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SCIENCE MEDICINES HEALTH

Activities of the European Medicine Agency on ethics of biomedical research

Fergus Sweeney, PhD

European Medicines Agency

International Conference on "Ethics Review of Biomedical Research Project"

Council of Europe and the Ministry of Health and Social Development of the Russian Federation

Moscow 28-29 Nov 2011

Presented by: Fergus Sweeney, PhD
Head of Sector, Compliance and Inspection, European Medicines Agency.

Disclaimer

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European Medicines Agency

Science. Medicines. Health.

The mission of the
European Medicines Agency
is to foster scientific excellence in
the evaluation and supervision of
medicines, for the benefit of
public and animal health.

EU Regulatory Network

European Commission DG SANCO

European Medicines Agency (EMA)

- Centralised procedure
- CHMP and WPs, COMP, PDCO, SAWP..
- Clinical trial database EudraCT, EudraVigilance database (clinical trial and post-marketing)

National Competent Authorities (NCAs)

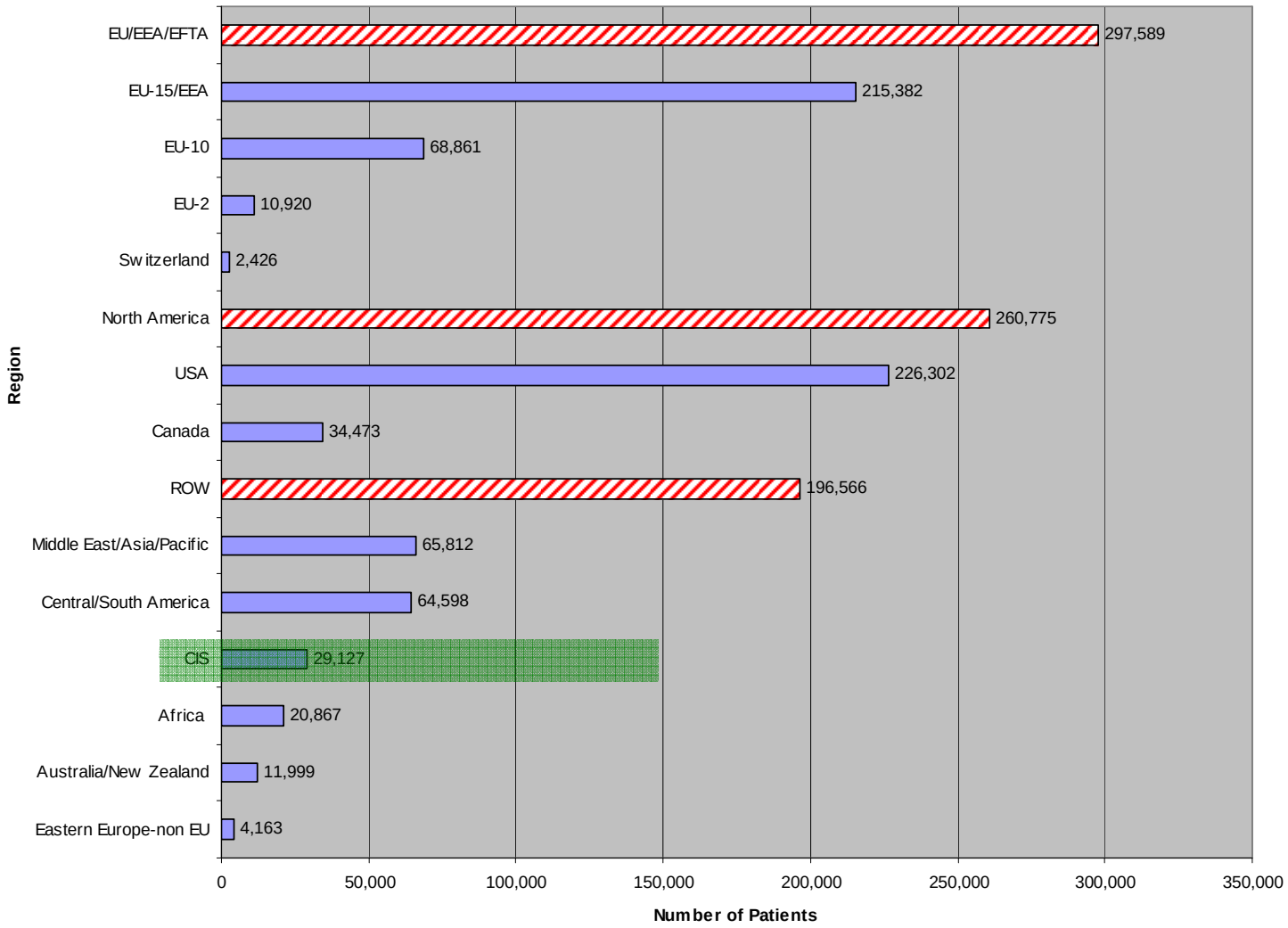
- National marketing authorisations via DCP/MRP
- National authorisation of Clinical Trials

