European Medicines Agency
Inspections

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Clinical trials submitted in marketing authorisation applications to the EMEA:

Overview of patient recruitment and the geographical location of investigator site

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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 document provides an overview of the distribution of the number of patients, investigator sites and pivotal clinical trials included in MAA submitted to the EMEA, on the number of sites subject to inspection and the geographic location of these inspections.

2. SCOPE

The information presented in this report covers the period from January 2005 to December 2008 and relates mainly to new applications (244) and line extensions (41) but also includes some variations (23) 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**.

	2005	2006	2007	2008	total
New applications	39	60	68	77	**244**
Line extensions	3	8	17	13	**41**
Type II variations	2	5	4	12	**23**
	44	**73**	**89**	**102**	**308**

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

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 these 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 2009 will only appear in MAAs of 2010-2015.

- 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 (2005-2008) 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. Maybe a bias in the data is because the pharmaceutical companies may prefer to conduct (part of) their pivotal trials in the key EU and North American markets.

Information on GCP inspections in relation to the centralised procedure and GCP inspections of bioequivalence trials (BE) recorded in EudraCT (up to December 2008) 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 EMEA 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/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:

[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 (Consolided version : 30/12/2008).
[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).

- 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 Signatures 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 EMEA Pre-Submission Procedural Advice[4]

The modules referred to are those of the Common Technical Dossier (Volume 2B[5] 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 where 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/EFTA[6] countries with the information split by:
  - EU-15/EEA: the member countries in the European Union prior to the accession of the ten candidate 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) (i.e. Croatia, Serbia etc.)

[4] Human Medicines - EMEA 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

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 2008 come from EU/EEA/EFTA (38%) and North America (35.4%). The regions Central/South America and Middle East/Asia/Pacific follow with a 9.8% and 7.8%, respectively. Smaller numbers were recruited in the CIS region (3.6%), Africa (3.1%), Australia-New Zealand (1.6%) and Eastern Europe-non EU (0.7%).

No patients per region	2005	%	2006	%	2007	%	2008	%	Total	%
EU/EEA/EFTA	**32,090**	**37.0**	**49,960**	**44.2**	**55,667**	**44.1**	**42,024**	**28.6**	**179,741**	**38.0**
Comprising:										
EU-15/EEA	27,822	32.1	30,714	27.2	42,894	34.0	27,561	18.7	128,991	27.3
EU-10	3,412	3.9	16,601	14.7	11,016	8.7	11,706	8.0	42,735	9.0
EU-2	656	0.8	2,146	1.9	1,251	1.0	2,447	1.7	6,500	1.4
Switzerland	200	0.2	499	0.4	506	0.4	310	0.2	1,515	0.3
North America	**37,117**	**42.8**	**33,389**	**29.6**	**41,810**	**33.2**	**55,165**	**37.5**	**167,481**	**35.4**
Comprising:										
Canada	3,477	4.0	3,919	3.5	6,231	4.9	4,454	3.0	18,081	3.8
USA	33,640	38.8	29,470	26.1	35,579	28.2	50,711	34.5	149,400	31.6
ROW	**17,585**	**20.3**	**29,637**	**26.2**	**28,628**	**22.7**	**49,948**	**33.9**	**125,798**	**26.6**
Comprising:										
Africa	523	0.6	1,938	1.7	2,061	1.6	9,962	6.8	14,484	3.1
Middle East/Asia/Pacific	1,694	2.0	9,925	8.8	7,801	6.2	17,458	11.9	36,878	7.8
Australia/New Zealand	1,560	1.8	1,892	1.7	2,663	2.1	1,219	0.8	7,334	1.6
CIS	664	0.8	6,939	6.1	2,731	2.2	6,677	4.5	17,011	3.6
Non-EU/Eastern Europe	69	0.1	862	0.8	1,202	1.0	1,370	0.9	3,503	0.7
Central/South America	13,075	15	8,081	7	12,170	10	13,262	9	46,588	9.8
Total	***86,792***	***100***	***112,986***	***100***	***126,105***	***100***	***147,137***	***100***	***473,020***	***100***

Table 2: Number of patients in pivotal trials submitted in MAAs to the EMEA 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.

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**.

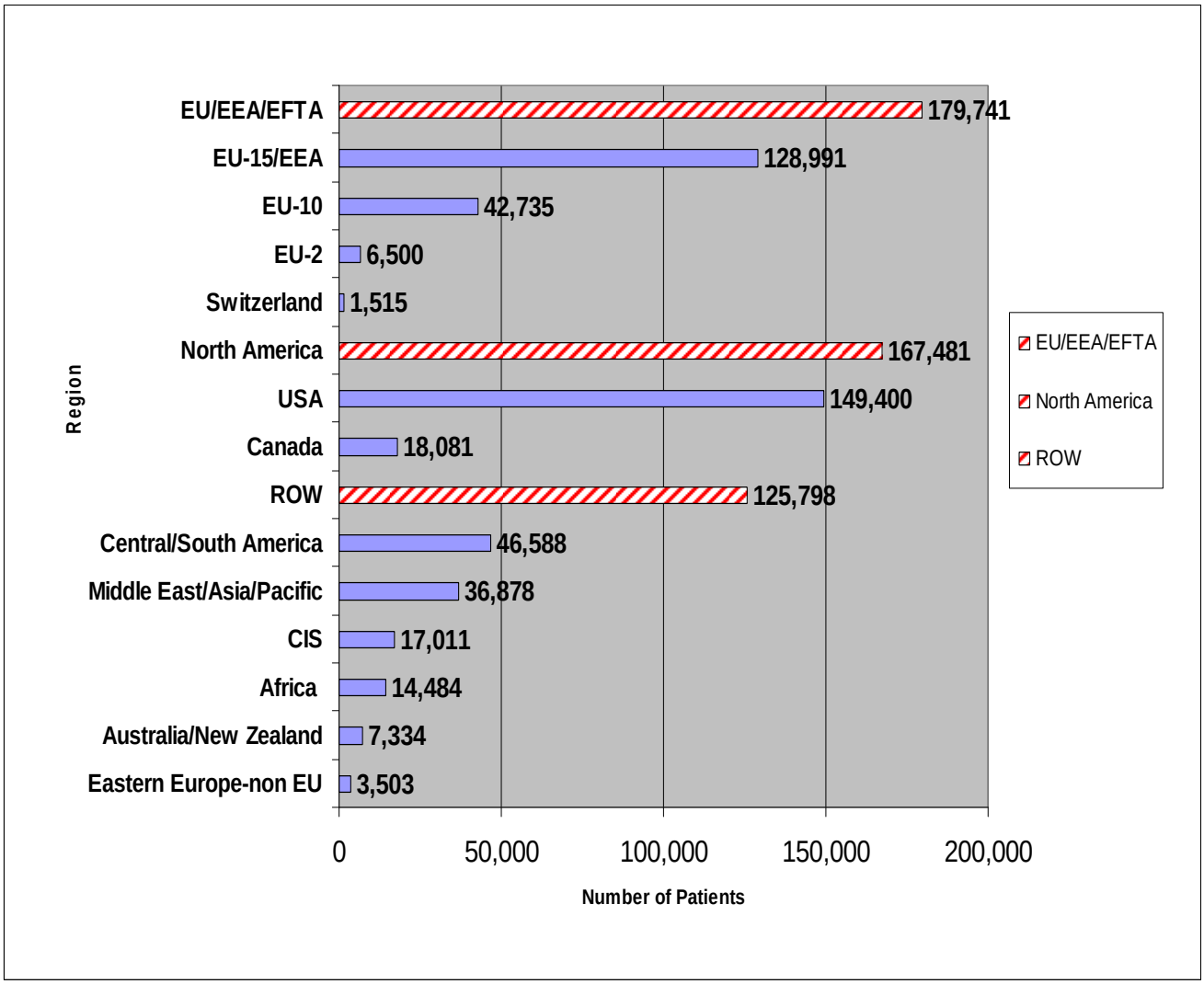

Figure 1: Number of patients in pivotal trials submitted in MAAs to the EMEA per region/sub-region during the period 2005-2008. The data are shown as three "global regions" – EU/EEA/EFTA, North America and ROW (Rest of the World) and then split into its component sub-regions.

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.

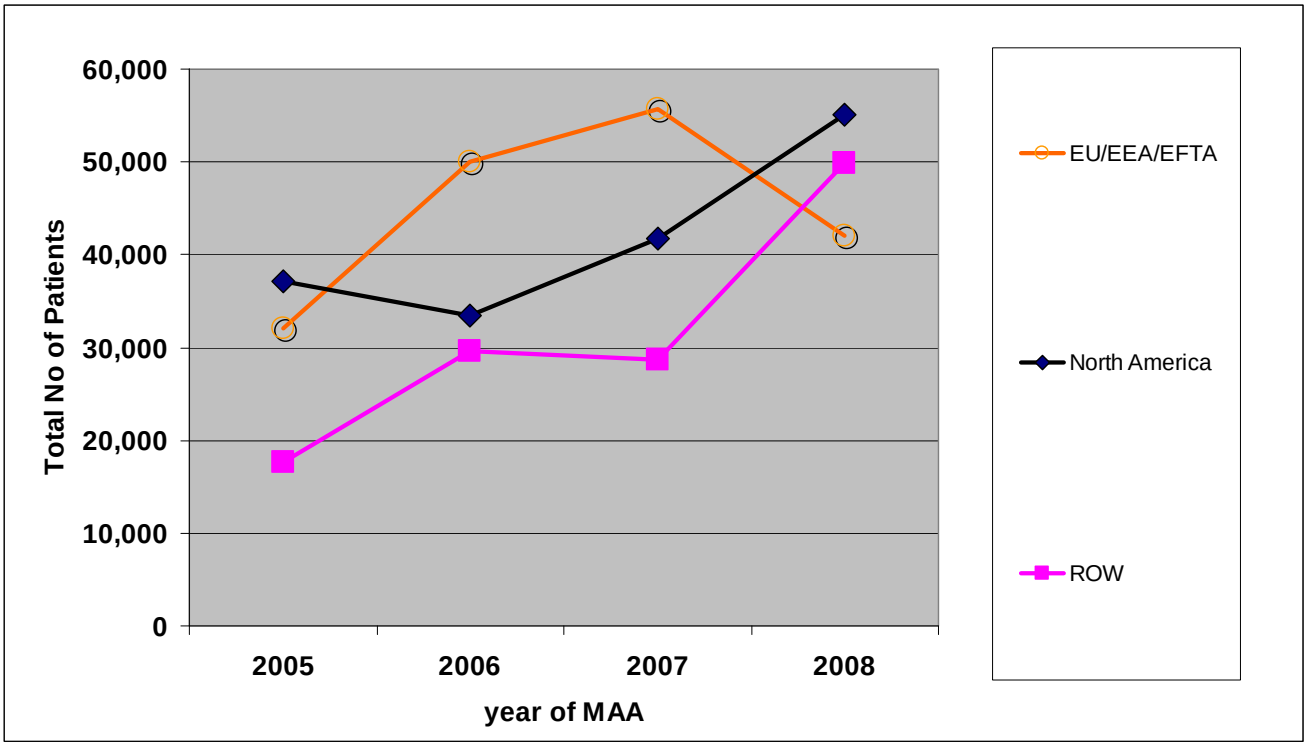

Figure 2: Number of patients in pivotal trials submitted in MAAs to the EMEA per region and year. The data are shown as three "global regions" – EU/EEA/EFTA, North America and ROW (Rest of the World).

