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Compliance and Inspection

Clinical trials submitted in marketing authorisation applications to the EMA

Overview of patient recruitment and the geographical location of investigator sites

- updated with data from marketing authorisation applications submitted in 2009



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1. 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 mid 2004.

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 EMA, 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 to 2008. This second report is an update adding data from MAAs submitted in 2009.

2. SCOPE

The information presented in this report covers the period from January 2005 to December 2009 and relates mainly to new applications (347) and line extensions (63) but also includes some variations (42) where new clinical trial information was provided. A 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	Total
New applications	39	60	68	77	103	347
Line extensions	3	8	17	13	22	63
Type II variations	2	5	4	12	19	42
	44	73	89	102	144	452

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 2010 will only appear in MAAs of 2011-2016.
- 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 (2005-2009) is very 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 reflected in the MAAs or involves trials that will not all be included in MAAs and 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 2009) relating to generic applications is also provided.

3. METHODS AND RESULTS

3.1. *The GCP validation process for MAAs*

During the validation phase, prior to the start of the assessment phase of a centralized MAA, the EMA 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. An overview of the regulatory framework for the GCP information provided in the dossier is given in **appendix 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/EC¹. 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 Applicants².
- 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)

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 \(Consolidated version : 30/12/2008\)](#).

² [EudraLex - Volume 2 - Pharmaceutical Legislation Notice to applicants and regulatory guidelines medicinal products for human use](#)

- The study was conducted in accordance with the ethical principles equivalent to those of Directive 2001/20/EC³
- 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).

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 Advice⁴.

The modules referred to are those of the Common Technical Dossier (Volume 2B⁵ of the Notice to Applicants).

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

It should be noted that the information from four clinical trials included in four 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.

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

- EU/EEA/EFTA⁶ 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)

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 \(Official Journal L 121, 1/5/2001 p. 34 - 44\).](#)

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](#)

- 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) (i.e. Croatia, Serbia etc.)

3.2.1. Number of Patients

The total number of patients per country and per year is provided in **appendix 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 2009 come from EU/EEA/EFTA (38.8%) and North America (35.2%). The regions Central/South America and Middle East/Asia/Pacific follow with a 9.2% and 7.8%, respectively. Smaller numbers were recruited in the CIS region (3.8%), Africa (3.0%), Australia-New Zealand (1.5%) and Eastern Europe-non EU (0.7%).

Table 2: Number of patients in pivotal trials submitted in MAAs to the EMA 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 patients	2005		2006		2007		2008		2009		total	
	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	231,369	38.8
<i>Comprising:</i>												
EU-15/EEA	27,822	32.1	30,714	27.2	42,894	34.0	27,561	18.7	33,711	27.5	162,702	27.3
EU-10	3,412	3.9	16,601	14.7	11,016	8.7	11,706	8.0	14,768	12.0	57,503	9.7
EU-2	656	0.8	2,146	1.9	1,251	1.0	2,447	1.7	2,628	2.1	9,128	1.5
Switzerland	200	0.2	499	0.4	506	0.4	310	0.2	521	0.4	2,036	0.3
North America	37,117	42.8	33,389	29.6	41,810	33.2	55,165	37.5	42,269	34.5	209,750	35.2
<i>Comprising:</i>												
Canada	3,477	4.0	3,919	3.5	6,231	4.9	4,454	3.0	9,581	7.8	27,662	4.6
USA	33,640	38.8	29,470	26.1	35,579	28.2	50,711	34.5	32,688	26.7	182,088	30.6
ROW	17,585	20.3	29,637	26.2	28,628	22.7	49,948	33.9	28,663	23.4	154,461	25.9
<i>Comprising:</i>												
Africa	523	0.6	1,938	1.7	2,061	1.6	9,962	6.8	3,431	2.8	17,915	3.0
Middle East/Asia/Pacific	1,694	2.0	9,925	8.8	7,801	6.2	17,458	11.9	9,627	7.9	46,505	7.8
Australia/New Zealand	1,560	1.8	1,892	1.7	2,663	2.1	1,219	0.8	1,344	1.1	8,678	1.5
CIS	664	0.8	6,939	6.1	2,731	2.2	6,677	4.5	5,653	4.6	22,664	3.8
Eastern Europe-non EU	69	0.1	862	0.8	1,202	1.0	1,370	0.9	539	0.4	4,042	0.7
Central/South America	13,075	15.1	8,081	7.2	12,170	9.7	13,262	9.0	8,069	6.6	54,657	9.2
total	86,792	100	112,986	100	126,105	100	147,137	100	122,560	100	595,580	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**.

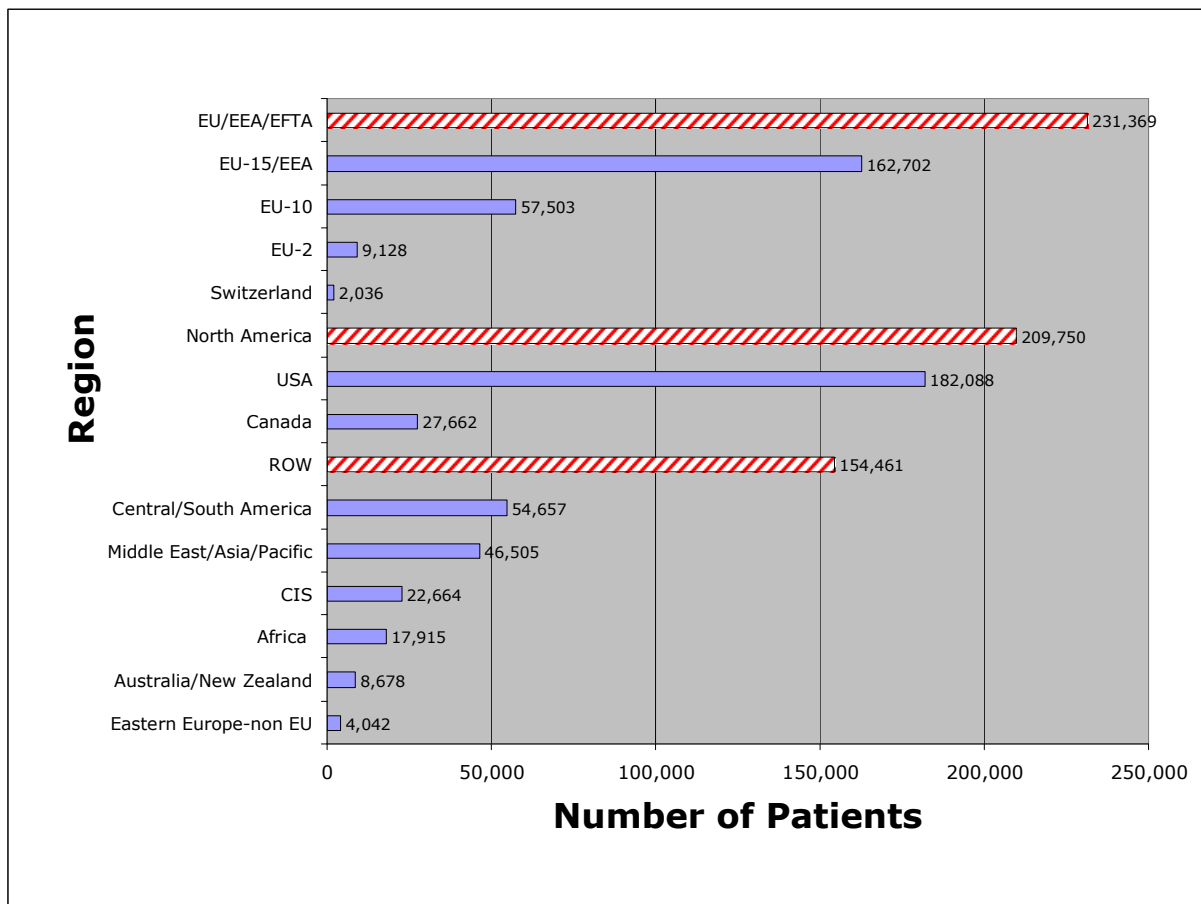


Figure 1: Number of patients in pivotal trials submitted in MAAs to the EMA per region/sub-region during the period 2005-2009. The data are shown as three “global regions” – EU/EEA/EFTA, North America and ROW (Rest of the World) and then split into its component sub-regions.

An overview of the trend per year in the three main regions is shown in **Figure 2**. It should be noted that the addition of small numbers of applications can alter this picture significantly.

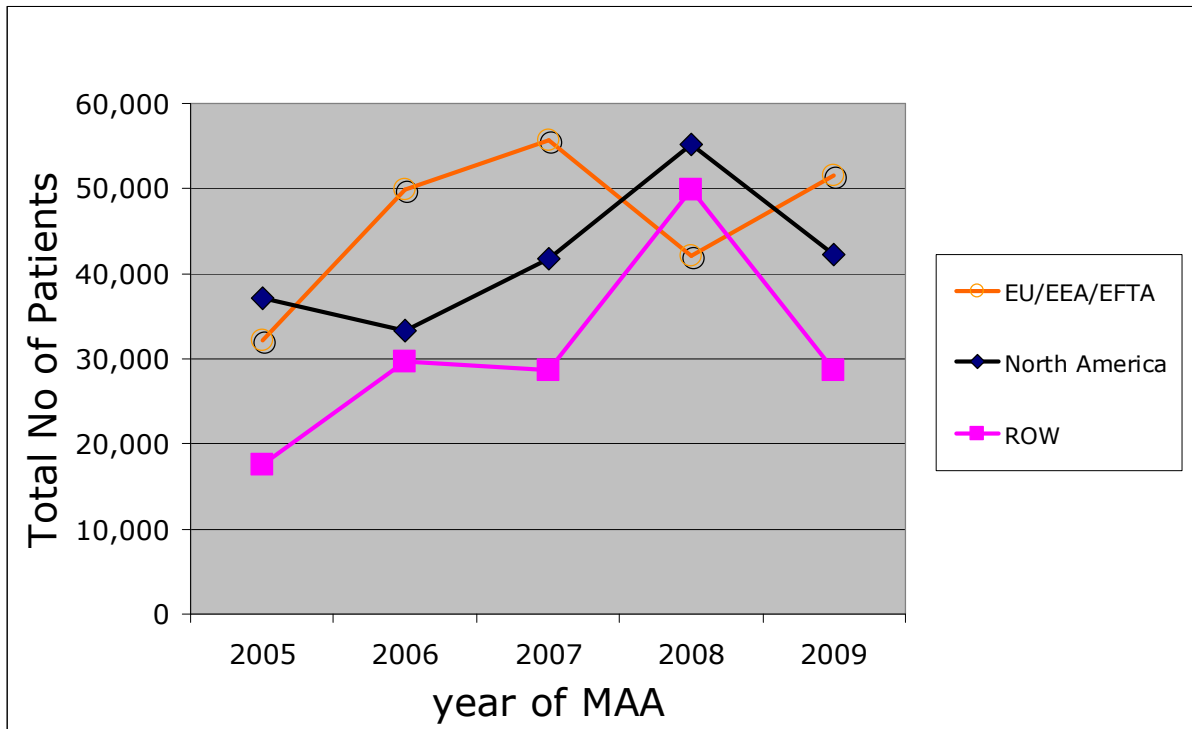


Figure 2: Number of patients in pivotal trials submitted in MAAs to the EMA per region and year. The data are shown as three "global regions" – EU/EEA/EFTA, North America and ROW (Rest of the World).