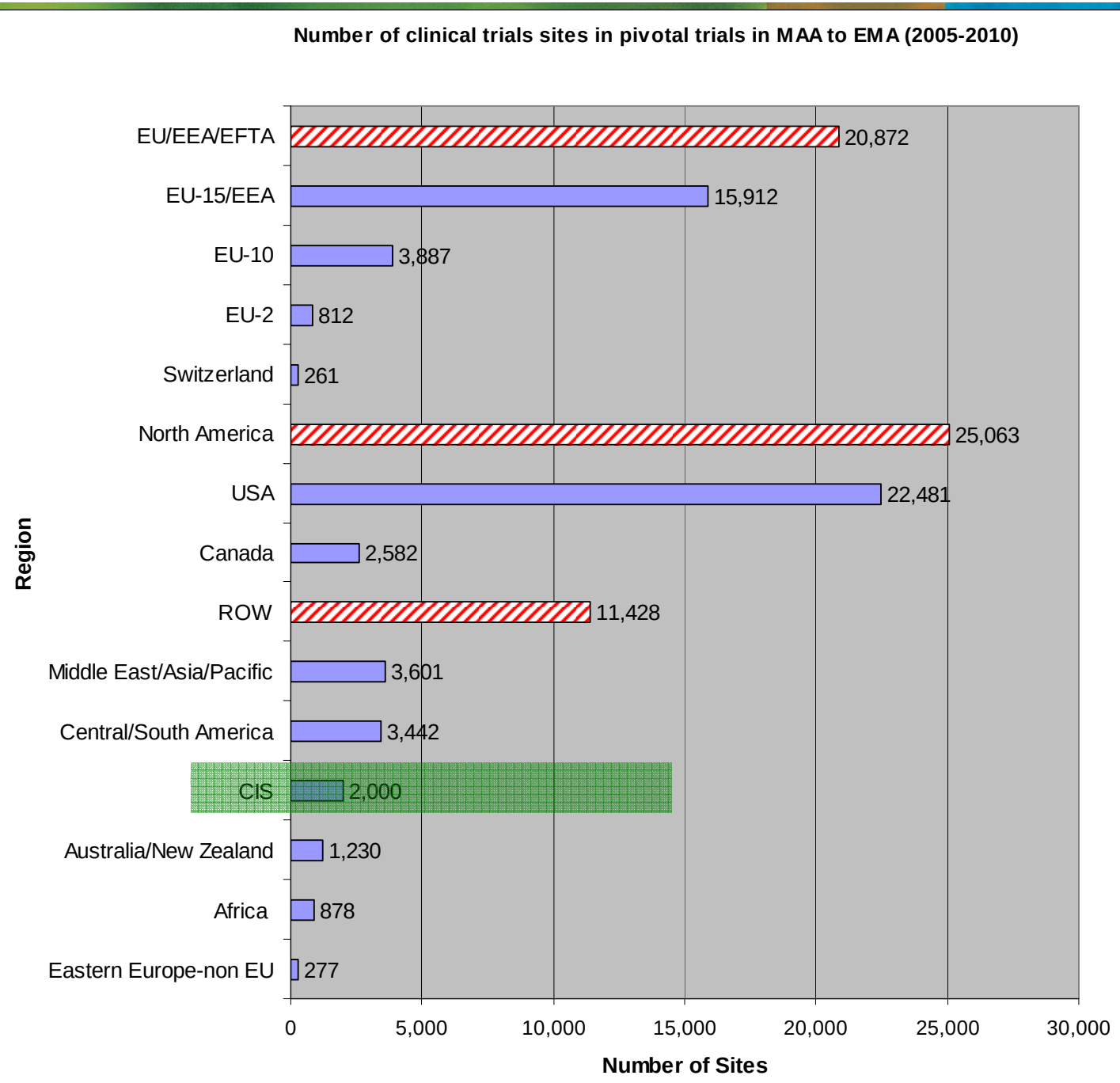
Role of EMA

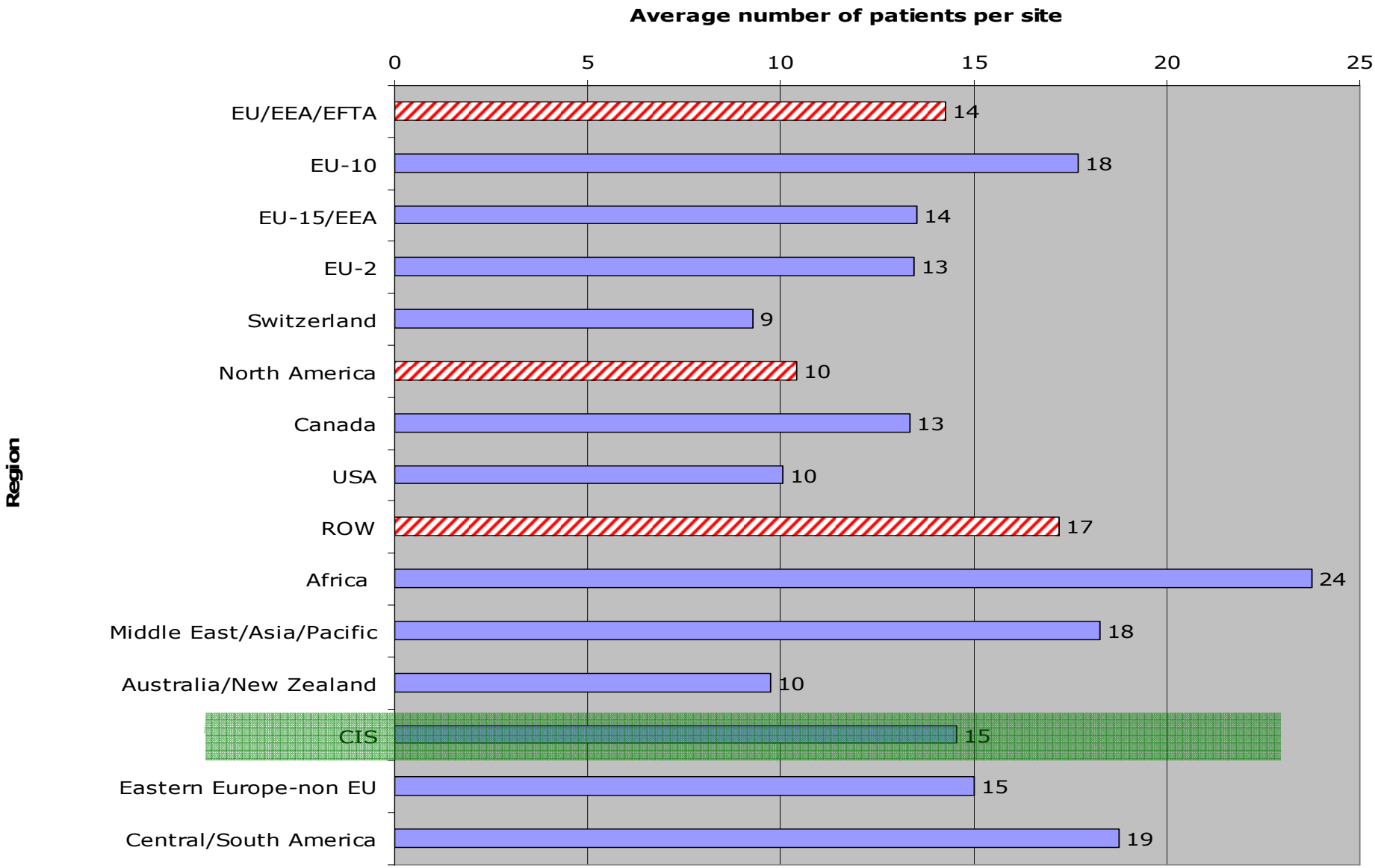
- Scientific Advice
- Development of guidelines
- Paediatric Investigation Plans
- Orphan Medicinal Product designation
- **Marketing Authorisation Application evaluation – Centralised Procedure**
