21	104	1,724	22	150	2,827	31	163	2,023	24	172	2,289	166	884	13,624
Latvia	4	13	175	10	38	505	7	26	402	8	22	220	7	22	263	9	37	784	10	29	509	55	187	2,858
Lithuania	3	5	84	13	59	841	19	53	1,364	12	48	744	11	44	583	8	30	1,005	10	32	487	76	271	5,108
Malta													2	2	32							2	2	32
Poland	15	79	1,299	36	250	8,953	41	305	5,088	39	321	5,705	36	289	6,246	39	253	3,392	53	406	4,456	259	1,903	35,139
Slovakia	6	11	37	14	50	846	8	24	245	12	45	467	10	64	1,005	18	78	643	18	81	837	86	353	4,080
Slovenia	1	2	37	5	16	223	2	2	20	2	3	15				1	2	17	5	10	120	16	35	432
EU-2	**11**	**52**	**656**	**16**	**126**	**2,146**	**23**	**110**	**1,251**	**39**	**177**	**2,447**	**26**	**170**	**2,628**	**35**	**177**	**1,792**	**45**	**256**	**3,269**	**195**	**1,068**	**14,189**
Bulgaria	5	23	332	6	44	759	9	43	512	16	65	633	12	85	1,260	12	84	924	18	108	1,657	78	452	6,077
Romania	6	29	324	10	82	1,387	14	67	739	23	112	1,814	14	85	1,368	23	93	868	27	148	1,612	117	616	8,112
Switzerland	**10**	**22**	**200**	**25**	**44**	**499**	**17**	**44**	**506**	**15**	**31**	**310**	**12**	**50**	**521**	**28**	**70**	**390**	**11**	**29**	**161**	**118**	**290**	**2,587**
Switzerland	10	22	200	25	44	499	17	44	506	15	31	310	12	50	521	28	70	390	11	29	161	118	290	2,587
North America	**104**	**3,042**	**37,117**	**175**	**4,168**	**33,389**	**171**	**4,150**	**41,810**	**163**	**4,182**	**55,165**	**151**	**3,820**	**42,269**	**173**	**5,701**	**51,025**	**171**	**4,744**	**44,987**	**1,108**	**29,807**	**305,762**
Canada	31	282	3,477	65	392	3,919	57	361	6,231	67	398	4,454	66	621	9,581	72	528	6,811	69	524	5,078	427	3,106	39,551
USA	73	2,760	33,640	110	3,776	29,470	114	3,789	35,579	96	3,784	50,711	85	3,199	32,688	101	5,173	44,214	102	4,220	39,909	681	26,701	266,211

[10] Please note that cumulated per region results in multiple counting of the same trial and it is included only for statistical porpoises.