Figure 3 shows that the number of patients in pivotal trials submitted in MAAs to the EMA in the sub-regions of ROW region per year.

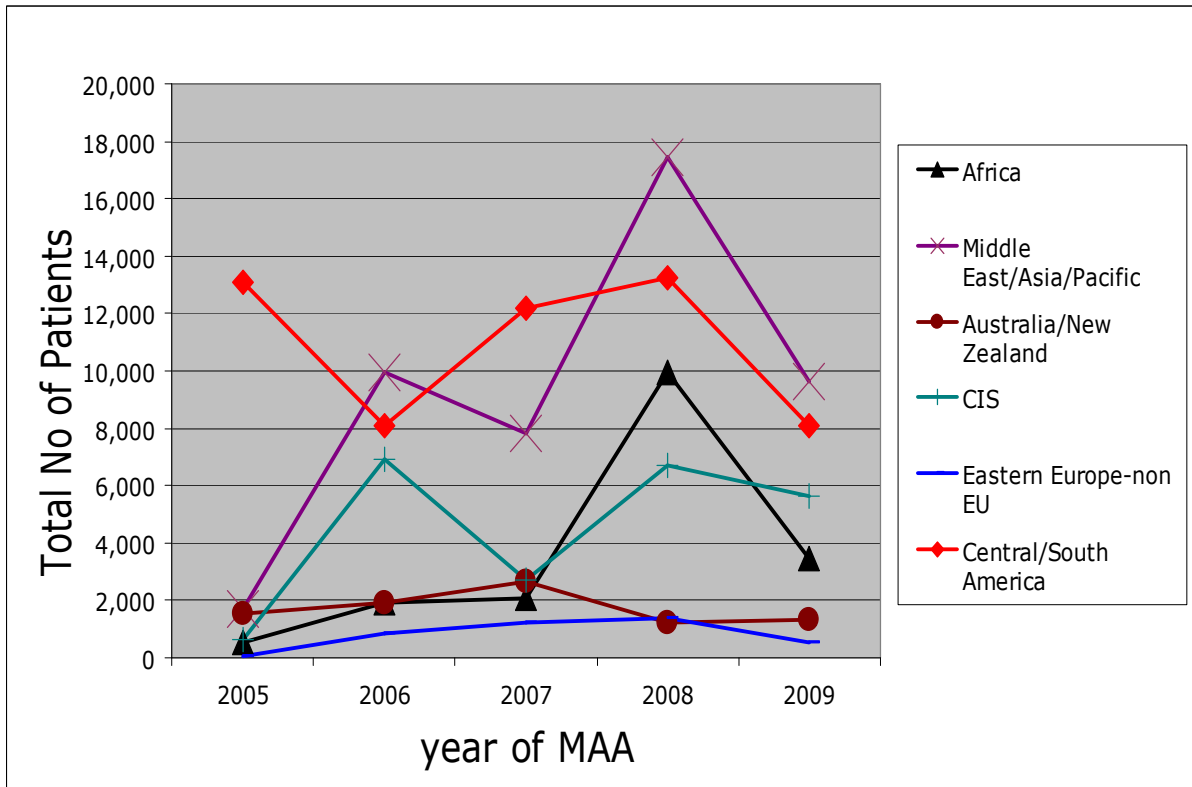


Figure 3: Number of patients in pivotal trials submitted in MAAs to the EMA in the sub-regions of ROW region per year.

When the data from the EU-10 and EU-2 accession countries is added to the ROW region as shown in **Table 3**, then, as can be observed in **Figure 4**, with the exception of 2005 and 2007, the number of patients is greater in this new region in comparison with the EU-15/EEA and North America. This is an important consideration given that many of these patients may have been recruited prior to the 2004 and 2007 accessions.

Table 3: Patient numbers presented from a pre-2004/2007 accession perspective based on an assumption that many of the patients, particularly in the earlier years, may have been recruited prior to accession. (Note that totals do not include Switzerland)

Patients per region/year	2005	2006	2007	2008	2009	Total
EU-15/EEA	27,822	30,714	42,894	27,561	33,711	162,702
North America	37,117	33,389	41,810	55,165	42,269	209,705
ROW + EU-10+ EU-2	21,653	48,384	40,895	64,101	46,059	221,092

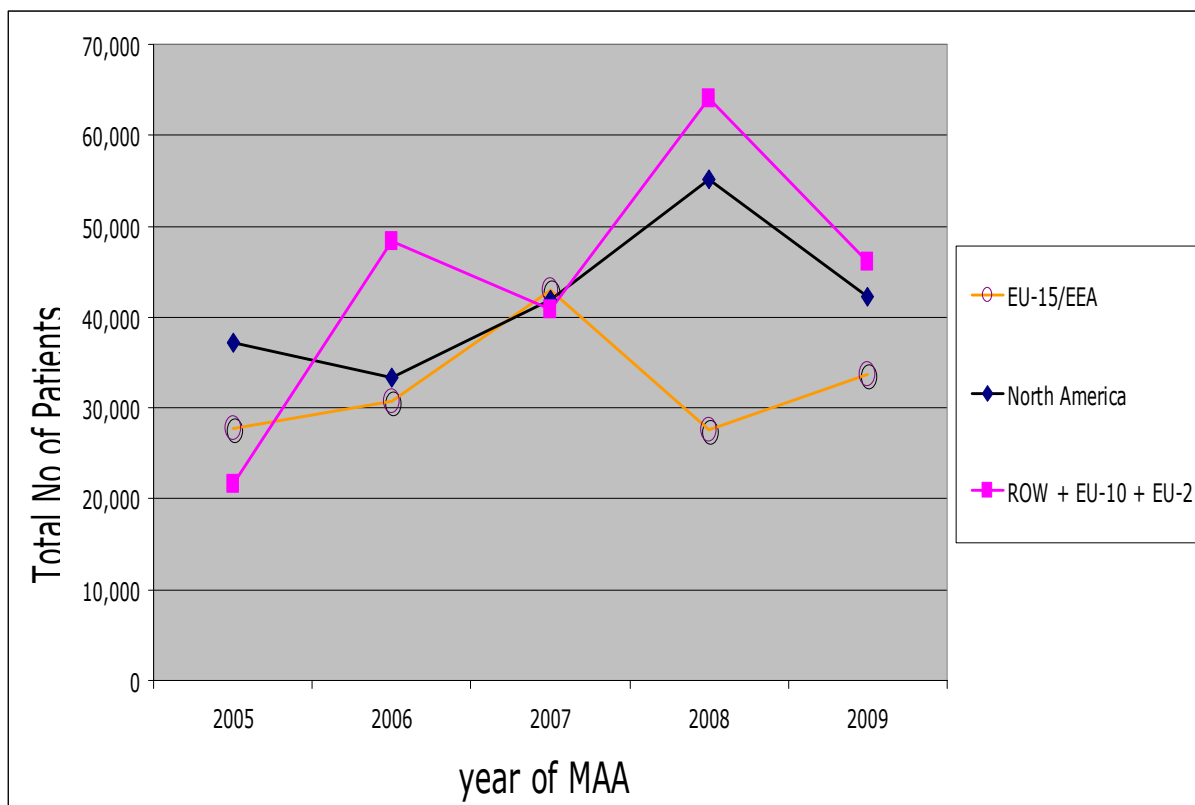


Figure 4: Patient numbers are presented from a pre-2004/2007 accession perspective per region and year, based on an assumption that many of the patients, particularly in the earlier years, may have been recruited prior to accession.

The detailed information on patient recruitment per country and per year can be found in **appendix 2**. A summary of the overall situation during the period 2005-2009 referring mainly to countries recruiting 0.5% or more of the total is:

- EU/EEA/EFTA: the major contributors are Germany (6.5%), Poland (4.6%) and France (3.4%). They are followed in order by Spain, UK, Italy, Finland, Czech Republic, Belgium, Netherlands Hungary and Denmark contributing between 1.5 to 2.4% of the total patients.
- Non-EU Eastern European countries: the major contributor is Croatia with a 0.5% of the total number of patients.

- CIS (Commonwealth of Independent States): the major contributor is Russia with 2.9%, followed by Ukraine (0.8%).
- North America: USA is the major contributor with 30.6% while Canada contributes 4.6%.
- Australia-New Zealand: this area provides 1.5%, mainly from Australia (1.2%).
- Central/South America: the major contributor is Brazil (2.6%) followed by Argentina (2.2%), Mexico (1.3%), Costa Rica (0.7%) and Peru (0.6%).
- Middle East/Asia/Pacific: the major contributors are India (1.5%), Israel (1.3%), Philippines (0.9%), China and Thailand (both 0.7%). They are followed in order by South Korea, Chinese Taipei, Japan, Turkey, Malaysia and Hong Kong contributing between 0.3 and 0.6%.
- Africa: South-Africa is the major contributor with 2.6% of the patients.

The total number of patients in MAA submitted to the EMA during the 2005-2009 period in those third countries contributing with at least 0.5% of the patients is shown in **Figure 5**.