- Processes - Advice, guidance, assessment and inspection –
- Performed by experts of the EU Member States' Medicines Agencies

www.ema.europa.eu

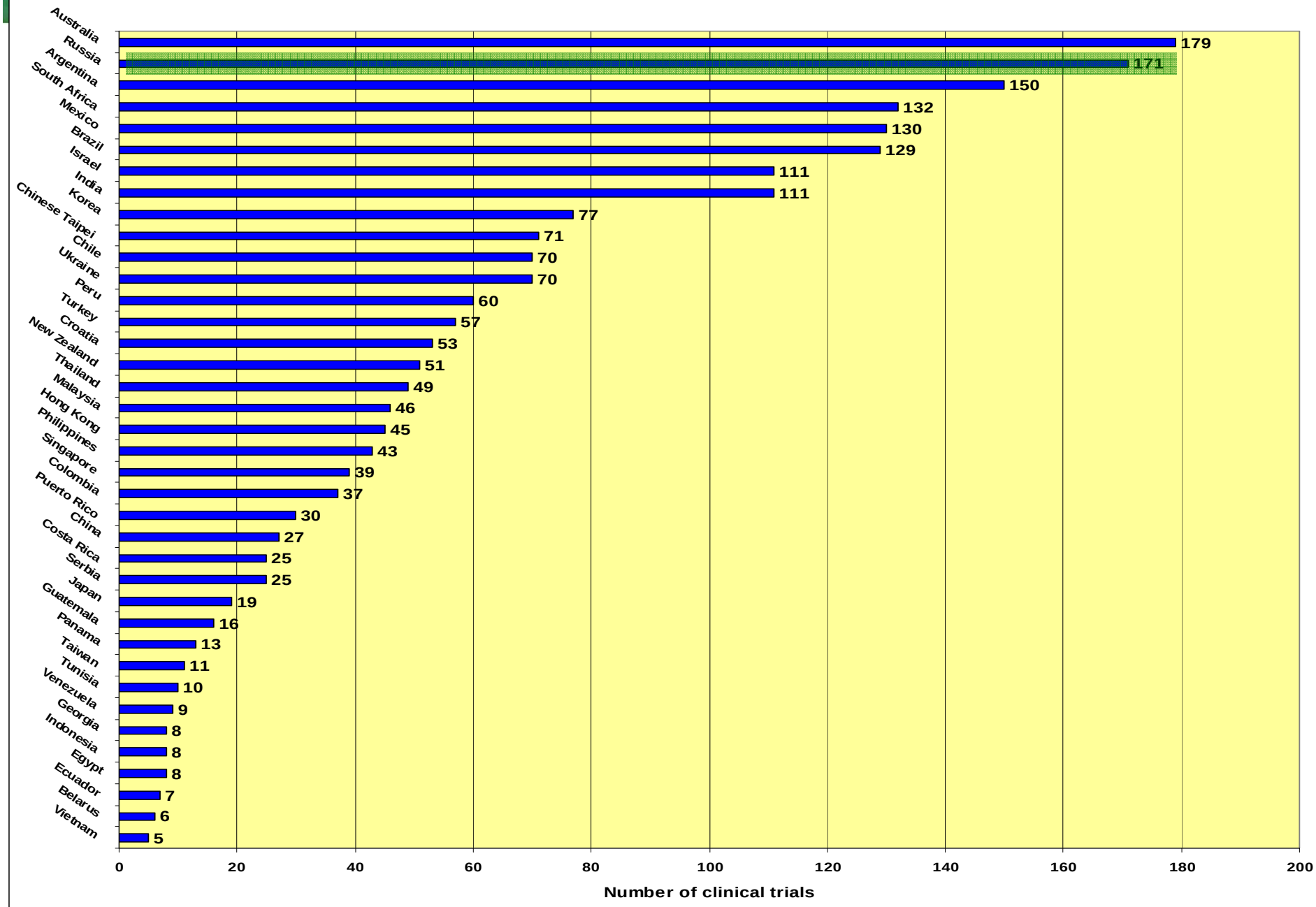
Number of patients in pivotal trials submitted in MAAs to EMA (2005-2010)