ROW	**155**	**589**	**17,585**	**352**	**1,737**	**29,637**	**353**	**1,699**	**28,628**	**411**	**2,320**	**49,948**	**405**	**2,264**	**28,663**	**493**	**2,819**	**42,105**	**547**	**3,636**	**53,384**	**2,716**	**15,064**	**249,950**
Africa	**13**	**59**	**523**	**25**	**140**	**1,938**	**29**	**141**	**2,061**	**29**	**216**	**9,962**	**33**	**151**	**3,431**	**47**	**171**	**2,952**	**32**	**146**	**2,298**	**208**	**1,024**	**23,165**
Burkina Faso													1	1	301	2	2	150				3	3	451
Congo Dem. Rep																2	2	382				2	2	382
Egypt	1	1	5	1	2	22				1	1	108	2	12	258	3	9	69	2	3	26	10	28	488
Gabon																1	1	80				1	1	80
Gambia, The																1	1	106				1	1	106
Ghana							1	1	280							1	1	7				2	2	287
Ivory Coast																2	2	185				2	2	185
Kenya													1	1	222	2	2	218	1	1	6	4	4	446
Mali																2	2	328				2	2	328
Morocco							1	2	20	1	3	20	1	4	22				1	3	7	4	12	69
Mozambique													1	1	445	1	1	133				2	2	578
Senegal																1	1	206				1	1	206
South Africa	11	55	427	22	133	1,894	27	138	1,761	24	205	9,746	22	123	1,640	26	143	1,044	25	131	2,200	157	928	18,712
Swaziland																1	1	2				1	1	2
Tanzania																1	1	38	3	8	59	4	9	97
Tunisia	1	3	91	2	5	22				3	7	88	3	7	63	1	2	4				10	24	268
Uganda													1	1	176							1	1	176
Zambia													1	1	304							1	1	304
Middle East/Asia/Pacific	**38**	**119**	**1,694**	**121**	**551**	**9,925**	**94**	**417**	**7,801**	**153**	**682**	**17,458**	**139**	**808**	**9,627**	**193**	**1,024**	**19,307**	**214**	**1,405**	**18,243**	**952**	**5,006**	**84,055**
Bangladesh										1	1	150										1	1	150
Cambodia																2	2	365				2	2	365
China				3	77	2,214	4	33	611	5	25	755	5	50	837	10	62	1,493	12	161	2,143	39	408	8,053
Guam																1	1	1				1	1	1
Hong Kong	3	3	155	10	20	235	6	12	150	14	31	889	7	13	182	5	11	122	9	18	253	54	108	1,986
India	1	10	86	13	108	3,121	4	41	222	22	136	2,710	25	233	2,781	46	217	3,558	37	311	4,315	148	1,056	16,793
Indonesia							1	2	12	1	2	13	2	7	75	4	9	191	2	13	131	10	33	422
Iran	1	1	3																			1	1	3
Israel	6	18	187	21	74	597	22	102	1,878	15	167	3,565	21	87	1,441	26	143	1,714	23	140	1,339	134	731	10,721
Japan	1	25	217	2	35	680	2	50	563	3	34	462	1	25	143	10	201	1,146	11	215	1,259	30	585	4,470
Korea, North																			3	36	297	3	36	297
Korea, South	1	2	21	17	90	1,177	8	28	310	15	51	789	17	120	1,023	19	102	1,235	24	171	1,587	101	564	6,142
Kuwait	1	1	3																			1	1	3
Laos													1	2	200							1	2	200
Lebanon										1	2	216	2	5	44	1	4	32	3	3	581	7	14	873
Malaysia	1	1	51	10	26	450	7	19	165	12	28	719	8	24	237	8	21	359	14	67	574	60	186	2,555
Pakistan										3	11	248				1	4	73	1	3	17	5	18	338
Philippines	2	8	67	3	7	45	7	17	1,712	13	49	3,042	8	45	396	10	80	3,071	14	55	2,885	57	261	11,218
Saudi Arabia	1	1	16	1	1	2							1	2	5				1	1	100	4	5	123
Singapore	4	8	207	11	19	206	3	6	31	7	9	304	6	13	131	8	11	164	9	17	132	48	83	1,175
Syria	1	1	1																			1	1	1
Chinese Taipei	11	27	415	15	53	830	14	51	468	18	60	906	13	77	662	11	55	2,231	18	79	1,570	100	402	7,082
Thailand	1	1	124	5	13	194	8	20	1,057	11	30	2,181	10	34	845	14	40	3,082	15	45	384	64	183	7,867
Turkey	3	12	141	10	28	174	7	25	247	11	45	505	11	69	600	15	57	293	18	70	676	75	306	2,636
Vietnam							1	11	375	1	1	4	1	2	25	2	4	177				5	18	581