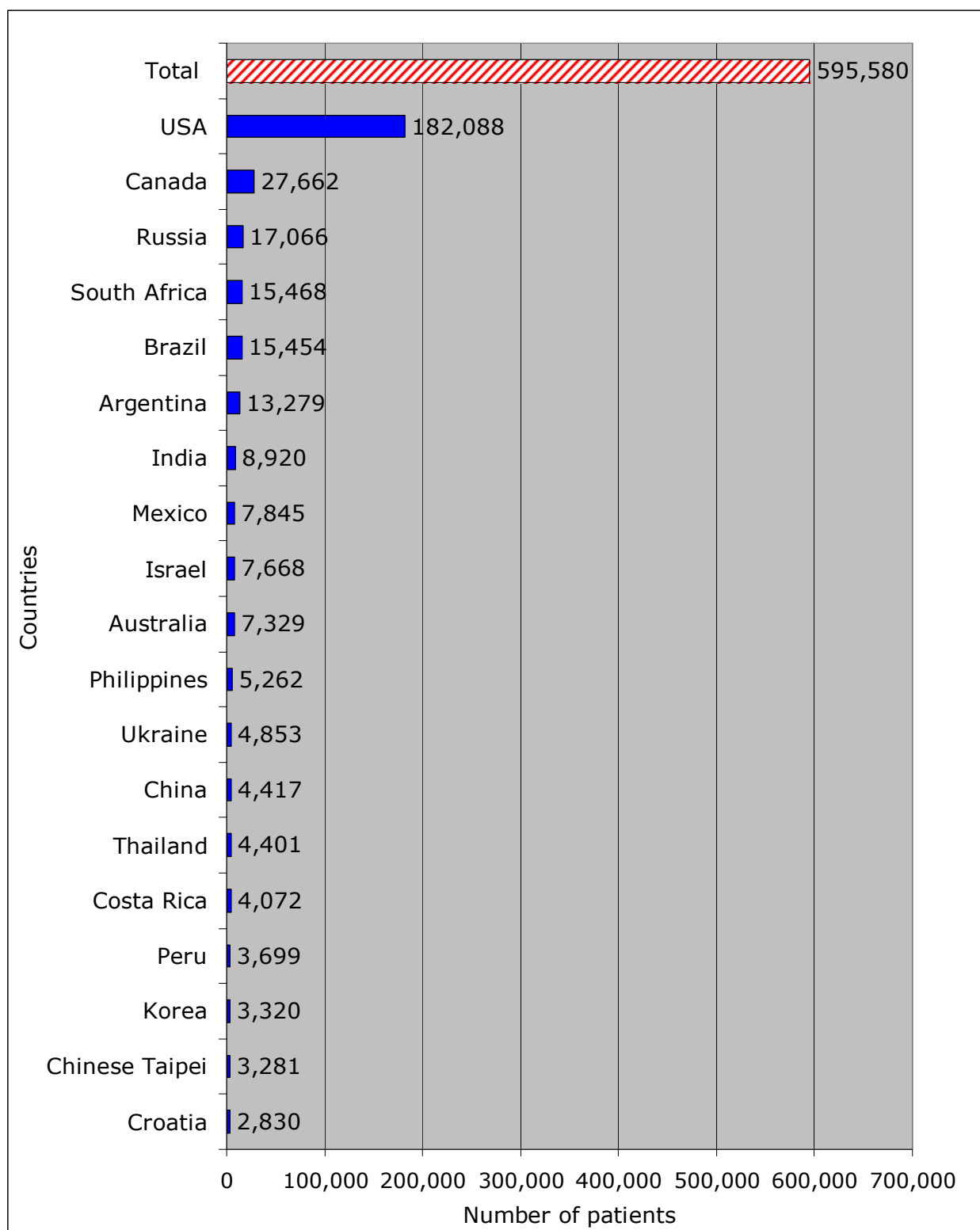


Figure 5: Third countries with at least 0.5% of patients in the pivotal trials included in the MAA submitted to the EMA during the 2005-2009 period

3.2.2. Number of Investigator Sites

The total number of investigator sites per country is also provided in **appendix 2**. A summary of this information per region is provided in **Table 4**. The highest number of sites were located in North America (44 %) and EU/EEA/EFTA (36.5 %), followed by Central/South America and Middle East/Asia/Pacific (6.0 and 5.9 %, respectively) and smaller numbers in the rest of the ROW region.

Table 4: The number of investigator sites involved in pivotal clinical trials submitted in MAAs to the EMA 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 per region/year	2005		2006		2007		2008		2009		total	
	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	38	16,063	36.5
<i>Comprising:</i>												
EU-15/EEA	1,676	29.9	2,759	29.1	2,648	28.5	2,431	24.6	2,730	28	12,244	27.8
EU-10	224	4.0	638	6.7	639	6.9	734	7.4	758	8	2,993	6.8
EU-2	52	0.9	126	1.3	110	1.2	177	1.8	170	2	635	1.4
Switzerland	22	0.4	44	0.5	44	0.5	31	0.3	50	1	191	0.4
North America	3,042	54.3	4,168	44.0	4,150	44.7	4,182	42.3	3,820	39	19,362	44.0
<i>Comprising:</i>												
Canada	282	5.0	392	4.1	361	3.9	398	4.0	621	6	2,054	4.7
USA	2,760	49.2	3,776	39.9	3,789	40.8	3,784	38.3	3,199	33	17,308	39.3
ROW	589	10.5	1,737	18.3	1,699	18.3	2,320	23.5	2,264	23	8,609	19.6
<i>Comprising:</i>												
Africa	59	1.1	140	1.5	141	1.5	216	2.2	151	2	707	1.6
Middle East/Asia/Pacific	119	2.1	551	5.8	417	4.5	682	6.9	808	8	2,577	5.9
Australia/New Zealand	118	2.1	229	2.4	220	2.4	175	1.8	177	2	919	2.1
CIS	72	1.3	320	3.4	226	2.4	498	5.0	450	5	1,566	3.6
Eastern Europe-non EU	8	0.1	29	0.3	51	0.5	73	0.7	54	1	215	0.5
Central/South America	213	3.8	468	4.9	644	6.9	676	6.8	624	6	2,625	6.0
total	5,605	100	9,472	100	9,290	100	9,875	100	9,792	100	44,034	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 6**.

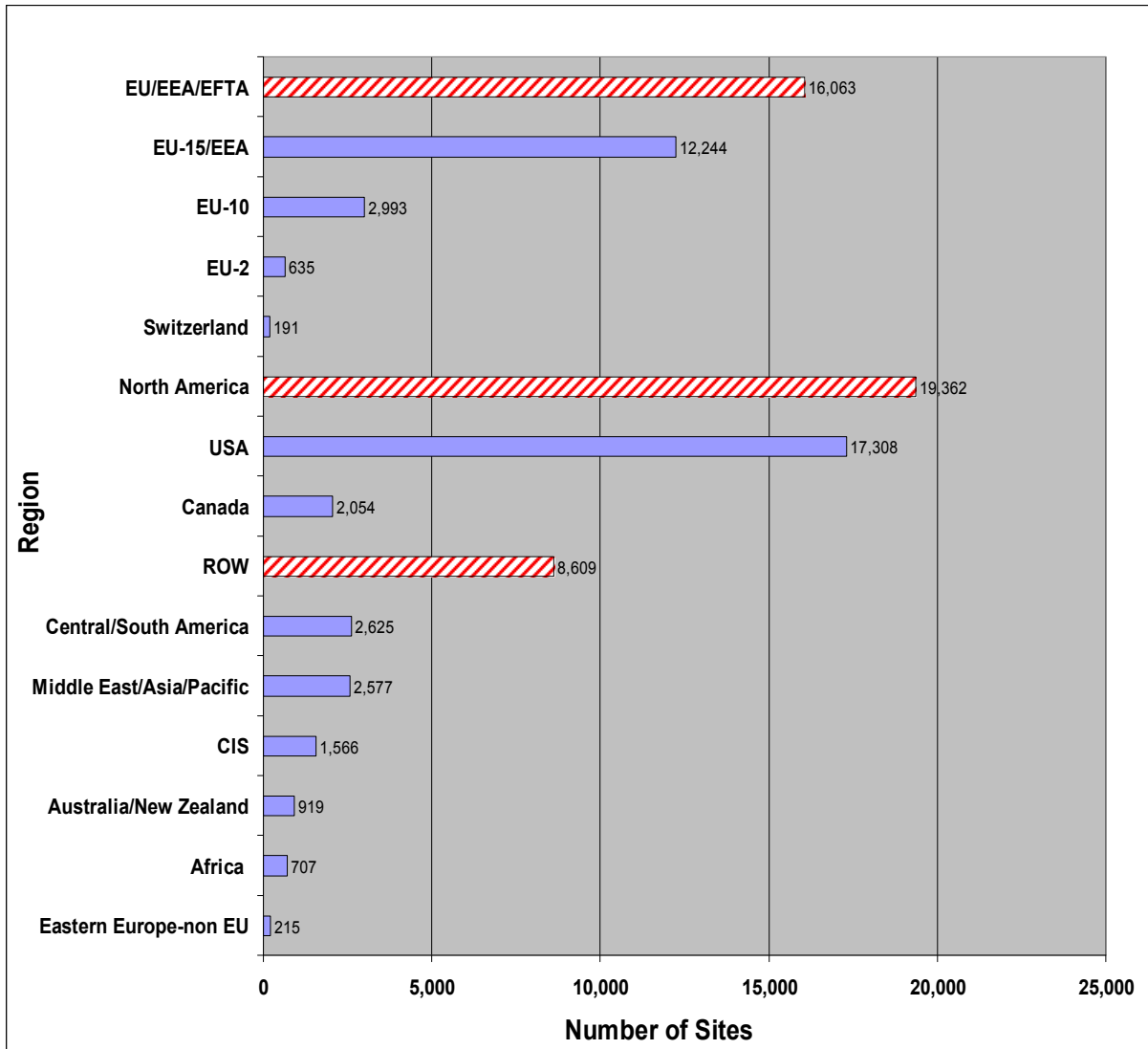


Figure 6: Number of investigator sites in pivotal trials submitted in MAAs to the EMA per region during the period 2005-2009. The data are shown as three “global regions” – EU/EEA/EFTA, North America and ROW (Rest of the World) and then split into its component sub-regions.

An overview of the trend per year is shown in **Figure 7**. In North America the trend is very similar to the EU/EEA/EFTA situation except in 2009; however the number of sites is higher than in Europe over all years, (except in 2009 with similar number), as opposed to the number of patients (Figure 2), which is less except in 2005 and 2008. The trend of these two regions shows an increase up to 2006, remain more or less stable up to 2008 and then decrease in North America but increase in Europe in 2009 (Figure 2). In the rest of the world region (ROW) the trend is similar to the trend observed for the number of patients up to 2008, however in 2009 the number of sites remains stable whereas the number of patients decreases.

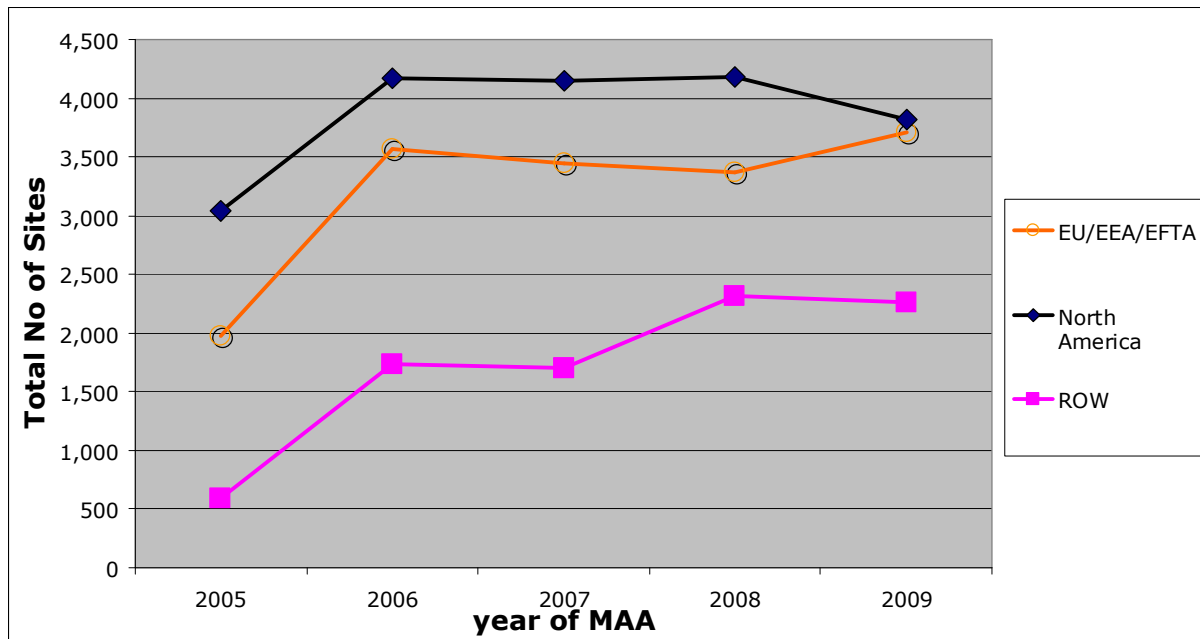


Figure 7: The number of investigator sites involved in pivotal clinical trials submitted in MAAs to the EMA per region and year. The data are shown as three "global regions" – EU/EEA/EFTA, North America and ROW (Rest of the World).