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

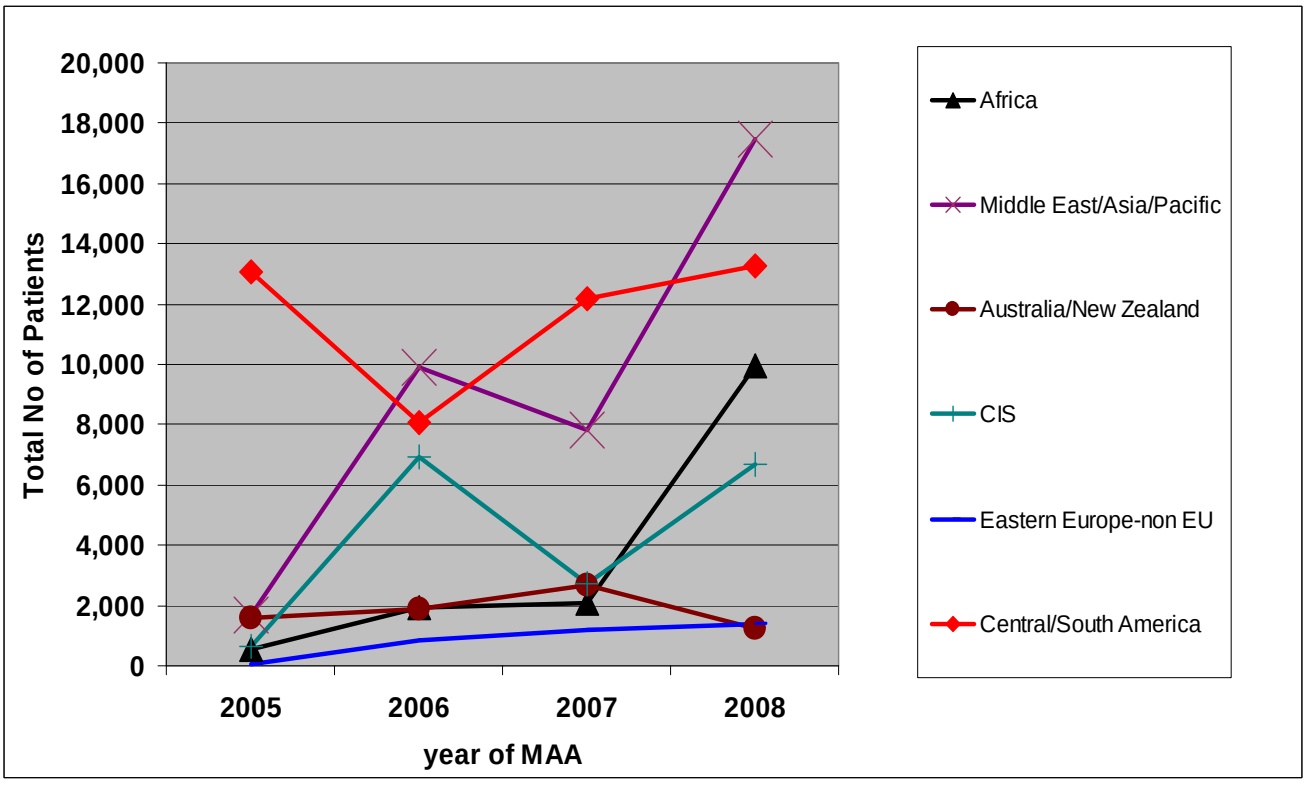

Figure 3: Number of patients in pivotal trials submitted in MAAs to the EMEA in the sub-regions of ROW region per year.

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 2007, where there is a decrease, 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.

Patients per region/year	2005	2006	2007	2008	Total
EU-15/EEA	27,822	30,714	42,894	27,561	12,8991
North America	37,117	33,389	41,810	55,165	167,481
ROW + EU-10+ EU-2	21,653	48,384	40,895	64,101	175,033

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.

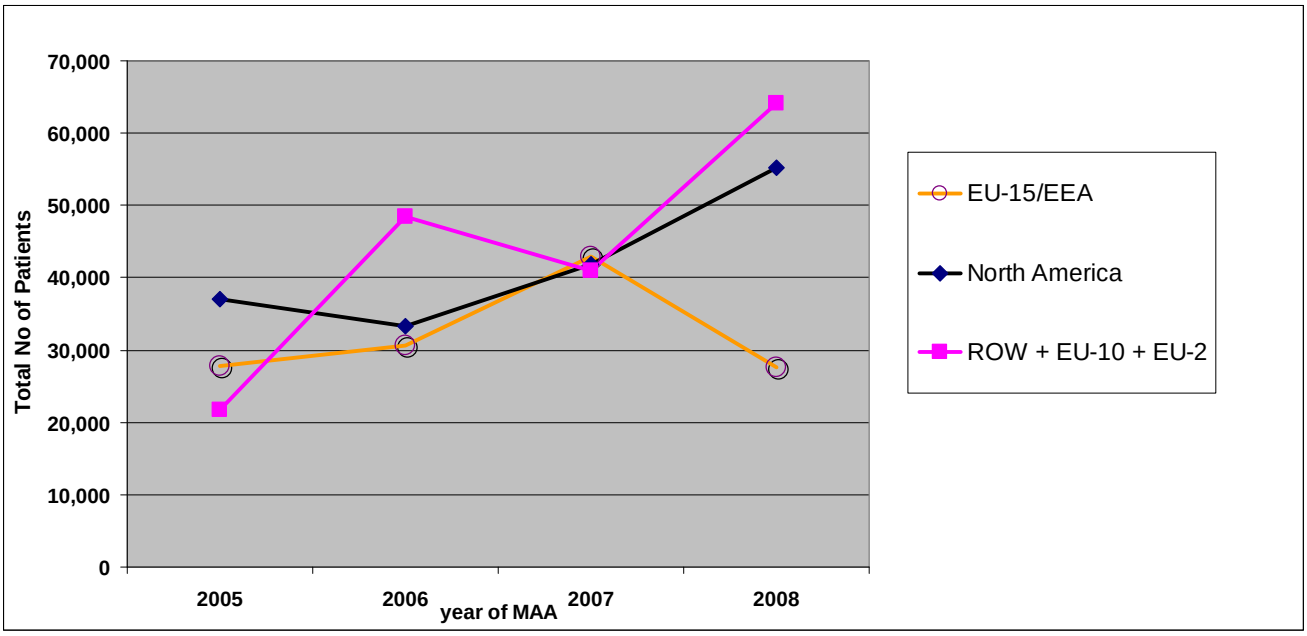

Figure 4: Patient numbers are presented from a pre-2004/2007 accession perspective per region and year, based on an assumption that many of the patients, particularly in the earlier years, may have been recruited prior to accession.

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 2005-2008 referring only to countries recruiting 0.5% or more of the total is:

- EU/EEA/EFTA: the major contributors are Germany (6.3%), Poland (4.4%) and France (3.6%). They are followed in order by Spain, UK, Italy, Belgium, Netherlands, Czech Republic, Finland, Hungary and Sweden contributing between 1.5 to 2.3% 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 (0.7%).

- North America: USA is the major contributor with 31.6% while Canada contributes 3.8%.

- Australia-New Zealand: this area provides 1.6%, mainly from Australia (1.3%).

- Central/South America: the major contributor is Brazil (2.8%) followed by Argentina (2.3%) and Mexico (1.4%).

- Middle East/Asia/Pacific: the major contributors are Israel and India (both 1.3%), Philippines (1.0%), China (0.8%) and Thailand (0.8%). They are followed in order by Taiwan, South Korea, Japan, Hong Kong and Malaysia contributing between 0.6 and 0.3%.

- Africa: South-Africa is the major contributor with 2.9% of the patients.

The total number of patients in MAA submitted to the EMEA during the 2005-2008 period in those third countries contributing with at least 0.5% of the patients is shown in **Figure 5.**