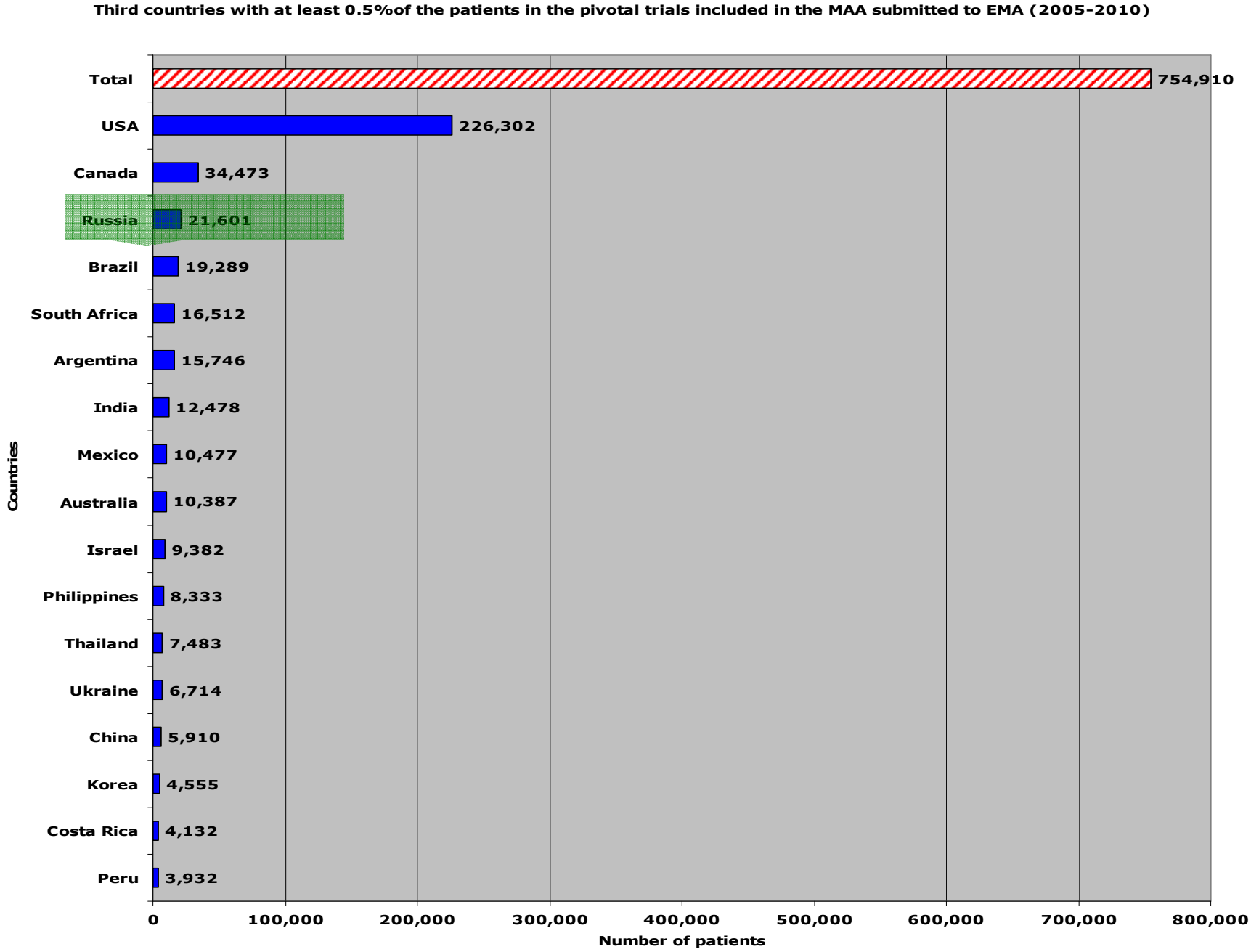



Number of clinical trials sites in pivotal trials in MAA to EMA (2005-2010)
EU/EEA/EFTA
20,872
EU-15/EEA
15,912
EU-10
3,887
EU-2
812
Switzerland
261
North America
25,063
USA
22,481
Canada
2,582
ROW
11,428
Middle East/Asia/Pacific
3,601
Central/South America
3,442
CIS
2,000
Australia/New Zealand
1,230
Africa
878
Eastern Europe-non EU
277
Region
0
5,000
10,000
15,000
20,000
25,000
30,000
Number of Sites


Average number of patients per site
0
5
10
15
20
25
Region
EU/EEA/EFTA
14
EU-10
18
EU-15/EEA
14
EU-2
13
Switzerland
9
North America
10
Canada
13
USA
10
ROW
17
Africa
24
Middle East/Asia/Pacific