The trend per year in the sub-regions of the ROW area, as shown in **Figure 8**, is very similar to the number of patients (Figure 2) with the exception of Central/South America in 2005 (with a decrease of sites but increase of patients) and Middle East/Asia Pacific in 2009 (with an increase of number of sites but with a decrease in the number of patients).

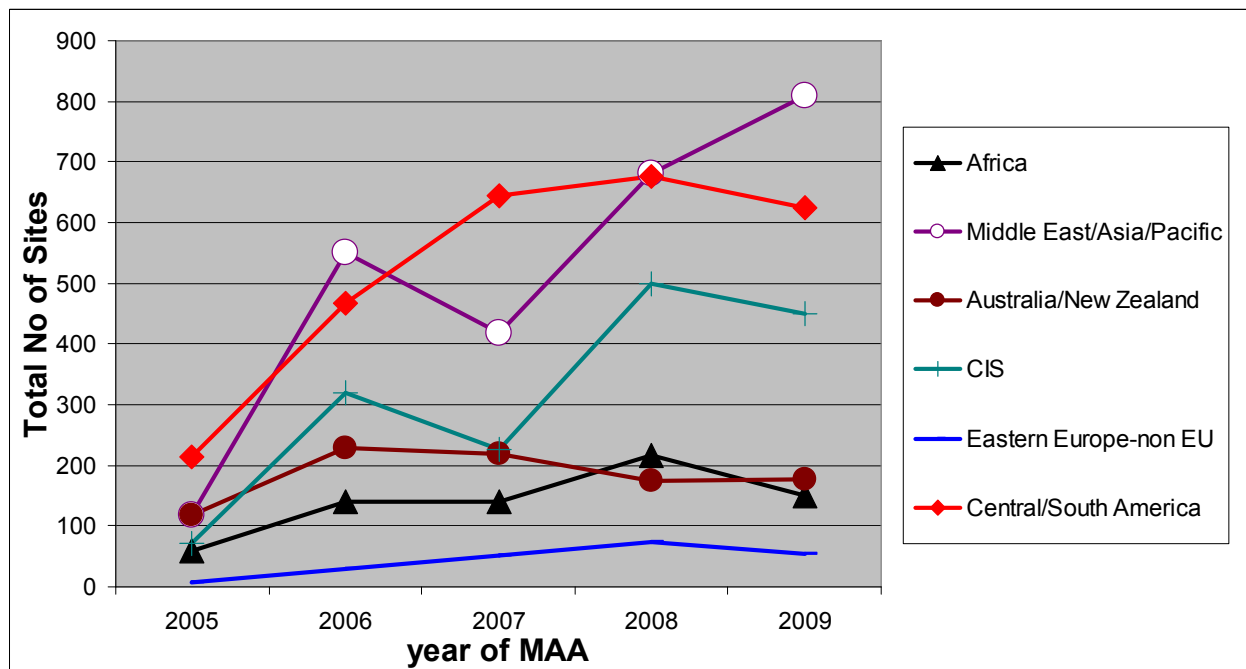


Figure 8: The number of investigator sites involved in pivotal clinical trials submitted in MAAs to the EMA in the sub-regions of ROW region per year.

3.2.3. Number of clinical trials

The overview of this information is provided only per country in **Figures 9** and **10**, as the data, if cumulated per region, results in multiple counting of the same trial.

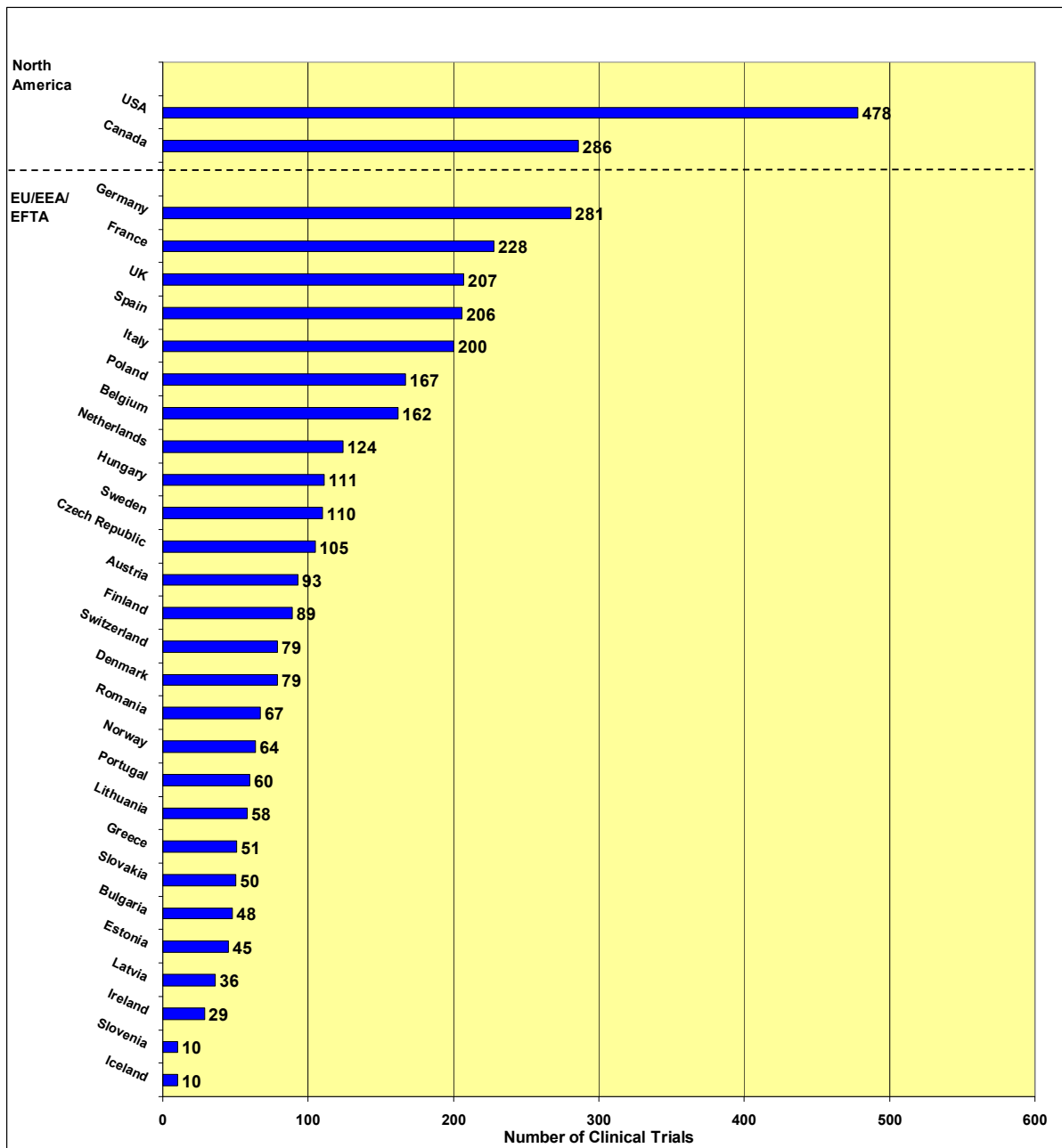


Figure 9: The number of pivotal clinical trials in MAA submitted to the EMA in each country of the North America and EU/EEA/EFTA region in the 2005-2009 period.

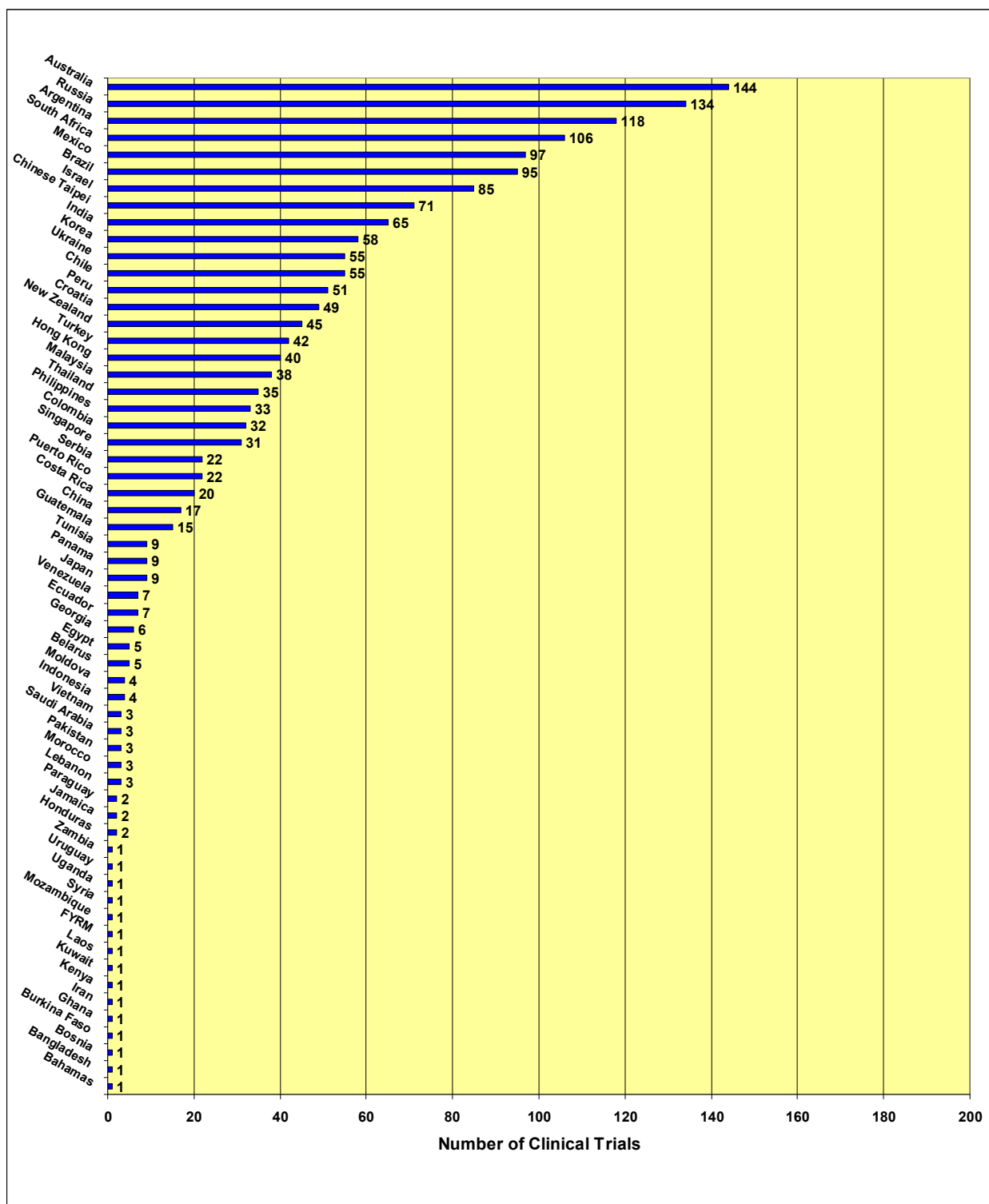


Figure 10: The number of pivotal clinical trials in MAA submitted to the EMA in each country of the ROW region in the 2005-2009 period.