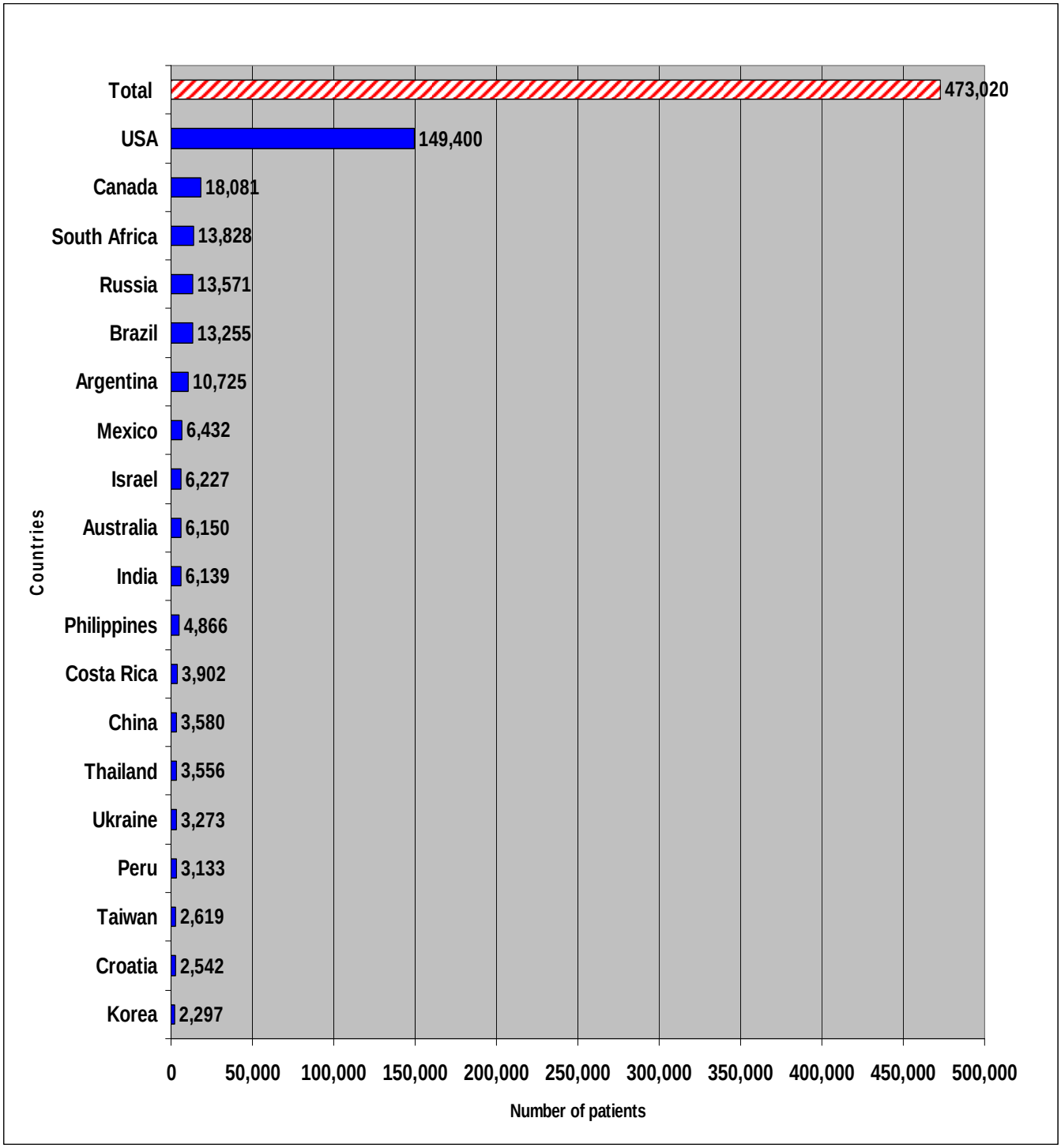

Figure 5: Third countries with at least 0.5% of patients in the pivotal trials included in the MAA submitted to the EMEA during the 2005-2008 period

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 (45.4 %) and EU/EEA/EFTA (36.1 %), followed by Central/South America and Middle East/Asia/Pacific (5.8 and 5.2 %, respectively) and smaller numbers in the rest of the ROW region.

No sites per region/year	**2005**	**%**	**2006**	**%**	**2007**	**%**	**2008**	**%**	**Total**	**%**
EU/EEA/EFTA	**1,974**	**35.2**	**3,567**	**37.7**	**3,441**	**37.0**	**3,373**	**34.2**	**12,355**	**36.1**
Comprising:										
EU-15/EEA	1,676	29.9	2,759	29.1	2,648	28.5	2,431	24.6	9,514	27.8
EU-10	224	4.0	638	6.7	639	6.9	734	7.4	2,235	6.5
EU-2	52	0.9	126	1.3	110	1.2	177	1.8	465	1.4
Switzerland	22	0.4	44	0.5	44	0.5	31	0.3	141	0.4
North America	**3,042**	**54.3**	**4,168**	**44.0**	**4,150**	**44.7**	**4,182**	**42.3**	**15,542**	**45.4**
Comprising:										
Canada	282	5.0	392	4.1	361	3.9	398	4.0	1,433	4.2
USA	2,760	49.2	3,776	39.9	3,789	40.8	3,784	38.3	14,109	41.2
ROW	**589**	**10.5**	**1,737**	**18.3**	**1,699**	**18.3**	**2,320**	**23.5**	**6,345**	**18.5**
Comprising:										
Africa	59	1.1	140	1.5	141	1.5	216	2.2	556	1.6
Middle East/Asia/Pacific	119	2.1	551	5.8	417	4.5	682	6.9	1,769	5.2
Australia/New Zealand	118	2.1	229	2.4	220	2.4	175	1.8	742	2.2
CIS	72	1.3	320	3.4	226	2.4	498	5.0	1,116	3.3
Eastern Europe-non EU	8	0.1	29	0.3	51	0.5	73	0.7	161	0.5
Central/South America	213	3.8	468	4.9	644	6.9	676	6.8	2,001	5.8
Total	***5,605***	***100***	***9,472***	***100***	***9,290***	***100***	***9,875***	***100***	***34,242***	***100***

Table 4: The number of investigator sites involved in pivotal clinical trials submitted in MAAs to the EMEA 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.

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.**

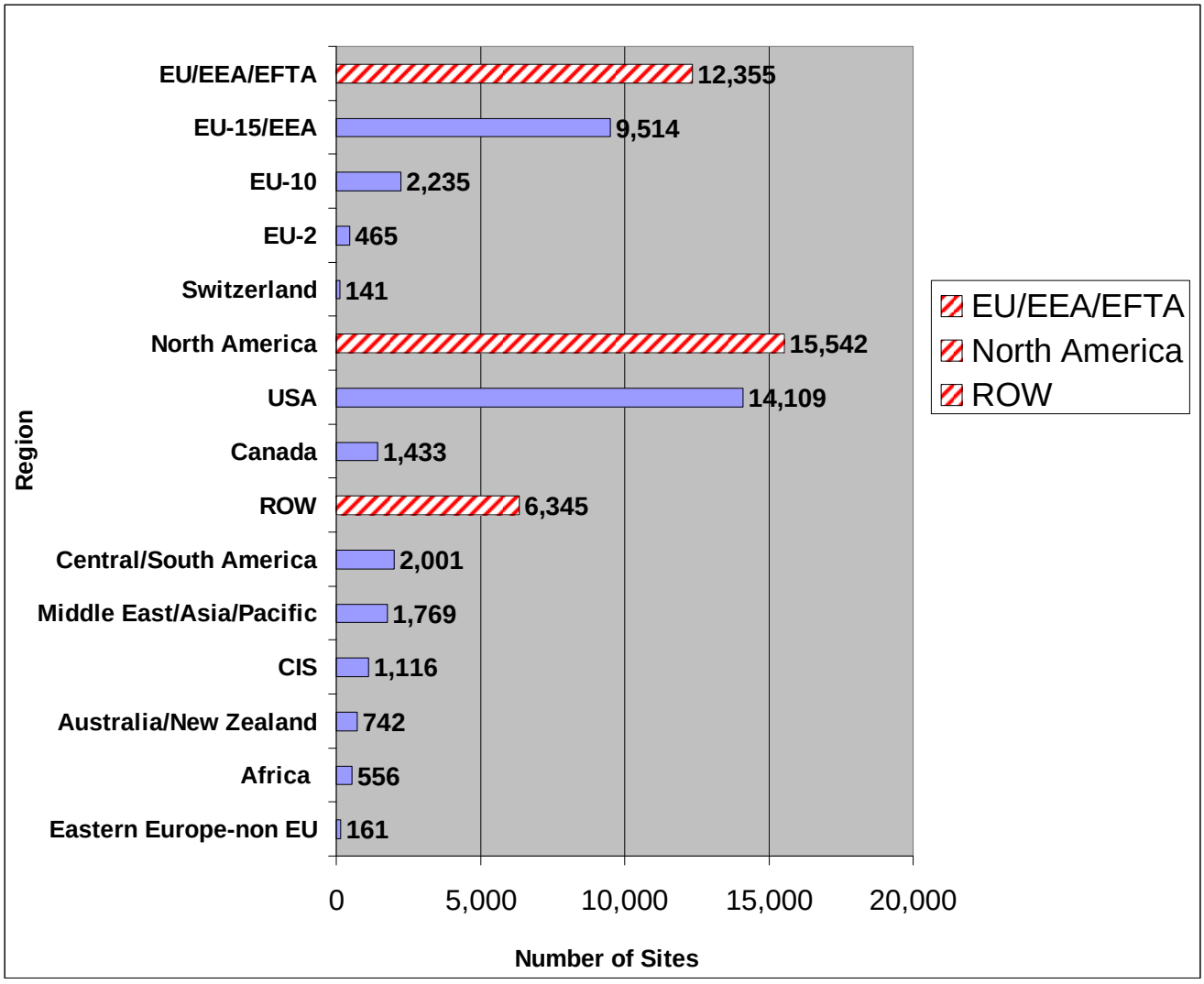

Figure 6: Number of investigator sites in pivotal trials submitted in MAAs to the EMEA per region during the period 2005-2008. The data are shown as three "global regions" – EU/EEA/EFTA, North America and ROW (Rest of the World) and then split into its component sub-regions.

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; however the number of sites is higher than in Europe over all years as opposed to the number of patients (Figure 2), who are less except in 2005 and 2008. The trend of these two regions shows an increase up to 2006 but remaining more or less stable afterwards and being different to that observed for the number of patients (Figure 2). However in the rest of the world region (ROW) the trend is similar to the trend observed for the number of patients i.e. an increase up to 2006 then the situation remains stable during 2007 followed by again another increase in 2008, but in this last case less significant than for the number of patients (Figure 2), which indicates a higher number of patients per site.

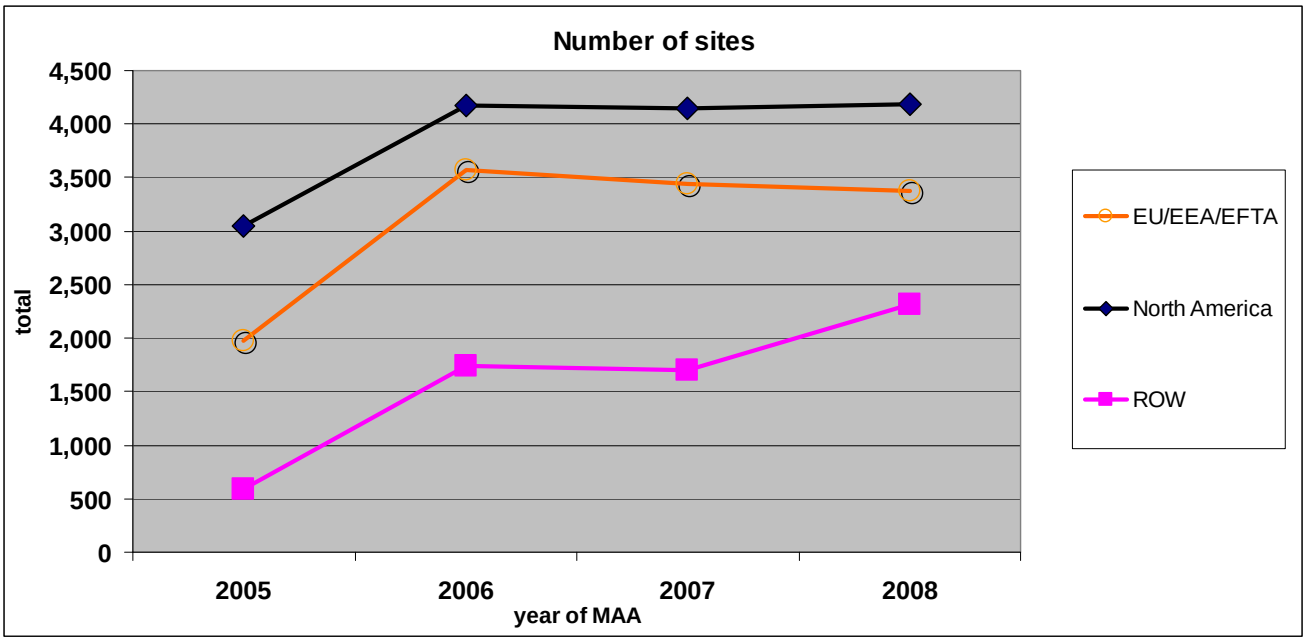

Figure 7: The number of investigator sites involved in pivotal clinical trials submitted in MAAs to the EMEA per region and year. The data are shown as three "global regions" – EU/EEA/EFTA, North America and ROW (Rest of the World).