18
Australia/New Zealand
10
CIS
15
Eastern Europe-non EU
15
Central/South America
19

Number of CT in MAA to EMA (2005-2010)



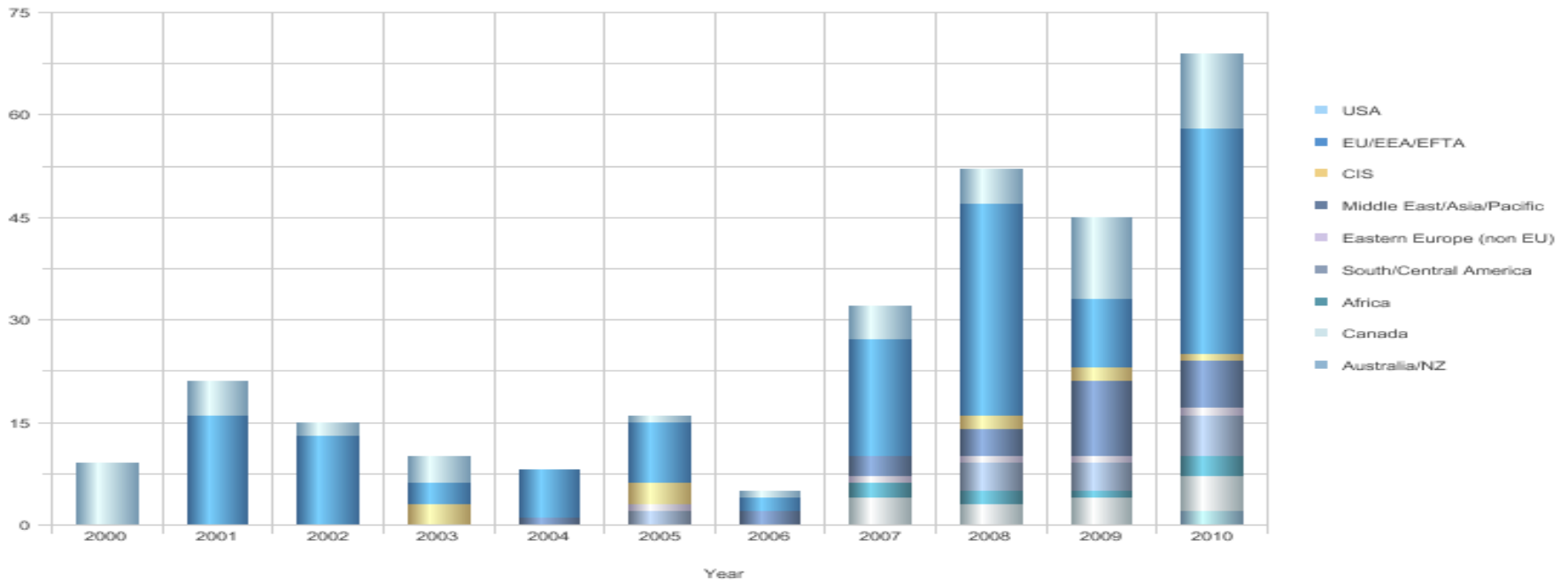

Third countries with at least 0.5%of the patients in the pivotal trials included in the MAA submitted to EMA (2005-2010)
Total
754,910
USA
226,302
Canada
34,473
Russia
21,601
Brazil
19,289
South Africa
16,512
Argentina
15,746
India
12,478
Mexico
10,477
Australia
10,387
Israel
9,382
Philippines
8,333
Thailand
7,483
Ukraine
6,714
China
5,910
Korea
4,555
Costa Rica
4,132
Peru
3,932
Countries
0
100,000
200,000
300,000
400,000
500,000
600,000
700,000
800,000
Number of patients