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: Belgium, Czech Republic, France, Germany, Hungary, Italy, Netherlands, Poland, Spain, Sweden and UK
- ROW: Argentina, Australia, South Africa and Russia

3.2.4. 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 11**. It should be noted that in the ROW area the average number of patients per site over the whole period 2005-2009 is higher than in the other regions. The average per region is shown in **Figure 12** with around 18 patients per site in the ROW, 14 patients per site in the EU/EEA/EFTA and 11 patients per site in North America regions.

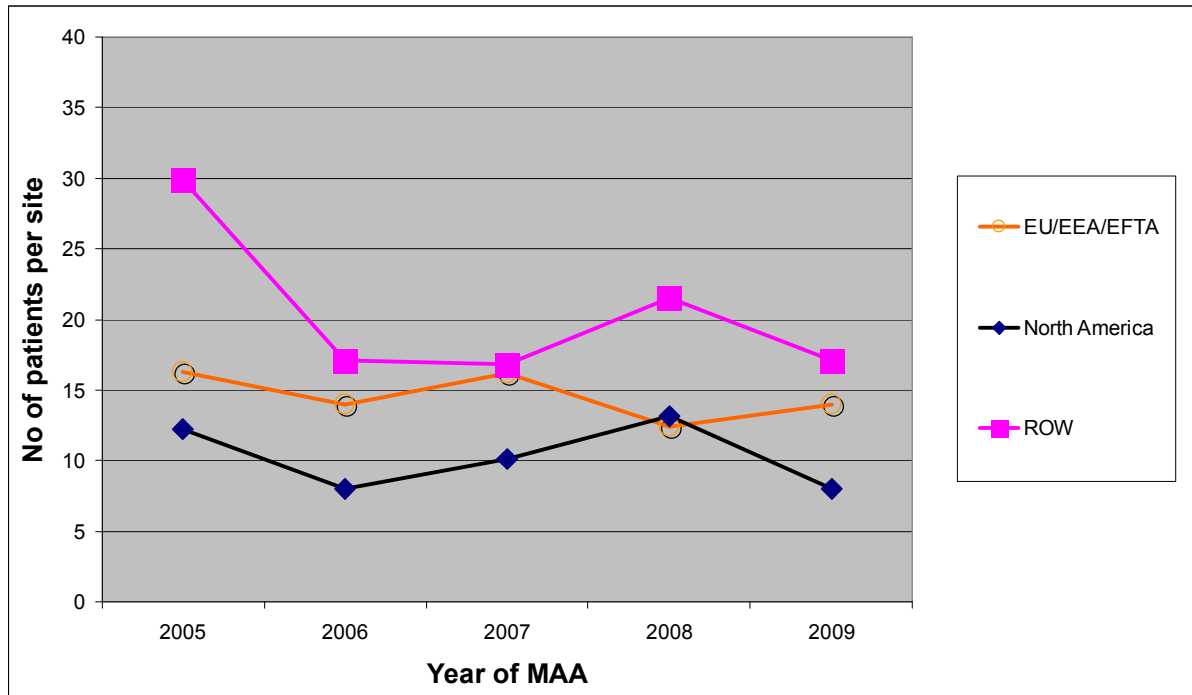


Figure 11: Average number of patients per site in pivotal trials submitted in MAAs to the EMA per region and year. The data are shown as three "global regions" – EU/EEA/EFTA, North America and ROW (Rest of the World).

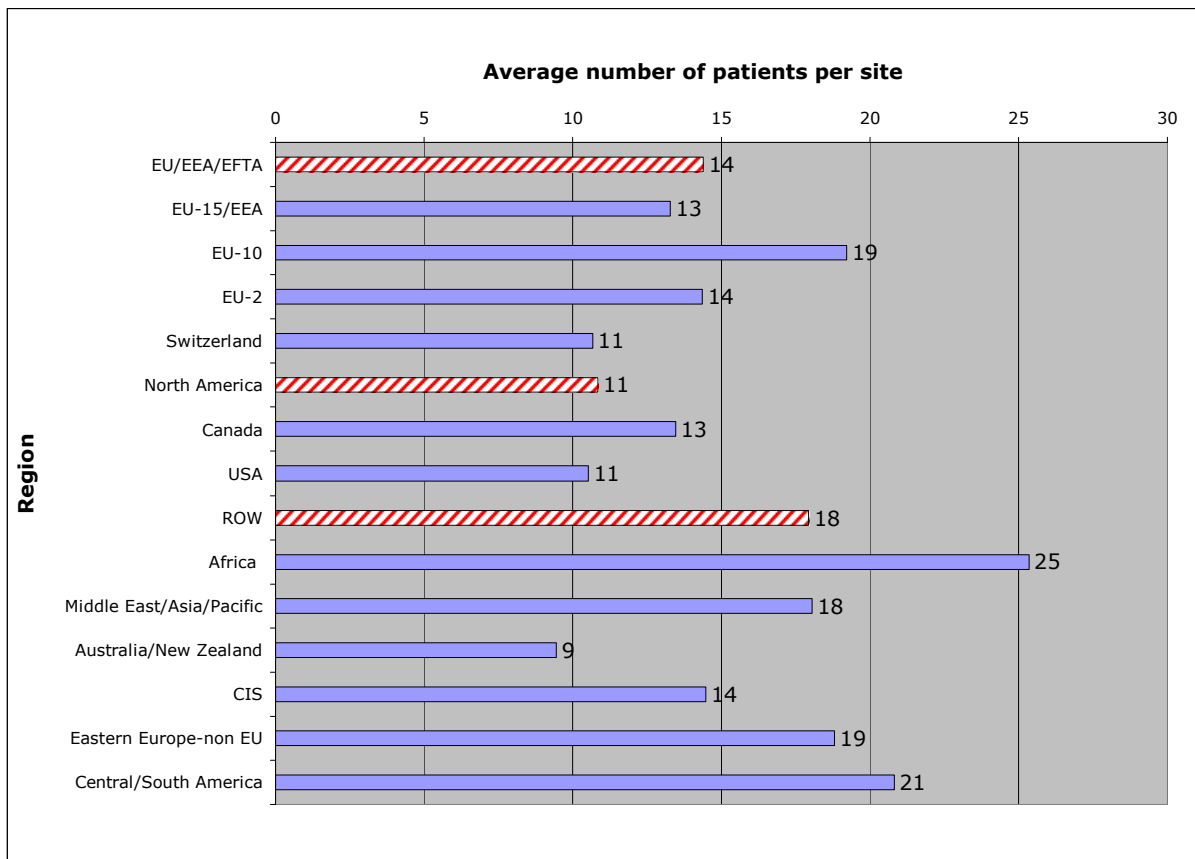


Figure 12: Average number of patients per trial site(s) in pivotal trials submitted in MAAs to the EMA per region during the period 2005-2009. The data are shown as three "global regions" – EU/EEA/EFTA, North America and ROW (Rest of the World) and then split into their component sub-regions.

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

An overview of this information per country is provided in **Figure 13 and Figure 14**. It should be noted that only those countries with 10 or more clinical trials (10 is the minimum number of clinical trials in the EU/EEA/EFTA region i.e. Iceland- see Figure 9) have been included.

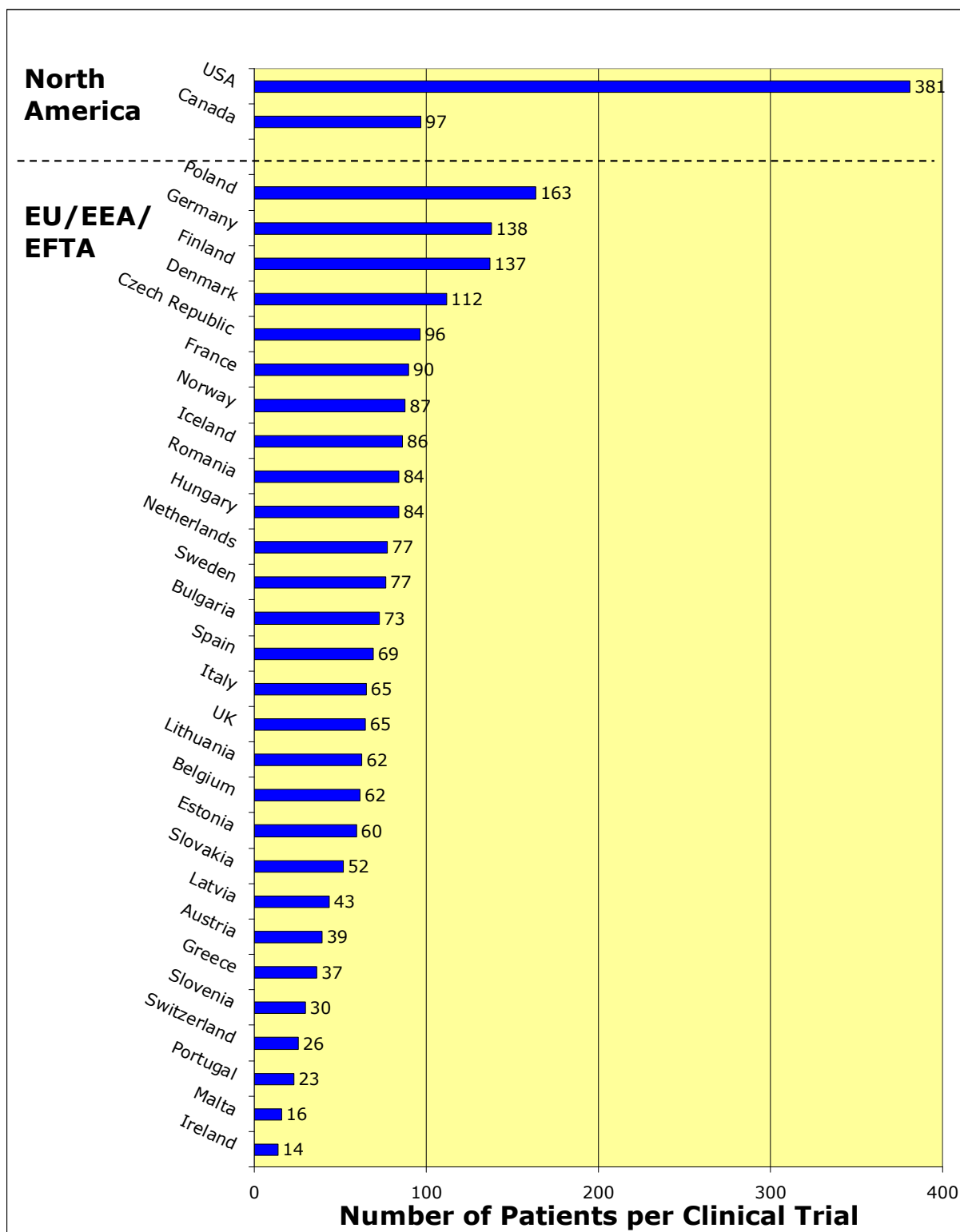


Figure 13: The average number of patients recruited per pivotal clinical trial per country in MAA submitted to the EMA in each country of the North America and EU/EEA/EFTA region in the 2005-2009 period.