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 with an increase of number of sites but with a decrease in the number of patients with respect to the previous year. In Africa there is an increase in 2008 for both patients and sites.

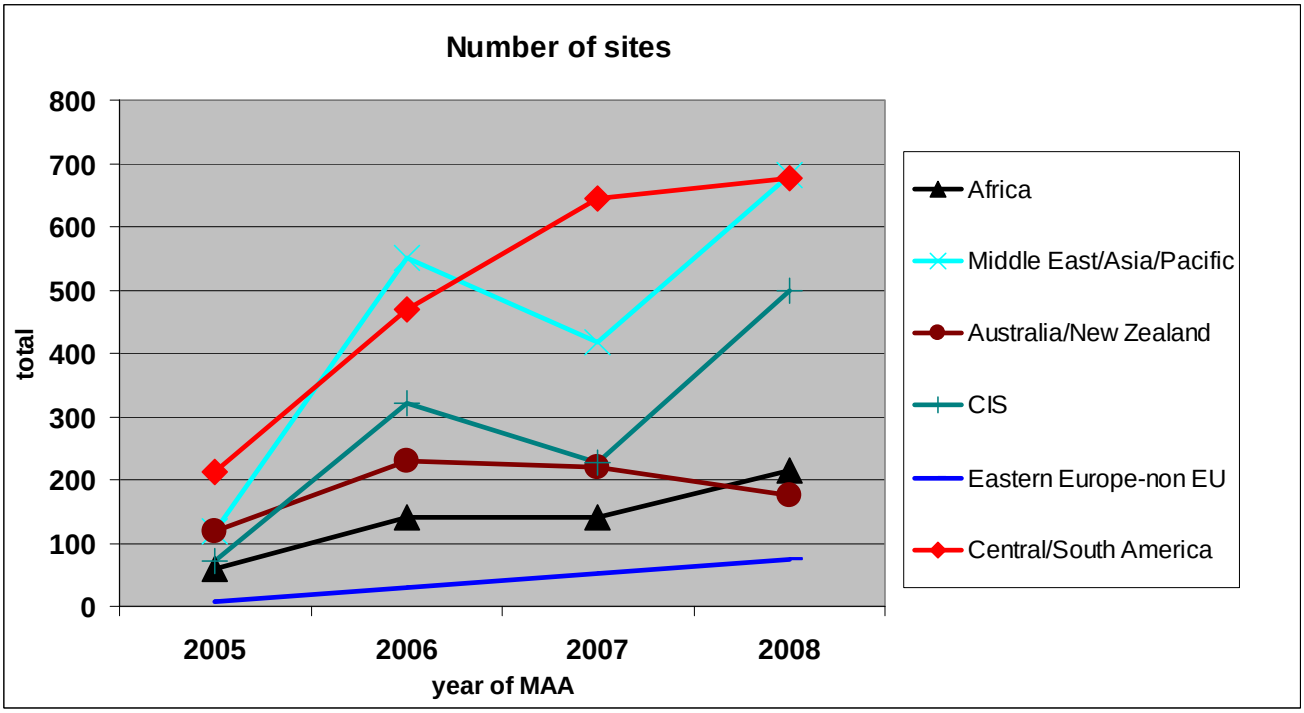

Figure 8: The number of investigator sites involved in pivotal clinical trials submitted in MAAs to the EMEA in the sub-regions of ROW region per year.

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.

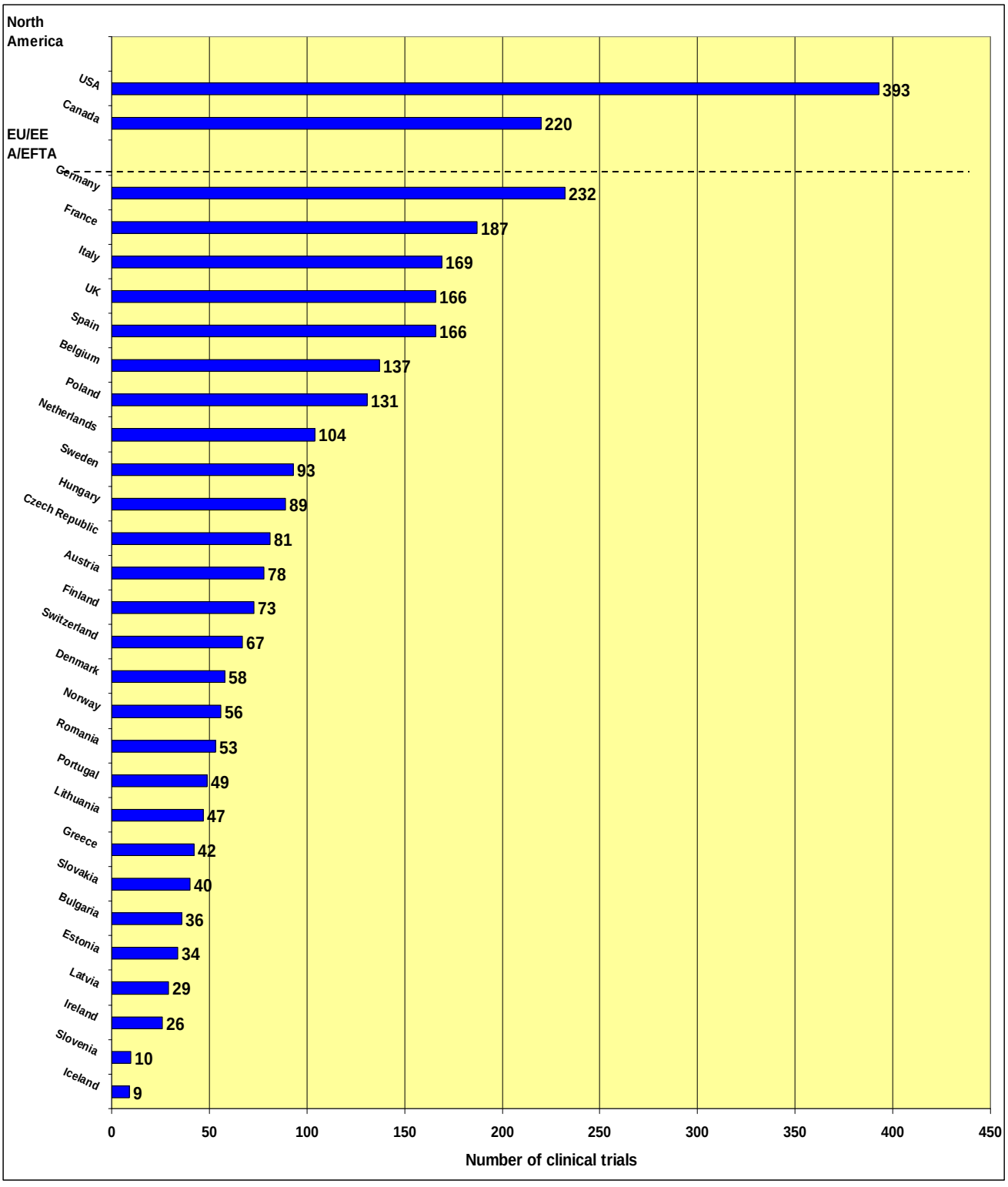

Figure 9: The number of pivotal clinical trials in MAA submitted to the EMEA in each country of the North America and EU/EEA/EFTA region in the 2005-2008 period.