171 pivotal clinical trials involving Russian investigators sites submitted to EMA between 2005 and 2010

Wide range of therapeutic areas including:

- Oncology
- Anti-infectives
- Neurological
- Antipsychotic
- Cardiovascular
- Endocrine/Metabolism
- Diabetes

Number of inspections by year and region



Region	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	Total per region
USA	9	5	2	4		1	1	5	5	12	11	55
EU/EEA/EFTA		16	13	3	7	9	2	17	31	10	33	141
CIS				3		3			2	2	1	11
Middle East/Asia/Pacific					1		2	3	4	11	7	28
Eastern Europe (non EU)						1		1	1	1	1	5
South/Central America						2			4	4	6	16
Africa								2	2	1	3	8
Canada								4	3	4	5	16
Australia/NZ											2	2
Total per year	**9**	**21**	**15**	**10**	**8**	**16**	**5**	**32**	**52**	**45**	**69**	**282**

11 in Russia by 2011

The Dilemna……

Between 2005 and 2010

754,930 Patients in pivotal trials

(39.4% in Europe, 34.5% in North America, 2.8% Africa, 8.7% Middle East/Asia Pacific, 3.9% CIS, 8.6 % Latin America, 2.1% other)

57,363 clinical trial sites in c. **90** countries

c. 400 new MAA applications, **282** GCP inspections

EU requirements for clinical trials conducted in support of Marketing Authorisation Applications (MAAs) submitted to the EU

Requirements apply:

- To all clinical trials that are included in a MAA submitted in the EU/EEA
  - regardless of the route (Centralised, Mutual Recognition, Decentralised)
  - regardless of the EU or third country involved (legislation does not differentiate developed, developing etc)
- Apply to the clinical trials included in a MAA
- There is no specific legal framework for review of a clinical trial dossier by an EU regulator before the conduct of the trial in a third country

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Clinical Trials included in MAA to the EU

Regulation (EC) No 726/2004 Recital 16:

"There is also a need to provide for the ethical requirements of Directive 2001/20/EC ……. 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."

Directive 2001/83/EC Annex I

" To be taken into account during the assessment of an application, clinical trials, conducted outside 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."

EMA Strategy

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- Two principles
  - Acceptability – ethics and data quality
  - Applicability – intrinsic and extrinsic factors
- Two sets of process:
  - Prospective – guidance, scientific advice, PIP….
  - Confirmatory – assessment, inspection….
- Global approach:
  - Network of regulators
  - International ethical and data quality standards in place and reinforced globally
  - International clinical development plan addressing ethical, data quality and scientific/medical needs of all regions

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London, 04 July 2011
EMA/389137/2011
The European Medicines Agency Working Group on Third Country Clinical Trials

Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted outside of the EU/EEA and submitted in marketing authorisation applications to the EU Regulatory Authorities

Draft

Draft Agreed by EMA Working Group on Third Country Clinical Trials	
End of consultation (deadline for comments)	30 September 2010
Agreed by EMA Working Group on Third Country Clinical Trials	
Adoption by EMA	

434521

Comments should be provided using this template. The completed comments form should be sent to ctrefpaper@ema.europa.eu

Keywords	***Clinical trials, GCP, Third Countries, Marketing Authorisation Applications, EMA, EU, Ethics***

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

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Draft 'Reflection paper on ethical and GCP aspects of clinical trials conducted in third countries for evaluation in marketing authorisation applications for medicines for human use, submitted to the EMA' Public consultation completed 30th September 2010.

Topic 1. Clarify the **practical** application of ethical standards for clinical trials, in the context of EMEA activities

Topic 2. Determine the **practical** steps to be undertaken during the provision of guidance and advice in the drug development phase

Topic 3. Determine the **practical** steps to be undertaken during the Marketing Authorisation phase

Topic 4. International cooperation in the regulation of clinical trials, their review and inspection and capacity building in this area

http://www.ema.europa.eu/Inspections/docs/71239709en.pdf

Working group – members from CHMP/COMP/PDCO, PCWP, HCPWP, GCP IWG

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12 May 2011
EMA/601825/2010
Patient Health Protection

International workshop

Meeting Report

Draft reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted in third countries and submitted in marketing-authorisation applications to the EMA