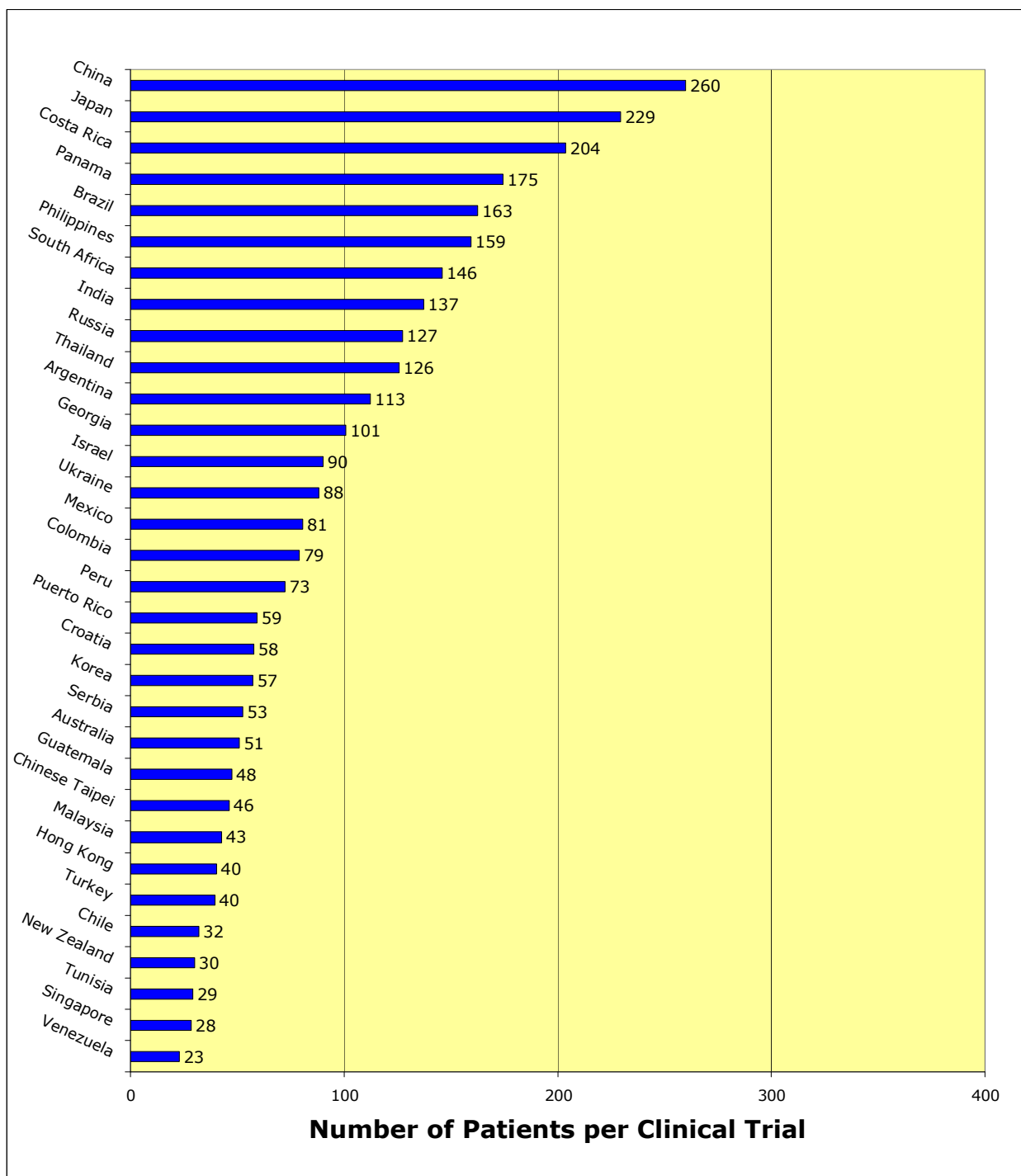


Figure 14 The average number of patients recruited per pivotal clinical trial per country in MAA submitted to the EMA in each country of the ROW region (excluding those countries with less than 20 sites) in the 2005-2009 period.

3.3. Additional Information on GCP Inspections

3.3.1. 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 2009 can be found in **appendix 3**. An overview is shown in **Table 5**, 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 1000 trials from around 452 MAAs submitted since 2005. GCP inspections have been requested for 228 sites (out of 44,034 investigator sites counted as part of the pivotal trials in these MAAs) from 1997 up to now, 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. The 228 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 (paediatric, 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 102 MAAs in 2008 are presented in this report of which 22 were subject to GCP inspection at the time of the MAA. For 2009 data from 144 MAAs are presented of which 15 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.

Table 5: GCP Inspections per year and by region requested by the CHMP.

	1997	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	total	
													#	%
Total	3	3	14	22	17	3	14	10	15	38	50	39	228	100.0
EU/EEA/EFTA	3	0	1	21	10	0	9	7	8	21	21	11	112	49.1
North America	0	3	13	1	4	2	0	2	3	9	10	16	63	27.6
ROW	0	0	0	0	3	1	5	1	4	8	19	12	53	23.2

Since 1997 112 (49.1%) inspections have been requested for sites in the EU/EEA/EFTA region, 63 (27.6%) have been requested for sites in North America and 53 (23.2%) in the rest of the world. Since 1997 up to now the number of inspections in the ROW region have increased since 2006 (4) and more considerably in 2008 and 2009 (19 and 12, respectively). An overview of these results can be found in **Figure 15**.

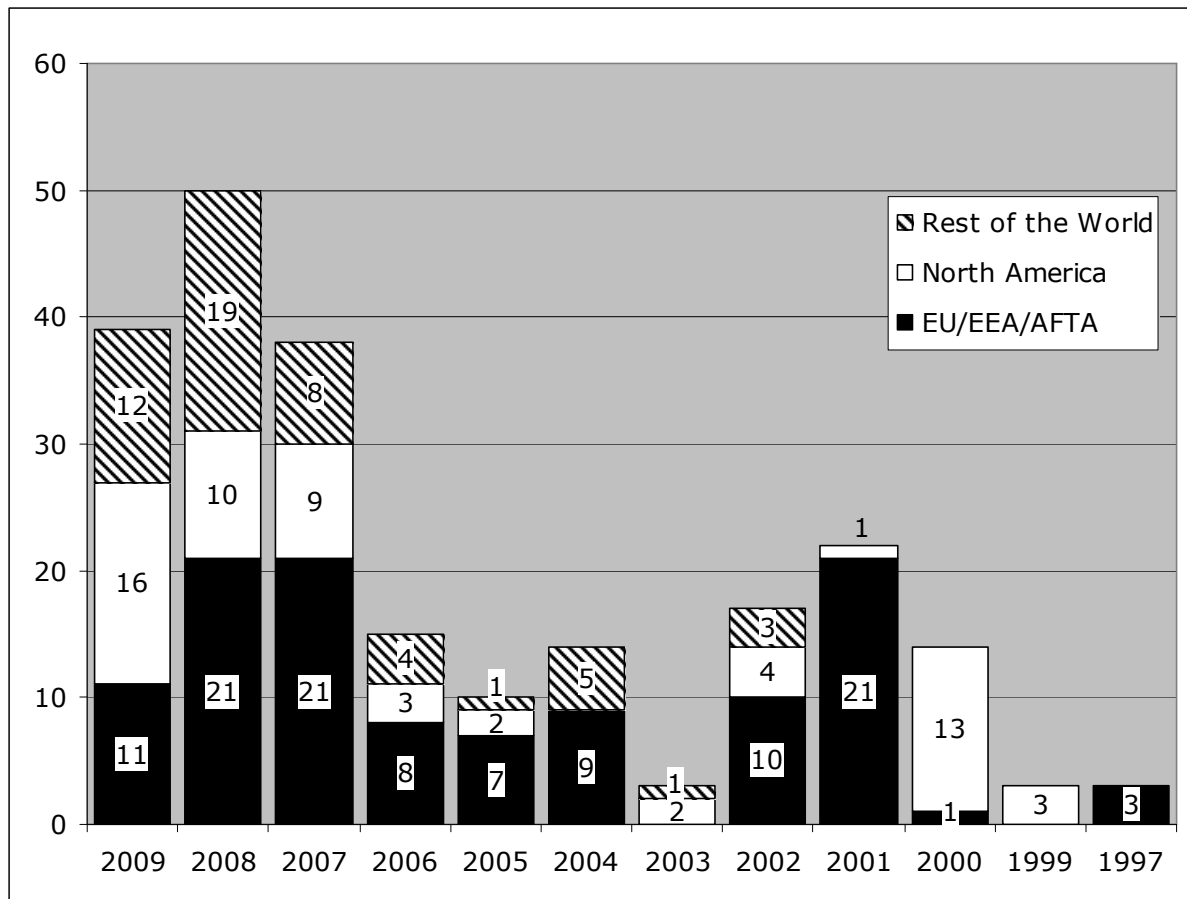


Figure 15: GCP Inspections per year and by region conducted at the request of the CHMP.

The total GCP inspections per 3rd country (North America+ROW) is shown in **Table 6**. According to this data the country with highest number of sites inspected is USA (19.6%) followed by Canada (5.3%), India (4.2%), Russia (4.2%) and China (2.1%).

Table 6: GCP inspections conducted in third countries at the request of CHMP per region and per country.

Number of third country inspections	total	% of all inspections
Eastern-Europe-non EU	2	0.8
Croatia	1	0.4
Serbia	1	0.4
CIS	10	4.4
Russia	8	3.5
Ukraine	2	0.9
North America	63	27.6
Canada	13	5.7
USA	50	21.9
Central/South America	11	4.7
Argentina	2	0.9
Brazil	2	0.9
Chile	1	0.4
Colombia	1	0.4
Costa Rica	1	0.4
Mexico	3	1.3
Peru	1	0.4
Middle East/Asia/Pacific	25	10.9
China	4	1.8
India	9	3.9
Korea (South)	1	0.4
Malaysia	1	0.4
Philippines	4	1.8
Chinese Taipei	1	0.4
Thailand	3	1.3
Turkey	2	0.9
Africa	5	2.1
Ghana	1	0.4
Morocco	1	0.4
South Africa	3	1.3
Total	116	50.5

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 16**. In the case of the ROW region inspections, the 23.3% of inspections carried out is split between routine inspections (18.4%) and of triggered (4.8%).