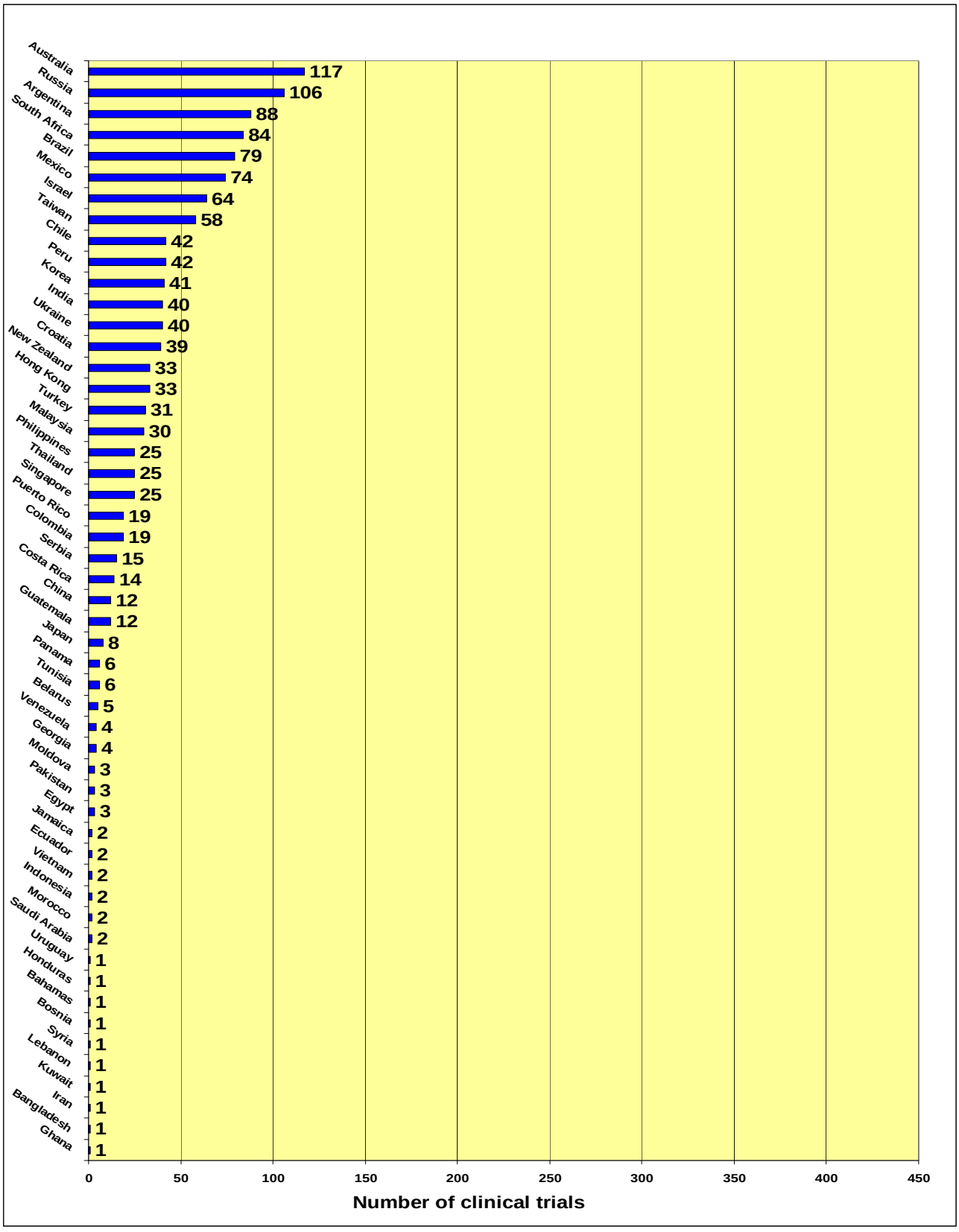

Figure 10: The number of pivotal clinical trials in MAA submitted to the EMEA in each country of the ROW region in the 2005-2008 period.

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

- North America: USA and Canada
- EU/EEA/EFTA: Germany, France, Italy, UK, Spain, Belgium, Poland and Netherlands
- ROW: Australia 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 2005-2008 is higher than in the other regions. The average per region is shown in **Figure 12** with around 20 patients per site with respect to 15 and 10 patients per site in the EU/EEA/EFTA and North America regions, respectively.

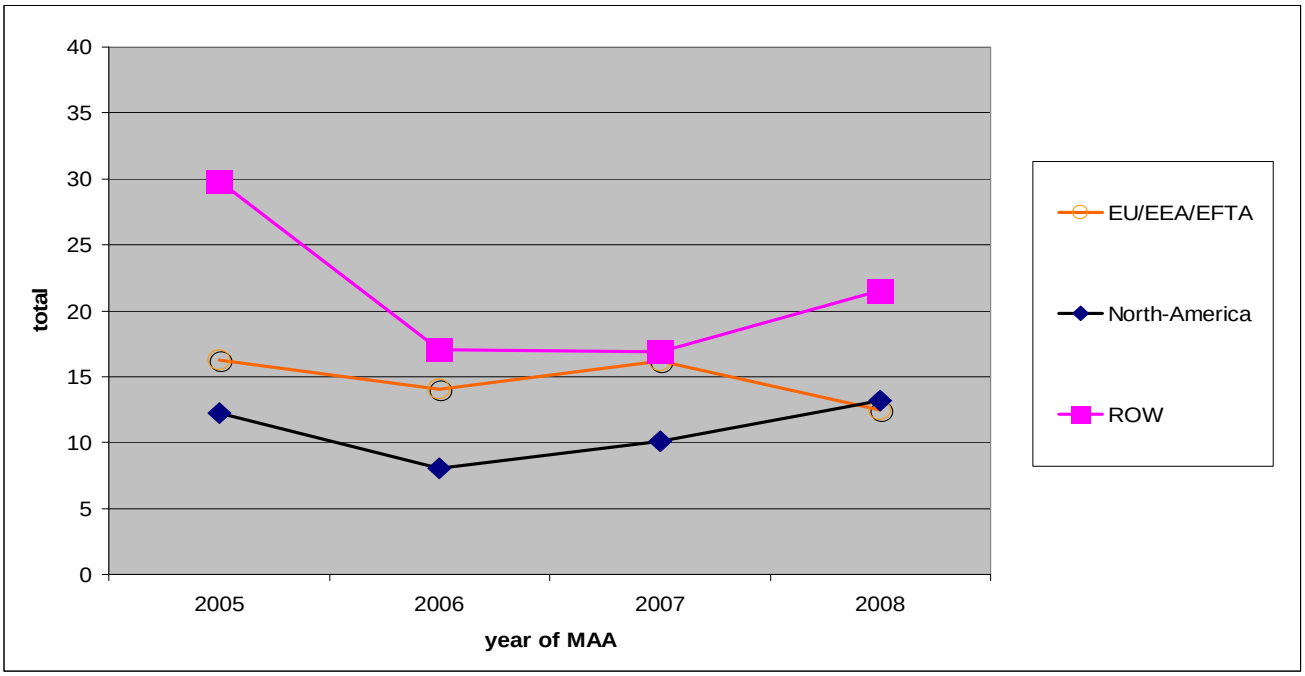

Figure 11: Average number of patients per site in pivotal trials submitted in MAAs to the EMEA per region and year. The data are shown as three "global regions" – EU/EEA/EFTA, North America and ROW (Rest of the World).

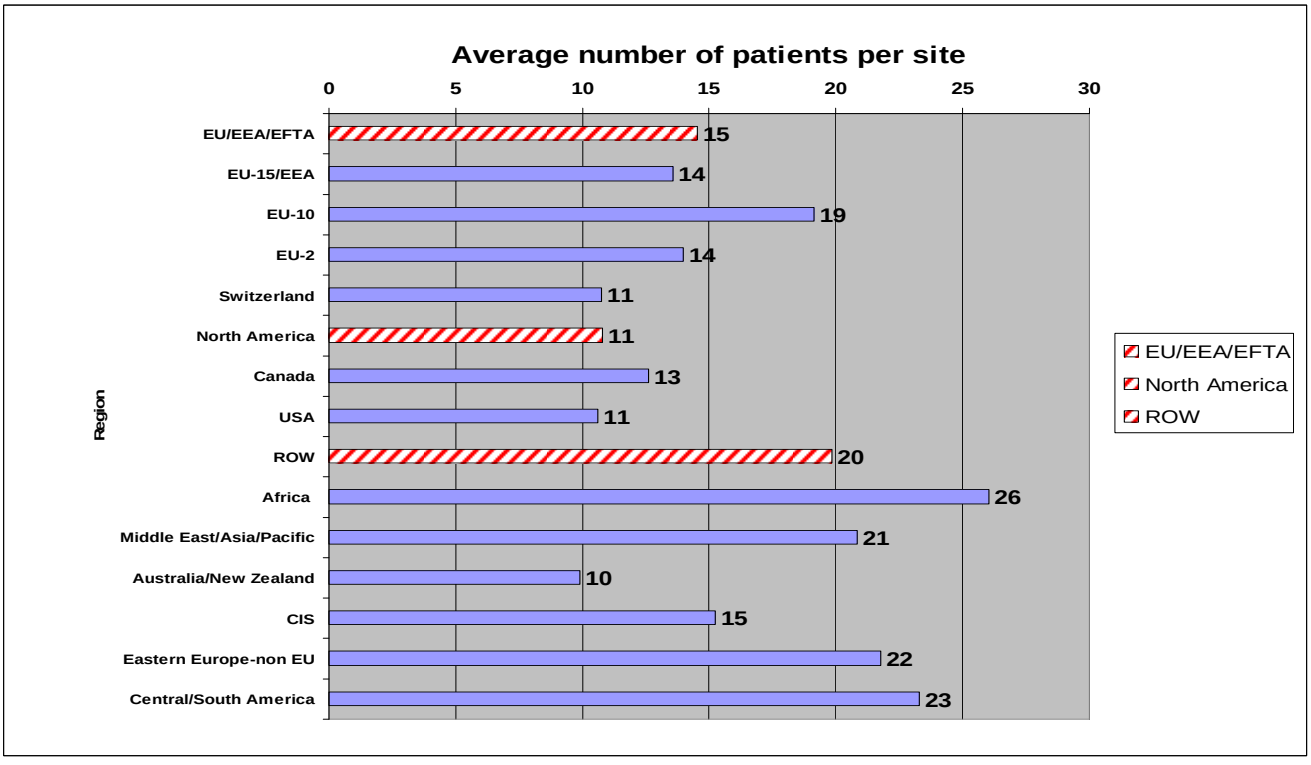

Figure 12: Average number of patients per trial site(s) in pivotal trials submitted in MAAs to the EMEA per region during the period 2005-2008. The data are shown as three "global regions" –

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 to make these statistics it has been considered only those countries with 9 or more clinical trials (9 is the minimum number of clinical trials in the EU/EEA/EFTA region i.e. Iceland- see Figure 9 in page 14).