6-7 September 2010
European Medicines Agency, London, UK

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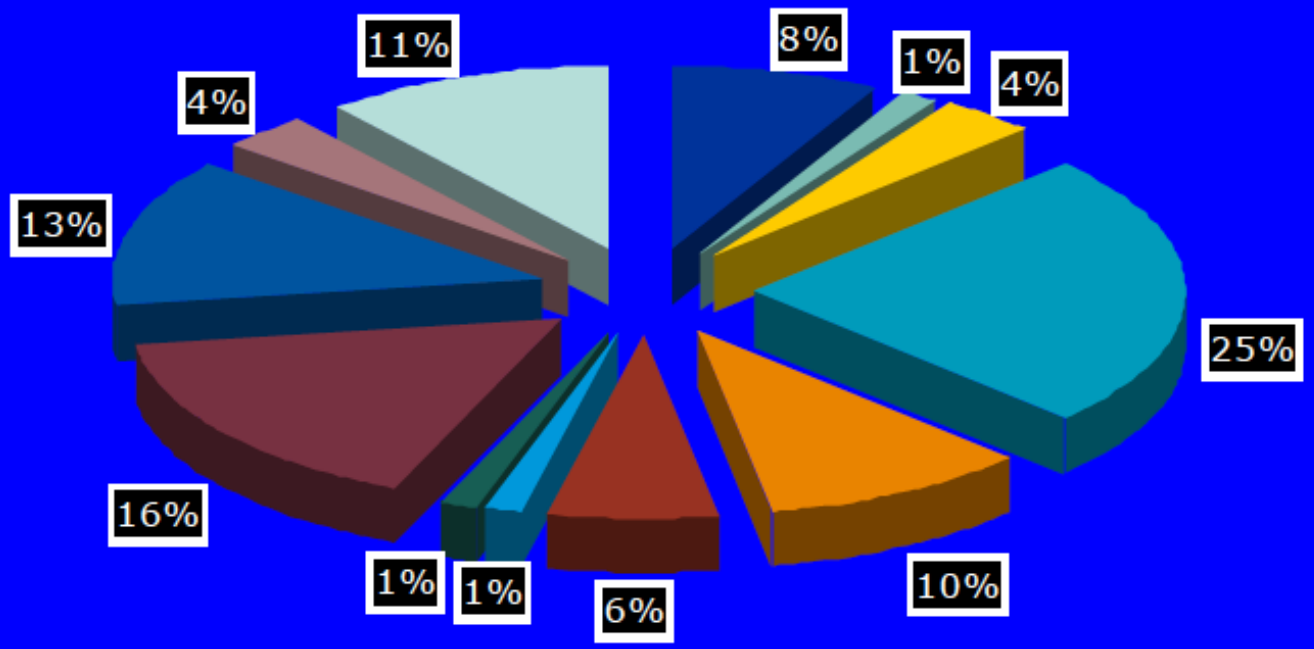
Participation by country

Argentina, Austria, Belgium, Brazil, Burkina Faso, Canada, China, Croatia, Cyprus, Denmark, Estonia, Finland, France, Germany, Ghana, Greece, Hungary, India, Indonesia, Ireland, Italy, Japan, Kazakhstan, Korea, Malawi, Mexico, Montenegro, Netherlands, Norway, Poland, Portugal, Russia, Serbia, Singapore, South Africa, Spain, Sweden, Switzerland, Taiwan, Thailand, Turkey, UK, USA

Participation by Stakeholders



A number of practical proposals and recommendations are set out in the draft reflection paper. It was considered that EU regulators should only expect or require studies in support of an EU marketing authorisation application that would also be ethically acceptable in the EU. There should not be a different standard applied to trials conducted in the EU compared to those conducted elsewhere.

The discussions over the course of the two-day conference highlighted a number of points including:

- Ethical principles are universal and not negotiable. Equivalent ethical and scientific standards should be applied everywhere in the world regardless of the current strengths or weaknesses of regulatory or other systems.
- There was a consensus on the important role to be played by greater practical cooperation and networking between regulatory authorities and ethics committees involved in the supervision of clinical trials, including capacity building activities.
- Increased transparency of information on clinical trials is essential to establishing public confidence in the clinical trial process and the assessment of trial information at the time of marketing authorisation. This includes prospective clinical trial registers used at the time studied are initiated and the provision of information about ethical and GCP aspects of the Marketing Authorisation application and assessment in the European Public Assessment Report (EPAR).
- The greatest impact is achieved by building the ethical and scientific standards into the conduct and supervision of clinical trials from their outset, assessment at the time of marketing authorisation can only reinforce that process but not replace it. Patients' views should be included from early on in this process to ensure the adequate protection of clinical trial subjects.

"It is an important element of international cooperation that regulators support compliance with local requirements in each country as well as reinforcing international ethical and good clinical practice standards.

In every case the trial must receive a positive opinion or approval from an ethics committee with appropriate jurisdiction for the investigator sites and trial concerned."

"As regulators, wherever in the world we stand, most clinical trials, most manufacturing activities, are carried out somewhere else, under someone else's jurisdiction – we rely on each other to supervise these activities for the benefit of all our citizens."

"What is needed is a robust framework for the oversight and conduct of clinical trials, no matter where in the world the clinical investigator's sites are located and patients recruited. The Agency is committed to build and extend its relationship with regulators in all parts of the world and with international organisations to work to standards agreed and recognised by all."

International cooperation in the regulation of clinical trials, their review and inspection and capacity building in this area

- Cooperation
- Information sharing
- Training
- Sharing best practice
- Regulatory authorities (assessors and inspectors), ethics committees….