Australia/New Zealand	**25**	**118**	**1,560**	**51**	**229**	**1,892**	**43**	**220**	**2,663**	**31**	**175**	**1,219**	**39**	**177**	**1,344**	**41**	**311**	**3,321**	**43**	**269**	**1,905**	**273**	**1,499**	**13,904**
Australia	21	110	1,229	39	195	1,624	34	192	2,180	23	152	1,117	27	157	1,179	35	285	3,058	38	242	1,675	217	1,333	12,062
New Zealand	4	8	331	12	34	268	9	28	483	8	23	102	12	20	165	6	26	263	5	27	230	56	166	1,842
CIS	**20**	**72**	**664**	**42**	**320**	**6,939**	**37**	**226**	**2,731**	**59**	**498**	**6,677**	**46**	**450**	**5,653**	**55**	**434**	**6,463**	**89**	**807**	**10,737**	**348**	**2,807**	**39,864**
Belarus				1	3	18	2	5	32	2	6	50				1	2	5	4	14	109	10	30	214
Georgia				2	4	24	1	1	29	1	1	4	2	14	549	2	5	62	2	5	62	10	30	730
Moldova										3	3	10	1	1	29							4	4	39
Russia	14	45	484	29	232	5,070	26	172	2,429	37	377	5,588	28	296	3,495	37	307	4,535	51	536	6,465	222	1,965	28,066
Ukraine	6	27	180	10	81	1,827	8	48	241	16	111	1,025	15	139	1,580	15	120	1,861	32	252	4,101	102	778	10,815
Eastern Europe-non EU	**4**	**8**	**69**	**9**	**29**	**862**	**19**	**51**	**1,202**	**23**	**73**	**1,370**	**18**	**54**	**539**	**8**	**62**	**121**	**24**	**107**	**742**	**105**	**384**	**4,905**
Bosnia										1	2	12				1	1	3	2	3	8	4	6	23
Croatia	4	8	69	5	18	581	14	31	748	16	49	1,144	10	34	288	4	13	100	9	27	242	62	180	3,172
FYRM													1	2	40				3	3	103	4	5	143
Serbia				4	11	281	5	20	454	6	22	214	7	18	211	3	48	18	10	74	389	35	193	1,567
Central/South America	**55**	**213**	**13,075**	**104**	**468**	**8,081**	**131**	**644**	**12,170**	**116**	**676**	**13,262**	**130**	**624**	**8,069**	**149**	**817**	**9,941**	**145**	**902**	**19,459**	**830**	**4,344**	**84,057**
Argentina	9	42	783	17	134	2,014	28	215	2,918	34	270	5,010	30	203	2,554	32	255	2,467	28	258	4,803	178	1,377	20,549
Bahamas	1	1	2																			1	1	2
Brazil	13	80	2,643	22	141	3,168	24	144	4,376	20	140	3,068	16	117	2,199	34	266	3,835	24	215	1,882	153	1,103	21,171
Chile	4	7	70	9	28	431	16	42	419	13	58	395	13	40	445	15	45	258	18	72	762	88	292	2,780
Colombia	4	12	1,267	6	17	295	9	36	559				13	55	416	5	18	215	12	50	1,876	49	188	4,628
Costa Rica	1	9	1,641	5	11	221	5	10	253	3	4	1,787	6	19	170	5	9	60	2	7	1,317	27	69	5,449
Dominican Republic																			2	2	22	2	2	22
Ecuador				1	1	3				1	4	83	5	13	69							7	18	155
Guatemala	2	5	372	4	11	117	4	8	147	2	4	27	3	7	52	1	2	19	1	7	1,096	17	44	1,830
Honduras				1	2	268							1	2	31							2	4	299
Jamaica	1	1	1,770							1	1	3										2	2	1,773
Mexico	9	32	2,219	16	56	674	23	106	1,319	26	137	2,220	23	105	1,413	33	154	2,632	34	211	4,941	164	801	15,418
Panama				1	2	174	3	14	1,312	2	3	32	3	4	54	4	9	75	1	3	302	14	35	1,949
Paraguay													2	2	16							2	2	16
Peru	5	10	1,434	17	55	675	14	58	718	6	22	306	9	44	566	9	35	233	13	51	2,353	73	275	6,285
Puerto Rico	5	12	858	2	3	7	5	11	149	7	29	288	3	5	5	8	19	130	8	22	92	38	101	1,529
Uruguay				1	1	10										1	2	6				2	3	16
Venezuela	1	2	16	2	6	24				1	4	43	3	8	79	2	3	11	2	4	13	11	27	186
Total	**604**	**5,605**	**86,792**	**1,195**	**9,472**	**112,986**	**1,172**	**9,290**	**126,105**	**1,175**	**9,875**	**147,137**	**1,065**	**9,792**	**122,560**	**1,416**	**13,329**	**159,350**	**1,397**	**12,928**	**142,961**	**8,024**	**70,291**	**897,891**

Annex 3 – Number of GCP inspections per year and type of inspection requested by CHMP