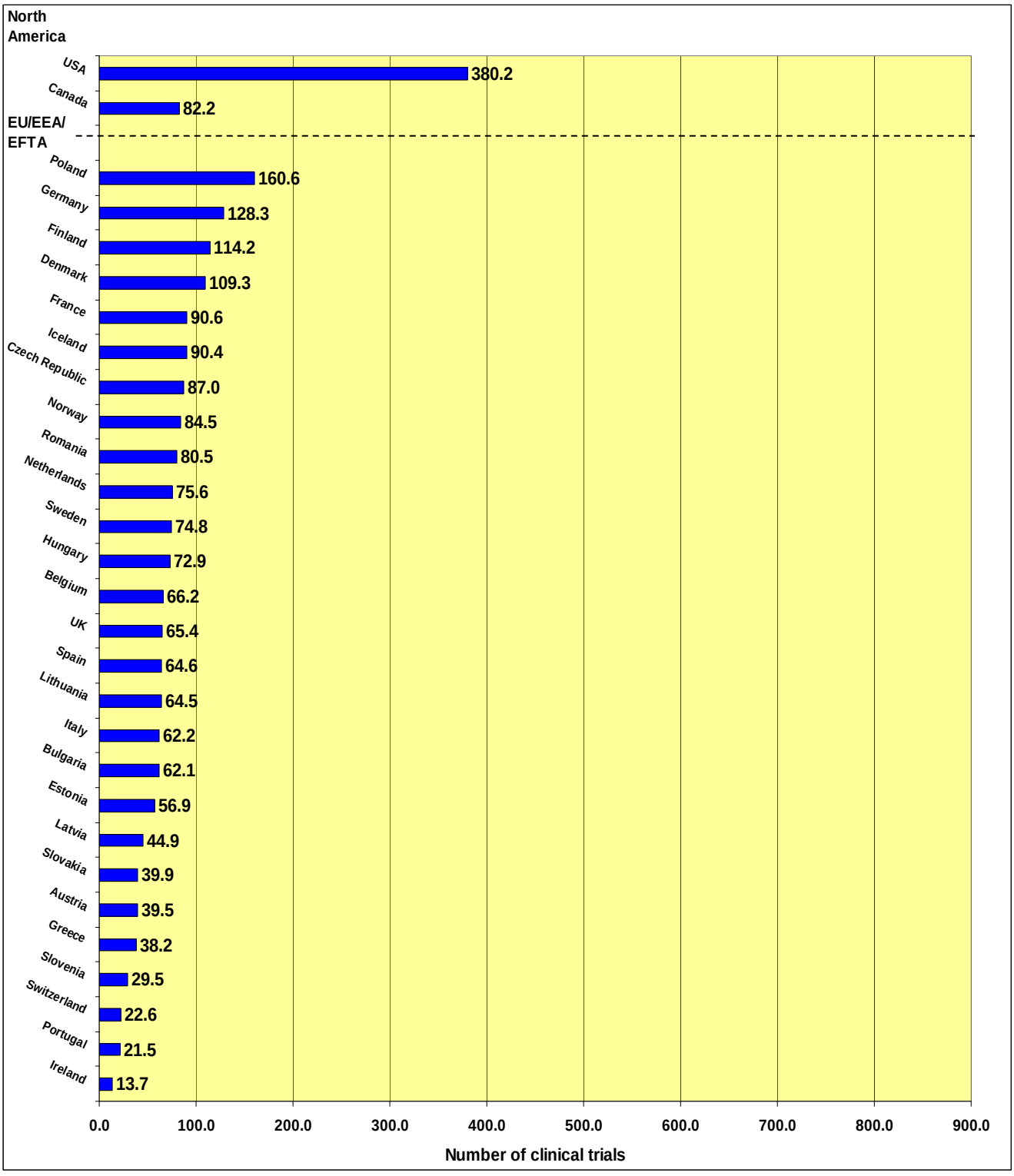

Figure 13: The average number of patients recruited per pivotal clinical trial per country in MAA submitted to the EMEA in each country of the North America and EU/EEA/EFTA region in the 2005-2008 period.

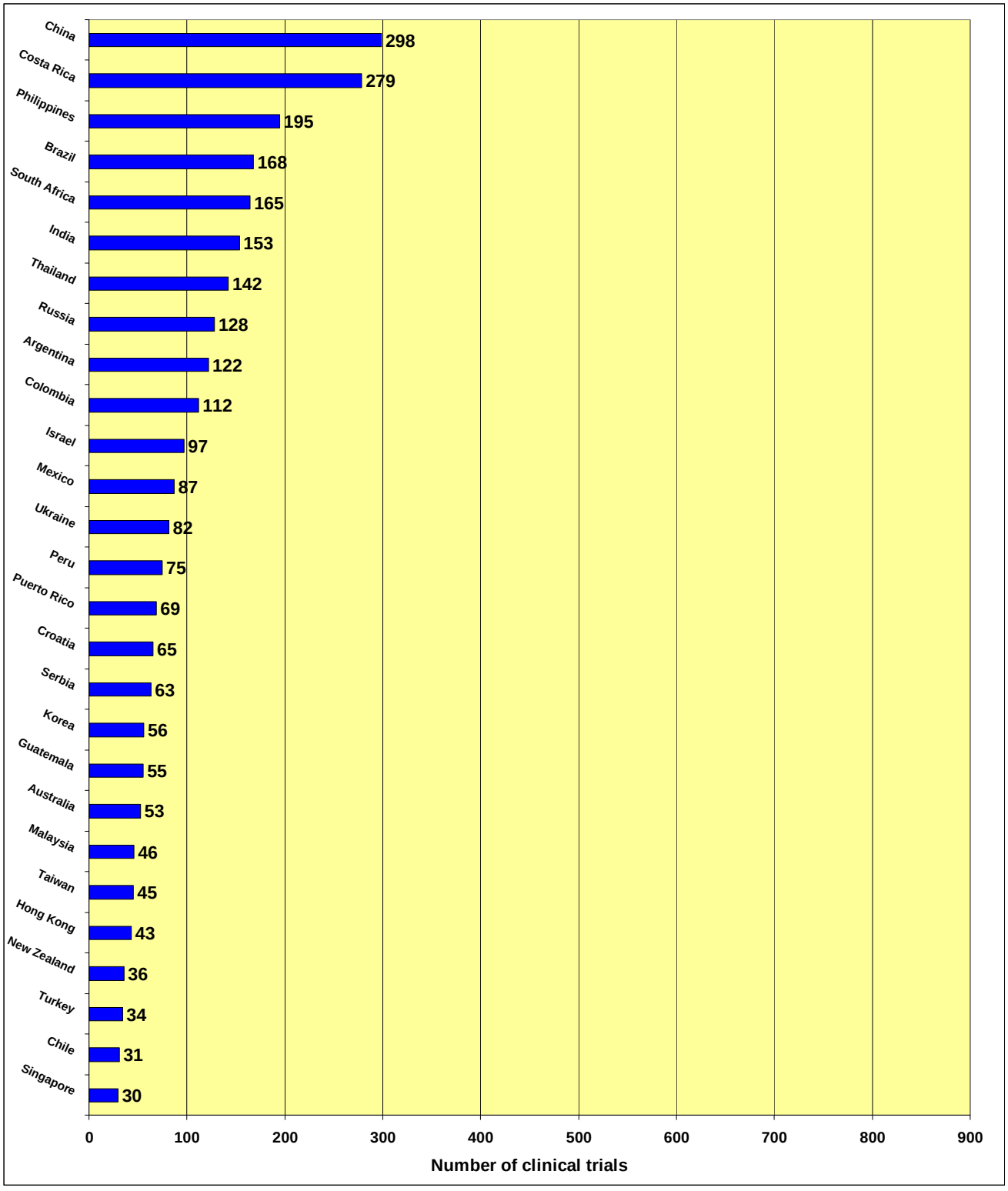

Figure 14: The average number of patients recruited per pivotal clinical trial per country in MAA submitted to the EMEA in each country of the ROW region (excluding those countries with less than 9 sites) in the 2005-2008 period.

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 2008 can be found in **appendix 3**. It should be noted that these numbers refer to inspections performed by the EU inspectors. 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 300 MAAs submitted since 2005. GCP inspections have taken place at 189 sites (out of 34,242 investigators 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 189 sites inspected 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 the subject of a GCP inspection. Data on pivotal trials from 99 MAAs in 2007 are presented in this report of which 15 were subject to GCP inspection at the time of the MAA. For 2008 data from 102 MAAs are presented of which 22 were subject to GCP inspection at the time of the MAA. The numbers of inspections are, ultimately, limited by the available resource 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 resource. 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 onsite due to translation issues etc.

Some of the trials, sites or sponsors will 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.

GCP INSPECTIONS PER REGION/YEAR	1997	2000	2001	2002	2003	2004	2005	2006	2007	2008	total	
											tot	%
Total	**3**	**17**	**22**	**17**	**3**	**14**	**10**	**15**	**38**	**50**	**189**	**100.0**
EU/EEA/EFTA	3	1	21	10	0	9	7	8	21	21	101	**53.4**
North America	0	16	1	4	2	0	2	3	9	10	47	**24.9**
ROW	0	0	0	3	1	5	1	**4**	**8**	**19**	41	**21.7**

Table 5: GCP Inspections per year and by region conducted at the request of CHMP.

The total of inspections in EU/EEA/EFTA is 101 (53.4%) against 47 (24.9%) in North America and 41 (21.7%) 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 2007 and 2008 (8 and 19, respectively). An overview of these results can be found in **Figure 15**.

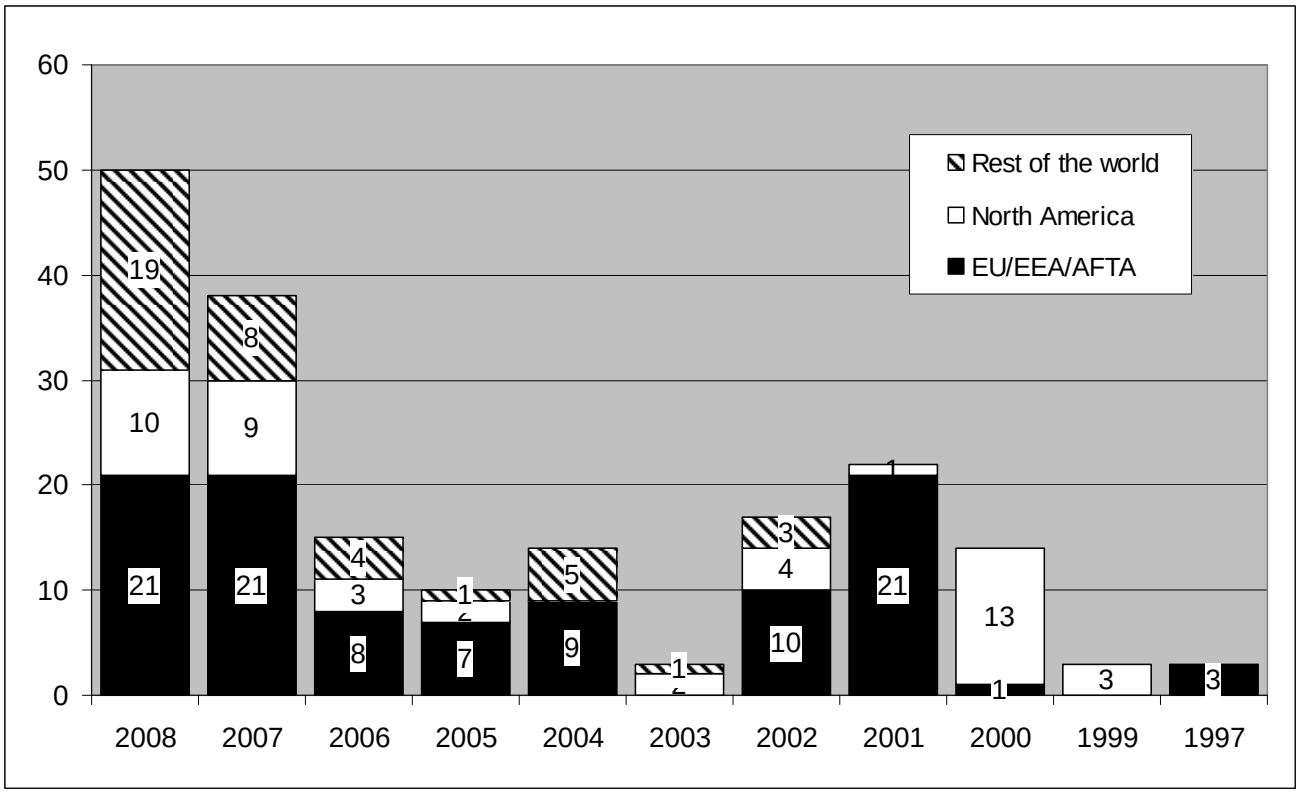

Figure 15: GCP Inspections per year and by region conducted at the request of the CHMP.