EU/EMA establishing exchanges

Confidentiality arrangements

- EU/USA, EU/Canada, EU/Japan
- Bilateral discussions between European Commission and Russia, India, China

EU/WHO

EMA – FDA GCP Initiative, harmonisation, synergy, information sharing, make best use of finite inspection resource

Global network

Shared training

Training together – network based

GCP Inspectors Workshops - EU Members States, Accession Countries

International from 2008 onwards:

Africa/Middle East, Ghana, Kenya, Malawi, Nigeria, South Africa, Tanzania, Zambia, Jordan, Saudi Arabia

Asia Pacific, Australia, China, Chinese Taipei, India, Indonesia, Philippines, Thailand

Russia

Latin America, Argentina, Brazil, Mexico

North America, USA, Canada

WHO

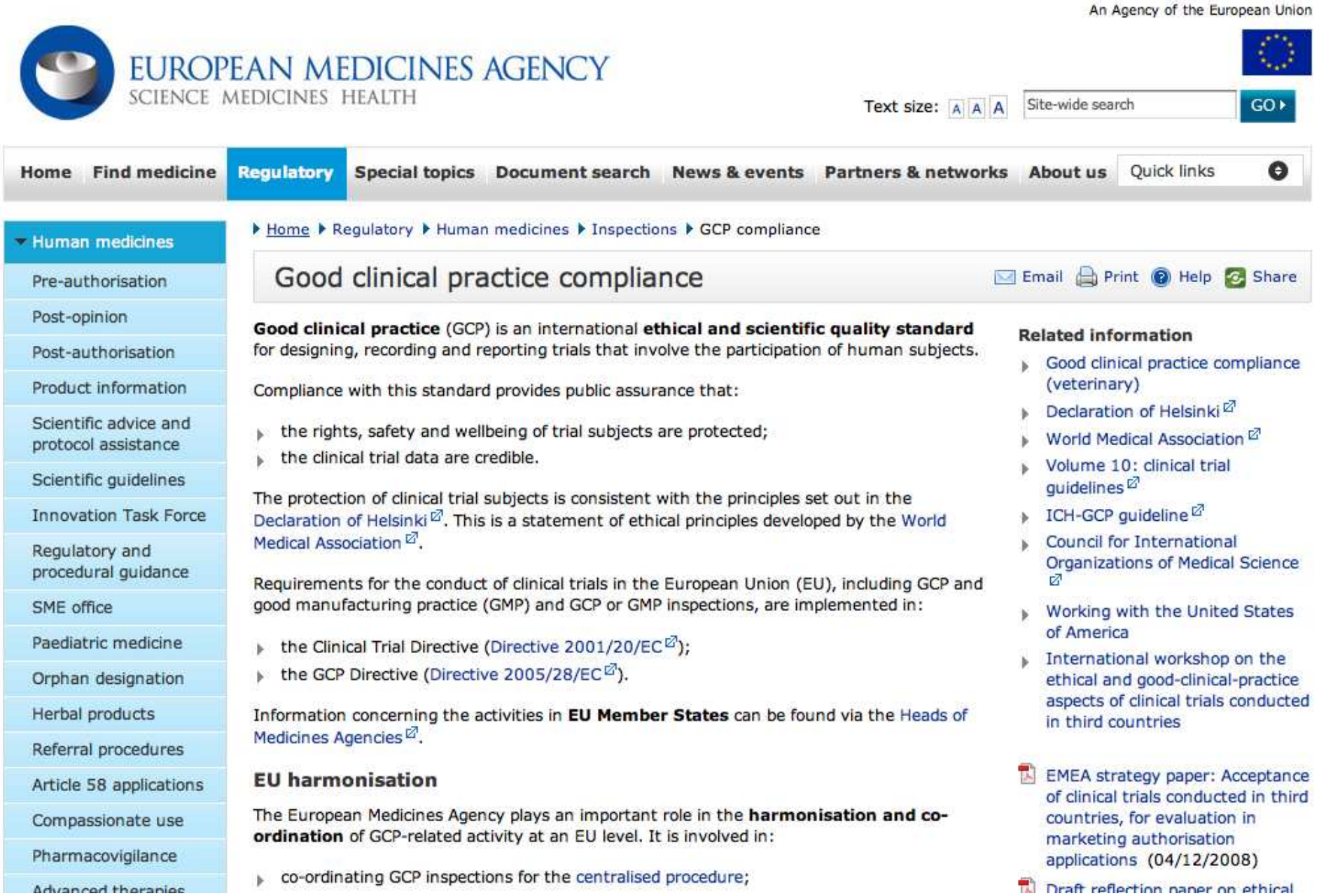
On site – EU inspectors notify local inspectors of site visits – invite them to observe

Ethics Committees – FERCAP (China, Thailand, Korea..), Council of Europe (Russia..)…

GOAL

Subjects/patients participating in trials are fully protected – wherever the trial takes places

Availability of safe and effective new medicines, as early as possible, with data relevant to all regions



http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000072.jsp&mid=WC0b01ac05800268ad

Thank you

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- Dr. Ana Rodriguez Sanchez Beato

- Dr. Maria Antonietta Antonelli