tr= triggered inspections
ro= routine inspections
to= total number of inspection

REGION	1997			1999			2000			2001			2002			2003			2004			2005			2006			2007			2008			2009			2010			2011			TOTAL		
	tr	ro	to	tr	ro	to	tr	ro	to	tr	ro	to	tr	ro	to	tr	ro	to	tr	ro	to	tr	ro	to	tr	ro	to	tr	ro	to	tr	ro	to	tr	ro	to	tr	ro	to	tr	ro	to	tr	ro	to
EU/EEA/EFTA	3		3				1		1	11	10	21	5	5	10				9		9	4	3	7	2	6	8	9	12	21	7	15	22	3	9	12	27	5	32	9	11	20	90	76	166
EU-15/EEA	3		3				1		1	10	8	18	4	2	6				8		8		3	3	2	5	7	2	9	11	5	10	15	1	7	8	17	4	21	8	8	16	61	56	117
Austria											1	1																			1	2	3		1	1							1	4	5
Belgium										2		2																	1	1							1		1		2	2	3	3	6
Denmark														1	1																1	1	2										1	2	3
Finland																									1		1										1		1	1		1	3	0	3
France										1	4	5	4		4				3		3								3	3		3	3				4	1	5	4	4	8	16	15	31
Germany											3	3		1	1				4		4		1	1	1	3	4	1	3	4	2	1	3		2	2	6	1	7	3	1	4	17	16	33
Greece																																					1		1				1	0	1
Iceland																																										0	0	0
Ireland																																		1		1							1	0	1
Italy										1		1														2	2										1		1				2	2	4
Liechtenstein																																										0	0	0
Luxembourg																																										0	0	0
Netherlands	1		1							2		2											1	1					1	1		1	1		2	2	1		1				4	5	9
Norway																																									1		0	1	1
Portugal																													1	1													0	1	1
Spain										3		3																1		1		1	1					1	1				4	2	6
Sweden	1		1																				1	1														1	1				1	2	3
UK	1		1				1		1	1		1							1		1										1	1	2		2	2	2		2				7	3	10
EU-10									0	0	2	2	1	1	2							4		4		1	1	7	2	9	2	1	3	2	2	4	8	1	9	1	3	4	25	13	38
Cyprus																																										0	0	0
Czech Republic																						2		2								1	1				2		2				4	1	5
Estonia														1	1																												0	1	1
Hungary											1	1																	1	1											1	1	0	3	3
Latvia																																		1		1	1	1	2				2	1	3
Lithuania																												1		1	1		1	1		1	2		2				5	0	5
Malta																																										0	0	0
Poland											1	1	1		1							2		2		1	1	6	1	7	1		1		2	2	3		3	1	2	3	14	7	21
Slovakia																																										0	0	0
Slovenia																																										0	0	0
EU-2														1	1														1	1		3	3				2		2				2	5	7
Bulgaria														1	1																						1		1				1	1	2
Romania																													1	1		3	3				1		1				1	4	5
Switzerland										1		1		1	1				1		1											1	1										2	2	4
Switzerland										1		1		1	1				1		1											1	1										2	2	4
North America				3		3	11	3	14				4		4	2		2				2	0	2	1	2	3	6	3	9	5	5	10	4	11	15	8	5	13		18	18	46	47	93
Canada																									1		1	3	2	5	3	1	4		2	2	2	2	4				9	7	16
USA				3		3	11	3					4			2		2				2		2		2	2	3	1	4	2	4	6	4	9	13	6	3	9		18	18	37	40	77

ROW																	1	1	5		5	1		1		4	4		8	8	2	17	19		12	12	14	5	19	1	25	26	23	72	95
Africa																													4	4					1	1	2	1	3		4	4	2	10	12
Ghana																													1	1													0	1	1
Kenya																																					1	1	2		1	1	1	2	3
Morocco																													1	1													0	1	1
South Africa																													2	2					1	1					3	3	0	6	6
Zambia																																					1		1				1	0	1
Middle East/Asia/ Pacific																	1	1	1	0	1	0	0	0	0	4	4	0	1	1	0	11	11	0	7	7	5	2	7		8	8	6	34	40
China																										1	1					3	3								2	2	0	6	6
India																										2	2					6	6		1	1	5		5		2	2	5	11	16
Korea, South																																			1	1		1	1				0	2	2
Malaysia																	1	1																							1	1	0	2	2
Philippines																													1	1		1	1		2	2					2	2	0	6	6
Chinese Taipei																																			1	1							0	1	1
Thailand																										1	1								2	2		1	1		1	1	0	5	5
Turkey																			1		1											1	1										1	1	2
Australia/New Zealand																																						2	2				0	2	**2**
Australia																																						2	2				0	2	2
CIS													3		3				3		3										1	3	4				1		1		4	4	8	7	**15**
Russia													3		3				2		2											3	3				1		1		2	2	6	5	11
Ukraine																			1		1										1		1								2	2	2	2	4
Eastern Europe- non EU																													1	1		1	1				1		1	1	2	3	2	4	**6**
Bosnia																																1	1										0	1	1
Croatia																													1	1							1		1				1	1	2
Serbia																																								1	2	3	1	2	3
Central/South America																			1		1	1		1					2	2	1	2	3		4	4	5		5		7	7	8	15	**23**
Argentina																																1	1		1	1	4		4		2	2	4	4	8
Brazil																															1		1		1	1					2	2	1	3	4
Chile																						1		1																			1	0	1
Colombia																													1	1													0	1	1
Costa Rica																																1	1				1		1				1	1	2
Mexico																			1		1														2	2					2	2	1	4	5
Peru																													1	1											1	1	0	2	2
Total	3	0	**3**	3	0	**3**	12	3	**15**	11	10	**21**	12	5	**17**	2	1	**3**	14	0	**14**	7	3	**10**	3	12	**15**	15	23	**38**	14	37	**51**	7	32	**39**	49	15	**64**	10	54	**64**	162	195	**357**