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%).

Number of third country inspections	total	%
Eastern-Europe-non EU	**2**	**1.1**
Croatia	*1*	*0.5*
Serbia	*1*	*0.5*
CIS	**10**	**5.3**
Russia	*8*	***4.2***
Ukraine	*2*	*1.1*
North America	**47**	**24.9**
Canada	*10*	***5.3***
USA	*37*	***19.6***
Central/South America	**7**	**3.7**
Argentina	*1*	*0.5*
Brazil	*1*	*0.5*
Chile	*1*	*0.5*
Colombia	*1*	*0.5*
Costa Rica	*1*	*0.5*
Mexico	*1*	*0.5*
Peru	*1*	*0.5*
Middle East/Asia/Pacific	**18**	**9.5**
China	*4*	***2.1***
India	*8*	***4.2***
Malaysia	*1*	*0.5*
Philippines	*2*	*1.1*
Thailand	*1*	*0.5*
Turkey	*2*	*1.1*
Africa	**4**	**2.1**
Ghana	*1*	*0.5*
Morocco	*1*	*0.5*
South Africa	*2*	***1.1***
Total	**88**	**46.3**

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

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 21.7% of inspections carried out is split between routine inspections (15.9%) and of triggered (5.8%).

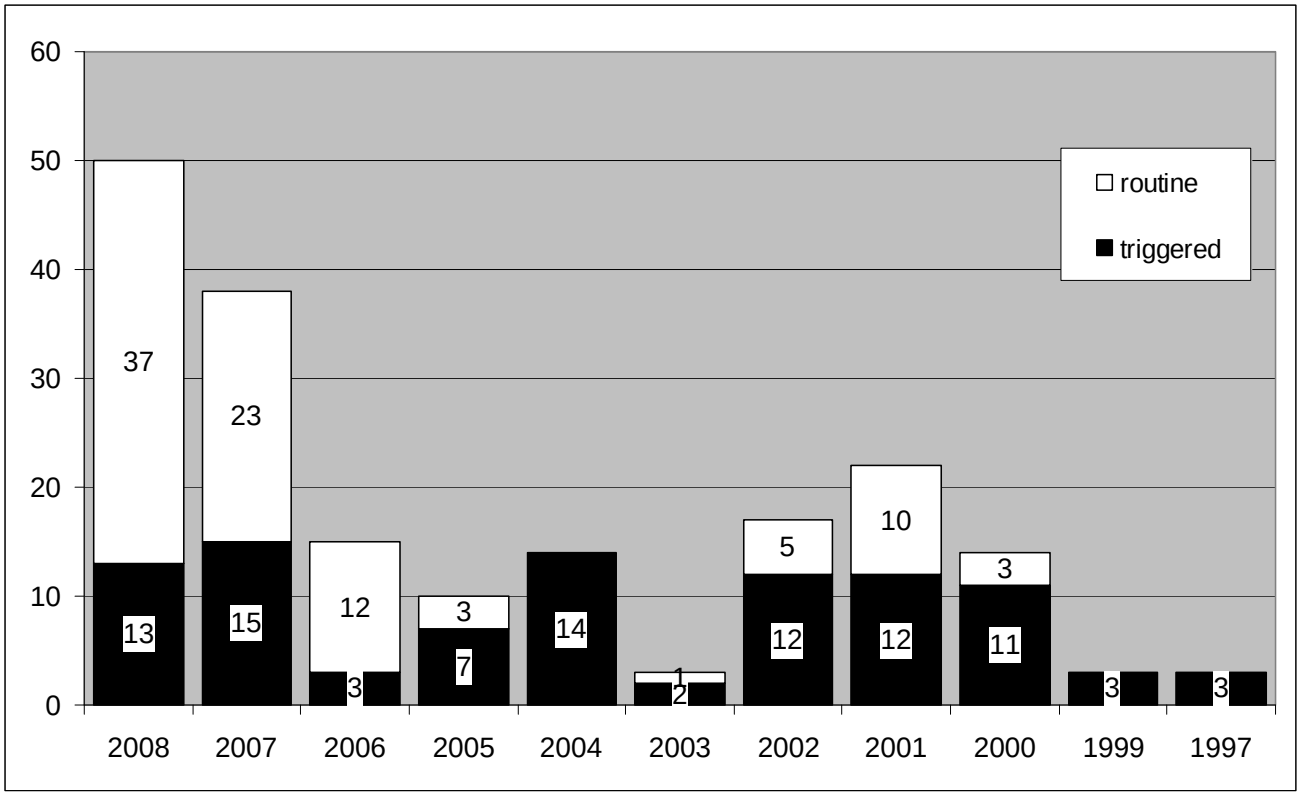

Figure 16: GCP Inspections requested by the CHMP per year and type of inspection (routine/triggered).

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 EMEA (Figure 5) with the exception of Israel, Australia, South Korea and Taiwan. Sites from these countries will be subject to inspections in 2009 where possible.

3.3.2 Inspections recorded in EudraCT (up to December 2008) 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 2008) 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 total trial inspections (2 - 6 %), while in Asia, North America and Eastern Europe this was about half of the trial inspections (60.6, 46.3 and 37.5 % 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 EMEA 2009 Road Map and cooperation with the Member States.

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)	21	2.2	957
EU-10 + EU-2	7	6.0	117
North America	19	46.3	41
CIS and Eastern Europe	3	37.5	8
Asia	20	60.6	33
Africa	0	0.0	4
South America	0	0.0	3
totals	70	6.0	1,163
top 5 countries where BE trial inspections have been carried out:			
India	20	66.7	30
Canada	18	62.1	29
Italy	6	4.1	145
Germany	5	3.4	149
Czech Republic	3	42.9	7

Table 7: list of inspections, retrieved from EudraCT, highlighting inspections carried out on bioequivalence (BE) trials

4. CONCLUSIONS

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

- 62% of the patients in pivotal trials submitted in MAA to the EMEA during the observation period from January 2005 to December 2008 were from third countries, and comprising 26.6% from the ROW region (Africa, Middle East/Asia/Pacific, Australia/New Zealand, Central/South America, CIS, Eastern Europe-non EU), and 35.4% from North America.
- 7.8% of patients in pivotal trials submitted in MAA to the EMEA during the observational period from January 2005 to December 2008 were included in trials in Middle East/Asia/Pacific.
- 9.8% of patients in pivotal trials submitted in MAA to the EMEA during the observational period from January 2005 to December 2008 were included in trials in Central/South America.
- 10.7% 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 (19.2% of patients), should be highlighted in terms of numbers patients included in pivotal trials submitted in MAA to the EMEA during the observational period January 2005 to December 2008:
    - Africa: South Africa (2.9%)
    - Middle East/Asia/Pacific: Israel (1.3%), India (1.3%), Philippines (1%), China (0.8%) and Thailand (0.8%)
    - Australia/New Zealand: Australia (1.3%)
    - Central/South America: Brazil (2.8%), Argentina (2.3%), Mexico (1.4%) and Costa Rica (0.8%)
    - CIS: Russia (2.9%) and Ukraine (0.7%)
    - Eastern Europe-non EU): Croatia (0.5%)

- The overall trend in terms of numbers of patients or sites is for an increase, but the observation period is short.

- Those countries with more than 100 pivotal clinical trials included in MAAs to the EMEA, during the whole period are:

    - North America: USA and Canada
    - EU/EEA/EFTA: Germany, France, Italy, UK, Spain, Belgium, Poland and Netherlands
    - ROW: Australia and Russia

- The average number of patients per site in the ROW (20) area over the whole period 2005-2008 is higher than in the other regions (15 and 10 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 2005-2008. If we consider a cut off point of 125 patients per trial the most relevant countries are USA (380.2), Poland (160.6), Germany (128.3), China, Costa Rica, Philippines, Brazil, South Africa, India, Thailand and Russia.

- There is an increase of GCP inspections in third counties 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 sites inspected are USA (19.6%) followed by Canada (5.3%), India (4.2%), Russia (4.2%) and China (2.1%). Further increase in inspections will require additional GCP inspection resource from the member states.

- Around 50% (26 out of 51) of the countries in the ROW region have more than 60 patients (the average in the EU/EEA/EFTA region) enrolled per clinical trial.

- The BE studies inspected were in Canada, India and South Africa based on information recorded in EudraCT. Germany and Czech Republic were the countries in the EU with most inspection of BE trial sites. This is also reflected in the generic applications submitted to the EMEA.