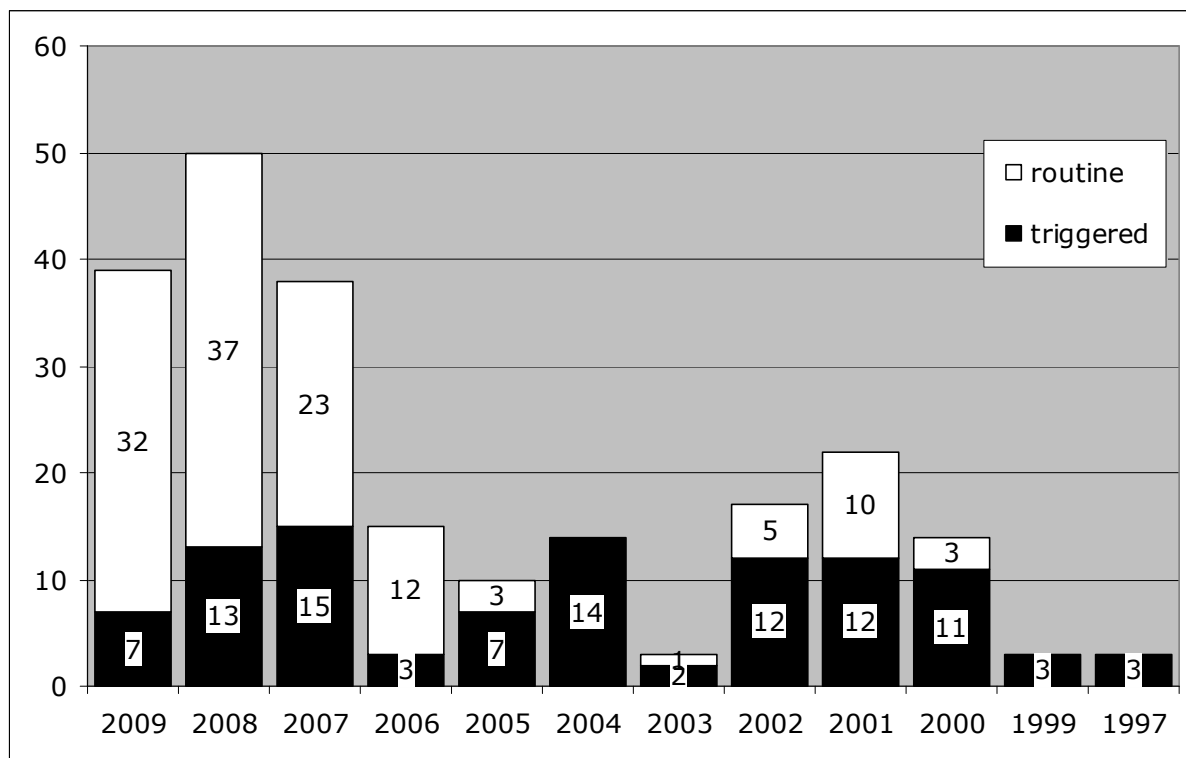


Figure 16: GCP Inspections requested by the CHMP per year and type of inspection (routine/triggered).

It should be noted that the countries with sites inspected in the ROW region as outlined in Table 6 are almost the same as those with at least 0.5% of patients in the pivotal trials included in the MAA submitted to the EMA (Figure 5) with the exceptions of Israel and Australia. Sites from these countries will be subject to inspections in 2010 where possible.

3.3.2. Inspections recorded in EudraCT (up to December 2009) 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 2009) is given in **Table 7**. 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 (2.6 %), while in Asia, North America and CIS-Eastern Europe this was about half of the trial inspections (66.1, 49.1 and 22.2 % respectively). There were no BE trial inspections reported in Africa or South America. Inspection of BE trials and sites has been one of the priorities for the EMA 2009 Road Map and cooperation with the Member States.

Table 7: 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)	33	2.6	1259
EU-10 + EU-2	16	12.0	135
North America	28	49.1	57
CIS and Eastern Europe	4	22.2	18
Asia	39	66.1	59
Africa	0	0.0	7
South America	0	0.0	4
totals	120	7.8	1,539
top 5 countries where BE trial inspections have been carried out:			
India	36	75	48
Canada	27	71.0	38
Italy	6	4.3	141
Germany	5	1.9	267
Czech Republic	5	62.50	8

4. CONCLUSIONS

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

- 61% of the patients in pivotal trials submitted in MAA to the EMA during the observation period from January 2005 to December 2009 were from third countries, comprising 25.9% from the ROW region (Africa, Middle East/Asia/Pacific, Australia/New Zealand, Central/South America, CIS, Eastern Europe-non EU), and 35.2% from North America.
- 7.8% of patients in pivotal trials submitted in MAA to the EMA during the observational period from January 2005 to December 2009 were included in trials in Middle East/Asia/Pacific.
- 9.2% of patients in pivotal trials submitted in MAA to the EMA during the observational period from January 2005 to December 2009 were included in trials in Central/South America.
- 11.2% of patients in the EU/EEU/EFTA region come from the EU-10 and EU-2 countries, which makes a significant contribution to the European figures.
- The contribution of certain third countries (21.5% of patients), should be highlighted in terms of numbers patients included in pivotal trials submitted in MAA to the EMA during the observational period January 2005 to December 2009:
 - Africa: South Africa (2.6%)
 - Middle East/Asia/Pacific: India (1.5%), Israel (1.3%), Philippines (0.9%), China (0.7%), Thailand (0.7%), Korea (0.5%) and Chinese Taipei (0.5%)
 - Australia/New Zealand: Australia (1.2%)
 - Central/South America: Brazil (2.6%), Argentina (2.2%), Mexico (1.3%), Costa Rica (0.7%), Peru (0.6%)

- CIS: Russia (2.9%) and Ukraine (0.8%)
- Eastern Europe-non EU): Croatia (0.5%)
- 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, Hungary, Sweden and Czech Republic,
 - ROW: Argentina, Australia, Russia and South Africa
- The average number of patients per site in the ROW (18) area over the whole period 2005-2009 is higher than in the other regions (14 and 11 patients per site in the EU/EEA/EFTA and North America regions, respectively).
- The total number of patients per clinical trial is considerable higher in North America followed by ROW and EU/EEA/EFTA over the whole period 2005-2009. If we consider a cut off point of 125 patients per trial the most relevant countries are USA, Poland, Germany, Finland, China, Japan, Costa Rica, Panama, Brazil, Philippines, South Africa, India, Russia and Thailand.
- Around 25% (15 out of 60) of the countries in the ROW region have more than 80 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 inspections are USA (21.9%) followed by Canada (5.7%), India (3.9%), Russia (3.5%), China (1.8%), Philippines (1.8%), South-Africa (1.3%) and Thailand (1.3%). Further increase in inspections will require additional GCP inspection resource from the member states.
- The third countries with more BE studies inspected were in Canada and India based on information recorded in EudraCT. Czech Republic was the country in the EU with most inspection of BE trial sites. This is also reflected in the generic applications submitted to the EMA.

APPENDIX 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 meet 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)

APPENDIX 2- NUMBER OF PATIENTS, SITES AND PIVOTAL CLINICAL TRIALS IN MAA SUBMITTED TO THE EMA FROM 2005 TO 2009

	2005			2006			2007			2008			2009			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
Globally	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	5,211	44,034	595,580
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	2,771	16,063	231,369
<i>EU-15/EEA</i>	<i>269</i>	<i>1,676</i>	<i>27,822</i>	<i>496</i>	<i>2,759</i>	<i>30,714</i>	<i>467</i>	<i>2,648</i>	<i>42,894</i>	<i>413</i>	<i>2,431</i>	<i>27,561</i>	<i>348</i>	<i>2,730</i>	<i>33,711</i>	<i>1,993</i>	<i>12,244</i>	<i>162,702</i>
Austria	10	18	233	24	48	482	23	79	1,389	21	64	978	15	53	586	93	262	3,668
Belgium	28	145	2,526	31	82	1,136	41	158	2,956	37	158	2,453	25	101	917	162	644	9,988
Denmark	10	67	2,854	13	50	788	17	70	1,996	18	66	702	21	129	2,474	79	382	8,814
Finland	12	53	2,564	18	62	783	21	80	1,595	22	113	3,395	16	89	3,857	89	397	12,194
France	31	282	2,330	57	371	3,876	59	578	8,818	40	289	1,918	41	371	3,464	228	1,891	20,406
Germany	36	436	7,095	76	838	9,161	63	482	7,835	57	521	5,664	49	691	9,064	281	2,968	38,819
Greece	6	23	146	16	50	776	7	27	253	13	46	428	9	33	263	51	179	1,866
Iceland	3	3	740	1	1	6	2	2	6	3	3	62	1	4	49	10	13	863
Ireland	4	11	60	10	29	79	5	21	134	7	16	84	3	10	40	29	87	397
Italy	30	146	1,002	54	274	3,069	46	253	3,093	39	308	3,352	31	286	2,551	200	1,267	13,067
Liechtenstein	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Luxembourg	0	0	0	0	0	0	0	0	0	0	0	0	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	124	620	9,586
Norway	7	52	2,193	18	58	730	17	70	986	14	52	822	8	53	868	64	285	5,599
Portugal	10	33	166	12	30	235	17	64	466	10	42	187	11	41	322	60	210	1,376
Spain	25	118	849	54	293	2,879	46	269	4,648	41	250	2,343	40	353	3,498	206	1,283	14,217
Sweden	14	71	2,156	30	153	1,729	31	137	2,079	18	91	995	17	120	1,458	110	572	8,417
UK	27	143	2,179	51	274	2,047	42	235	3,695	46	286	2,931	41	246	2,573	207	1,184	13,425
<i>EU-10</i>	<i>55</i>	<i>224</i>	<i>3,412</i>	<i>131</i>	<i>638</i>	<i>16,601</i>	<i>141</i>	<i>639</i>	<i>11,016</i>	<i>134</i>	<i>734</i>	<i>11,706</i>	<i>123</i>	<i>758</i>	<i>14,768</i>	<i>584</i>	<i>2,993</i>	<i>57,503</i>

	2005			2006			2007			2008			2009			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
Cyprus	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Czech Republic	10	42	869	18	79	2,565	21	85	1,368	32	174	2,243	24	150	3,069	105	530	10,114
Estonia	3	6	98	13	38	537	10	23	712	8	17	588	11	37	743	45	121	2,678
Hungary	13	66	813	22	108	2,131	33	121	1,817	21	104	1,724	22	150	2,827	111	549	9,312
Latvia	4	13	175	10	38	505	7	26	402	8	22	220	7	22	263	36	121	1,565
Lithuania	3	5	84	13	59	841	19	53	1,364	12	48	744	11	44	583	58	209	3,616
Malta	0	0	0	0	0	0	0	0	0	0	0	0	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	167	1,244	27,291
Slovakia	6	11	37	14	50	846	8	24	245	12	45	467	10	64	1,005	50	194	2,600
Slovenia	1	2	37	5	16	223	2	2	20	2	3	15				10	23	295
EU-2	11	52	656	16	126	2,146	23	110	1,251	39	177	2,447	26	170	2,628	115	635	9,128
Bulgaria	5	23	332	6	44	759	9	43	512	16	65	633	12	85	1,260	48	260	3,496
Romania	6	29	324	10	82	1,387	14	67	739	23	112	1,814	14	85	1,368	67	375	5,632
Switzerland	10	22	200	25	44	499	17	44	506	15	31	310	12	50	521	79	191	2,036
Switzerland	10	22	200	25	44	499	17	44	506	15	31	310	12	50	521	79	191	2,036
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	764	19,362	209,750
Canada	31	282	3,477	65	392	3,919	57	361	6,231	67	398	4,454	66	621	9,581	286	2,054	27,662
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	478	17,308	182,088
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	1,676	8,609	154,461
Africa	13	59	523	25	140	1,938	29	141	2,061	29	216	9,962	33	151	3,431	129	707	17,915
Burkina Faso	0	0	0	0	0	0	0	0	0	0	0	0	1	1	301	1	1	301
Egypt	1	1	5	1	2	22	0	0	0	1	1	108	2	12	258	5	16	393
Ghana	0	0	0	0	0	0	1	1	280	0	0	0	0	0	0	1	1	280
Kenya	0	0	0	0	0	0	0	0	0	0	0	0	1	1	222	1	1	222
Morocco	0	0	0	0	0	0	1	2	20	1	3	20	1	4	22	3	9	62
Mozambique	0	0	0	0	0	0	0	0	0	0	0	0	1	1	445	1	1	445