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 EMEA FROM 2005 TO 2008

	2005			2006			2007			2008			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
EU/EEA/EFTA	***345***	***1,974***	***32,090***	***668***	***3,567***	***49,960***	***648***	***3,441***	***55,667***	***601***	***3,373***	***42,024***	***2,262***	***12,355***	***179,741***
EU-15/EEA	*269*	*1,676*	*27,822*	*496*	*2,759*	*30,714*	*467*	*2,648*	*42,894*	*413*	*2,431*	*27,561*	*1,645*	*9,514*	*128,991*
Austria	10	18	233	24	48	482	23	79	1,389	21	64	978	78	209	3,082
Belgium	28	145	2,526	31	82	1,136	41	158	2,956	37	158	2,453	137	543	9,071
Denmark	10	67	2,854	13	50	788	17	70	1,996	18	66	702	58	253	6,340
Finland	12	53	2,564	18	62	783	21	80	1,595	22	113	3,395	73	308	8,337
France	31	282	2,330	57	371	3,876	59	578	8,818	40	289	1,918	187	1,520	16,942
Germany	36	436	7,095	76	838	9,161	63	482	7,835	57	521	5,664	232	2,277	29,755
Greece	6	23	146	16	50	776	7	27	253	13	46	428	42	146	1,603
Iceland	3	3	740	1	1	6	2	2	6	3	3	62	9	9	814
Ireland	4	11	60	10	29	79	5	21	134	7	16	84	26	77	357
Italy	30	146	1,002	54	274	3,069	46	253	3,093	39	308	3,352	169	981	10,516
Liechtenstein													0	0	0
Luxembourg													0	0	0
Netherlands	16	75	729	31	146	2,938	30	123	2,945	27	126	1,247	104	470	7,859
Norway	7	52	2,193	18	58	730	17	70	986	14	52	822	56	232	4,731
Portugal	10	33	166	12	30	235	17	64	466	10	42	187	49	169	1,054
Spain	25	118	849	54	293	2,879	46	269	4,648	41	250	2,343	166	930	10,719
Sweden	14	71	2,156	30	153	1,729	31	137	2,079	18	91	995	93	452	6,959
UK	27	143	2,179	51	274	2,047	42	235	3,695	46	286	2,931	166	938	10,852
EU-10	*55*	*224*	*3,412*	*131*	*638*	*16,601*	*141*	*639*	*11,016*	*134*	*734*	*11,706*	*461*	*2,235*	*42,735*
Cyprus													0	0	0
Czech Republic	10	42	869	18	79	2,565	21	85	1,368	32	174	2,243	81	380	7,045
Estonia	3	6	98	13	38	537	10	23	712	8	17	588	34	84	1,935
Hungary	13	66	813	22	108	2,131	33	121	1,817	21	104	1,724	89	399	6,485
Latvia	4	13	175	10	38	505	7	26	402	8	22	220	29	99	1,302

	2005			2006			2007			2008			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
Lithuania	3	5	84	13	59	841	19	53	1,364	12	48	744	47	165	3,033
Malta													0	0	0
Poland	15	79	1,299	36	250	8,953	41	305	5,088	39	321	5,705	131	955	21,045
Slovakia	6	11	37	14	50	846	8	24	245	12	45	467	40	130	1,595
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*	*89*	*465*	*6,500*
Bulgaria	5	23	332	6	44	759	9	43	512	16	65	633	36	175	2,236
Romania	6	29	324	10	82	1,387	14	67	739	23	112	1,814	53	290	4,264
Switzerland	*10*	*22*	*200*	*25*	*44*	*499*	*17*	*44*	*506*	*15*	*31*	*310*	*67*	*141*	*1,515*
Switzerland	10	22	200	25	44	499	17	44	506	15	31	310	67	141	1,515
North America	***104***	***3,042***	***37,117***	***175***	***4,168***	***33,389***	***171***	***4,150***	***41,810***	***163***	***4,182***	***55,165***	***613***	***15,542***	***167,481***
Canada	31	282	3,477	65	392	3,919	57	361	6,231	67	398	4,454	220	1,433	18,081
USA	73	2,760	33,640	110	3,776	29,470	114	3,789	35,579	96	3,784	50,711	393	14,109	149,400
ROW	***155***	***589***	***17,585***	***352***	***1,737***	***29,637***	***353***	***1,699***	***28,628***	***411***	***2,320***	***49,948***	***1,271***	***6,345***	***125,798***
Africa	*13*	*59*	*523*	*25*	*140*	*1,938*	*29*	*141*	*2,061*	*29*	*216*	*9,962*	*96*	*556*	*14,484*
Egypt	1	1	5	1	2	22				1	1	108	3	4	135
South Africa	11	55	427	22	133	1,894	27	138	1,761	24	205	9,746	84	531	13,828
Tunisia	1	3	91	2	5	22				3	7	88	6	15	201
Ghana							1	1	280				1	1	280
Morocco							1	2	20	1	3	20	2	5	40
Middle East/ Asia/Pacific	*38*	*119*	*1,694*	*121*	*551*	*9,925*	*94*	*417*	*7,801*	*153*	*682*	*17,458*	*406*	*1,769*	*36,878*
Bangladesh										1	1	150	1	1	150
China				3	77	2,214	4	33	611	5	25	755	12	135	3,580
Hong Kong	3	3	155	10	20	235	6	12	150	14	31	889	33	66	1,429
India	1	10	86	13	108	3,121	4	41	222	22	136	2,710	40	295	6,139
Indonesia							1	2	12	1	2	13	2	4	25
Iran	1	1	3										1	1	3
Israel	6	18	187	21	74	597	22	102	1,878	15	167	3,565	64	361	6,227

	2005			2006			2007			2008			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
Japan	1	25	217	2	35	680	2	50	563	3	34	462	8	144	1,922
Korea	1	2	21	17	90	1,177	8	28	310	15	51	789	41	171	2,297
Kuwait	1	1	3										1	1	3
Lebanon										1	2	216	1	2	216
Malaysia	1	1	51	10	26	450	7	19	165	12	28	719	30	74	1,385
Pakistan										3	11	248	3	11	248
Philippines	2	8	67	3	7	45	7	17	1,712	13	49	3,042	25	81	4,866
Saudi Arabia	1	1	16	1	1	2							2	2	18
Singapore	4	8	207	11	19	206	3	6	31	7	9	304	25	42	748
Syria	1	1	1										1	1	1
Taiwan	11	27	415	15	53	830	14	51	468	18	60	906	58	191	2,619
Thailand	1	1	124	5	13	194	8	20	1,057	11	30	2,181	25	64	3,556
Turkey	3	12	141	10	28	174	7	25	247	11	45	505	31	110	1,067
Vietnam							1	11	375	1	1	4	2	12	379
Australia/New Zealand	*25*	*118*	*1,560*	*51*	*229*	*1,892*	*43*	*220*	*2,663*	*31*	*175*	*1,219*	*150*	*742*	*7,334*
Australia	21	110	1,229	39	195	1,624	34	192	2,180	23	152	1,117	117	649	6,150
New Zealand	4	8	331	12	34	268	9	28	483	8	23	102	33	93	1,184
CIS	*20*	*72*	*664*	*42*	*320*	*6,939*	*37*	*226*	*2,731*	*59*	*498*	*6,677*	*158*	*1,116*	*17,011*
Belarus				1	3	18	2	5	32	2	6	50	5	14	100
Georgia				2	4	24	1	1	29	1	1	4	4	6	57
Moldova										3	3	10	3	3	10
Russia	14	45	484	29	232	5,070	26	172	2,429	37	377	5,588	106	826	13,571
Ukraine	6	27	180	10	81	1,827	8	48	241	16	111	1,025	40	267	3,273
Eastern Europe-non EU	*4*	*8*	*69*	*9*	*29*	*862*	*19*	*51*	*1,202*	*23*	*73*	*1,370*	*55*	*161*	*3,503*
Bosnia										1	2	12	1	2	12
Croatia	4	8	69	5	18	581	14	31	748	16	49	1,144	39	106	2,542
Serbia				4	11	281	5	20	454	6	22	214	15	53	949
Central/South America	*55*	*213*	*13,075*	*104*	*468*	*8,081*	*131*	*644*	*12,170*	*116*	*676*	*13,262*	*406*	*2,001*	*46,588*
Argentina	9	42	783	17	134	2,014	28	215	2,918	34	270	5,010	88	661	10,725

	2005			2006			2007			2008			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
Bahamas	1	1	2										1	1	2
Brazil	13	80	2,643	22	141	3,168	24	144	4,376	20	140	3,068	79	505	13,255
Chile	4	7	70	9	28	431	16	42	419	13	58	395	42	135	1,315
Colombia	4	12	1,267	6	17	295	9	36	559				19	65	2,121
Costa Rica	1	9	1,641	5	11	221	5	10	253	3	4	1,787	14	34	3,902
Ecuador				1	1	3				1	4	83	2	5	86
Guatemala	2	5	372	4	11	117	4	8	147	2	4	27	12	28	663
Honduras				1	2	268							1	2	268
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	74	331	6,432
Panama				1	2	174	3	14	1,312	2	3	32	6	19	1,518
Peru	5	10	1,434	17	55	675	14	58	718	6	22	306	42	145	3,133
Puerto Rico	5	12	858	2	3	7	5	11	149	7	29	288	19	55	1,302
Uruguay				1	1	10							1	1	10
Venezuela	1	2	16	2	6	24				1	4	43	4	12	83

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

Tr= triggered inspections
Ro= routine inspections
To= total number of inspections

REGION	1997			2000			2001			2002			2003			2004			2005			2006			2007			2008			TOTAL		
	tr	ro	to	tr	ro	to	tr	ro	t	tr	ro	to	tr	ro	to	tr	ro	to	tr	ro	to	tr	ro	to	tr	ro	to	tr	ro	to	tr	ro	to
Total 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***	***50***	***51***	***101***
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***	***36***	***40***	***76***
Austria								1	1																			1	2	3	1	3	4
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	8	12	20
Italy							1		1														2	2							1	2	3
Netherlands	1		1				2		2											1	1					1	1		1	1	3	3	6
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
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***	***14***	***11***	***25***
Czech Republic																			2		2								1	1	2	1	3
Hungary								1	1																	1	1				0	2	2
Lithuania																									1		1	1		1	2	0	2
Poland								1	1	1		1							2		2		1	1	6	1	7	1		1	10	3	13
Bulgaria											1	1																			0	1	1
Romania																										1	1		3	3	0	4	4

REGION	1997			2000			2001			2002			2003			2004			2005			2006			2007			2008			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
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***	***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***	***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***	***34***	***13***	***47***
Canada																						1		1	3	2	5	3	1	4	7	3	10
USA				13	3	16	1		1	4		4	2		2				2		2		2	2	3	1	4	2	4	6	27	10	37
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***	***3***	***4***	***7***
Argentina																													1	1	0	1	1
Brazil																												1		1	1	0	1
Chile																			1		1										1	0	1
Colombia																										1	1				0	1	1
Costa Rica																													1	1	0	1	1
Mexico																1		1													1	0	1
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***	***1***	***17***	***18***
China																							1	1					3	3	0	4	4
India																							2	2					7	7	0	9	9
Malaysia														1	1																0	1	1
Philippines																										1	1		1	1	0	2	2
Thailand																							1	1							0	1	1
Turkey																1		1													1	0	1

REGION	1997			2000			2001			2002			2003			2004			2005			2006			2007			2008			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
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***	***4***	***4***
Ghana																										1	1				0	1	1
Morocco																										1	1				0	1	1
South Africa																										2	2				0	2	2
totals	**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**	**95**	**94**	**189**