	2005			2006			2007			2008			2009			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
South Africa	11	55	427	22	133	1,894	27	138	1,761	24	205	9,746	22	123	1,640	106	654	15,468
Tunisia	1	3	91	2	5	22	0	0	0	3	7	88	3	7	63	9	22	264
Uganda	0	0	0	0	0	0	0	0	0	0	0	0	1	1	176	1	1	176
Zambia	0	0	0	0	0	0	0	0	0	0	0	0	1	1	304	1	1	304
<i>Middle East/Asia/Pacific</i>	38	119	1,694	121	551	9,925	94	417	7,801	153	682	17,458	139	808	9,627	545	2,577	46,505
Bangladesh	0	0	0	0	0	0	0	0	0	1	1	150	0	0	0	1	1	150
China				3	77	2,214	4	33	611	5	25	755	5	50	837	17	185	4,417
Hong Kong	3	3	155	10	20	235	6	12	150	14	31	889	7	13	182	40	79	1,611
India	1	10	86	13	108	3,121	4	41	222	22	136	2,710	25	233	2,781	65	528	8,920
Indonesia	0	0	0	0	0	0	1	2	12	1	2	13	2	7	75	4	11	100
Iran	1	1	3	0	0	0	0	0	0	0	0	0	0	0	0	1	1	3
Israel	6	18	187	21	74	597	22	102	1,878	15	167	3,565	21	87	1,441	85	448	7,668
Japan	1	25	217	2	35	680	2	50	563	3	34	462	1	25	143	9	169	2,065
Korea	1	2	21	17	90	1,177	8	28	310	15	51	789	17	120	1,023	58	291	3,320
Kuwait	1	1	3	0	0	0	0	0	0	0	0	0	0	0	0	1	1	3
Laos	0	0	0	0	0	0	0	0	0	0	0	0	1	2	200	1	2	200
Lebanon	0	0	0	0	0	0	0	0	0	1	2	216	2	5	44	3	7	260
Malaysia	1	1	51	10	26	450	7	19	165	12	28	719	8	24	237	38	98	1,622
Pakistan	0	0	0	0	0	0	0	0	0	3	11	248	0	0	0	3	11	248
Philippines	2	8	67	3	7	45	7	17	1,712	13	49	3,042	8	45	396	33	126	5,262
Saudi Arabia	1	1	16	1	1	2	0	0	0	0	0	0	1	2	5	3	4	23
Singapore	4	8	207	11	19	206	3	6	31	7	9	304	6	13	131	31	55	879
Syria	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1

	2005			2006			2007			2008			2009			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
Chinese Taipei	11	27	415	15	53	830	14	51	468	18	60	906	13	77	662	71	268	3,281
Thailand	1	1	124	5	13	194	8	20	1,057	11	30	2,181	10	34	845	35	98	4,401
Turkey	3	12	141	10	28	174	7	25	247	11	45	505	11	69	600	42	179	1,667
Vietnam	0	0	0	0	0	0	1	11	375	1	1	4	1	2	25	3	14	404
<i>Australia/ New Zealand</i>	25	118	1,560	51	229	1,892	43	220	2,663	31	175	1,219	39	177	1,344	189	919	8,678
Australia	21	110	1,229	39	195	1,624	34	192	2,180	23	152	1,117	27	157	1,179	144	806	7,329
New Zealand	4	8	331	12	34	268	9	28	483	8	23	102	12	20	165	45	113	1,349
<i>CIS</i>	20	72	664	42	320	6,939	37	226	2,731	59	498	6,677	46	450	5,653	204	1,566	22,664
Belarus	0	0	0	1	3	18	2	5	32	2	6	50				5	14	100
Georgia	0	0	0	2	4	24	1	1	29	1	1	4	2	14	549	6	20	606
Moldova	0	0	0	0	0	0	0	0	0	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	134	1,122	17,066
Ukraine	6	27	180	10	81	1,827	8	48	241	16	111	1,025	15	139	1,580	55	406	4,853
<i>Eastern Europe-non EU</i>	4	8	69	9	29	862	19	51	1,202	23	73	1,370	18	54	539	73	215	4,042
Bosnia	0	0	0	0	0	0	0	0	0	1	2	12	0	0	0	1	2	12
Croatia	4	8	69	5	18	581	14	31	748	16	49	1,144	10	34	288	49	140	2,830
FYRM	0	0	0	0	0	0	0	0	0	0	0	0	1	2	40	1	2	40
Serbia				4	11	281	5	20	454	6	22	214	7	18	211	22	71	1,160
<i>Central/ South America</i>	55	213	13,075	104	468	8,081	131	644	12,170	116	676	13,262	130	624	8,069	536	2,625	54,657
Argentina	9	42	783	17	134	2,014	28	215	2,918	34	270	5,010	30	203	2,554	118	864	13,279
Bahamas	1	1	2	0	0	0	0	0	0	0	0	0	0	0	0	1	1	2
Brazil	13	80	2,643	22	141	3,168	24	144	4,376	20	140	3,068	16	117	2,199	95	622	15,454
Chile	4	7	70	9	28	431	16	42	419	13	58	395	13	40	445	55	175	1,760

	2005			2006			2007			2008			2009			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
Colombia	4	12	1,267	6	17	295	9	36	559	0	0	0	13	55	416	32	120	2,537
Costa Rica	1	9	1,641	5	11	221	5	10	253	3	4	1,787	6	19	170	20	53	4,072
Ecuador	0	0	0	1	1	3	0	0	0	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	15	35	715
Honduras	0	0	0	1	2	268	0	0	0	0	0	0	1	2	31	2	4	299
Jamaica	1	1	1,770	0	0	0	0	0	0	1	1	3	0	0	0	2	2	1,773
Mexico	9	32	2,219	16	56	674	23	106	1,319	26	137	2,220	23	105	1,413	97	436	7,845
Panama	0	0	0	1	2	174	3	14	1,312	2	3	32	3	4	54	9	23	1,572
Paraguay	0	0	0	0	0	0	0	0	0	0	0	0	2	2	16	2	2	16
Peru	5	10	1,434	17	55	675	14	58	718	6	22	306	9	44	566	51	189	3,699
Puerto Rico	5	12	858	2	3	7	5	11	149	7	29	288	3	5	5	22	60	1,307
Uruguay	0	0	0	1	1	10	0	0	0	0	0	0	0	0	0	1	1	10
Venezuela	1	2	16	2	6	24	0	0	0	1	4	43	3	8	79	7	20	162

APPENDIX 3- NUMBER OF GCP INSPECTIONS PER YEAR AND TYPE OF INSPECTION REQUESTED BY CHMP

tr= triggered inspections

ro= routine inspections

to= total number of inspections

REGION	1997			2000			2001			2002			2003			2004			2005			2006			2007			2008			2009			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						
Globally	3	0	3	14	3	17	12	10	22	12	5	17	2	1	3	14	0	14	7	3	10	3	12	15	15	23	38	13	37	50	7	32	39	102	126	228			
EU/EEA/EFTA	3	0	3	1	0	1	11	10	21	5	5	10	0	0	0	9	0	9	4	3	7	2	6	8	9	12	21	6	15	21	3	8	11	53	59	112			
EU-15/EEU/EFTA	3	0	3	1	0	1	11	8	19	4	4	8	0	0	0	9	0	9	0	3	3	2	5	7	2	9	11	4	11	15	1	6	7	37	46	83			
Austria								1	1																			1	2	3		1	1	1	4	5			
Belgium							2		2																1	1								2	1	3			
Denmark											1	1																1	1	2				1	2	3			
Estonia											1	1																						0	1	1			
Finland																					1			1										1	0	1			
France							1	4	5	4		4				3		3							3	3		3	3					8	10	18			
Germany								3	3		1	1				4		4		1	1	1	3	4	1	3	4	2	1	3		2	2	8	14	22			
Ireland																													1	1	2				1	1	2		
Italy							1		1														2	2										1	2	3			
Netherlands	1		1				2		2											1	1				1	1		1	1					2	2		3	5	8
Portugal																										1	1							0	1	1			
Sweden	1		1																	1	1													1	1	2			
Spain							3		3																1		1		1	1				4	1	5			
UK	1		1	1		1	1		1							1		1										1	1					4	1	5			

REGION	1997			2000			2001			2002			2003			2004			2005			2006			2007			2008			2009			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
Switzerland							1		1		1	1				1		1											1	1				2	2	4		
EU-10+EU-2	0	0	0	0	0	0	0	2	2	1	1	2	0	0	0	0	0	0	4	0	4	0	1	1	7	3	10	2	4	6	2	2	4	16	13	29		
Czech Republic																			2		2								1	1				2	1	3		
Hungary								1	1																1	1								0	2	2		
Latvia																													1			1		1	0	1		
Lithuania																									1		1	1		1	1		1	3	0	3		
Poland								1	1	1		1							2		2		1	1	6	1	7	1		1		2	2	10	5	15		
Bulgaria											1	1																						0	1	1		
Romania																										1	1		3	3				0	4	4		
Eastern-Europe non EU	0	0	0	0	0	0	0	0	0	3	0	3	0	0	0	3	0	3	0	0	0	0	0	0	0	1	1	1	4	5	0	0	0	7	5	12		
Croatia																										1	1							0	1	1		
Serbia																													1	1				0	1	1		
CIS	0	0	0	0	0	0	0	0	0	3	0	3	0	0	0	3	0	3	0	0	0	0	0	0	0	0	0	1	3	4	0	0	0	7	3	10		
Russia										3		3				2		2											3	3				5	3	8		
Ukraine																1		1										1		1				2	0	2		
North America	0	0	0	13	3	16	1	0	1	4	0	4	2	0	2	0	0	0	2	0	2	1	2	3	6	3	9	5	5	10	4	12	16	38	25	63		
Canada																						1		1	3	2	5	3	1	4		3	3	7	6	13		
USA				13	3	16	1		1	4		4	2		2				2		2		2	2	3	1	4	2	4	6	4	9	13	31	19	50		
Central/South America	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	1	0	1	0	0	0	0	2	2	1	2	3	0	4	4	3	8	11		
Argentina																													1	1		1	1	0	2	2		
Brazil																												1		1		1	1	1	1	2		

REGION	1997			2000			2001			2002			2003			2004			2005			2006			2007			2008			2009			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			
Chile																			1		1																1	0	1			
Colombia																												1	1								0	1	1			
Costa Rica																												1	1								0	1	1			
Mexico																1		1													2	2					1	2	3			
Peru																												1	1								0	1	1			
Middle East/Asia /Pacific	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	1	0	0	0	0	4	4	0	1	1	0	11	11	0	7	7	1	24	25						
China																												3	3								0	4	4			
India																												7	7		1	1					0	10	10			
Korea (South)																															1	1					0	1	1			
Malaysia																1	1																				0	1	1			
Philippines																												1	1					2	2					0	4	4
Chinese Taipei																															1	1					0	1	1			
Thailand																															2	2					0	3	3			
Turkey																1		1																			1	0	1			
Africa	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	4	0	0	0	0	1	1	0	5	5						
Ghana																												1	1								0	1	1			
Morocco																												1	1								0	1	1			
South Africa																																		1	1		0	3	3			