EUCROF
European CRO Federation

Europe's Attractiveness to Clinical Trials Can We contribute?

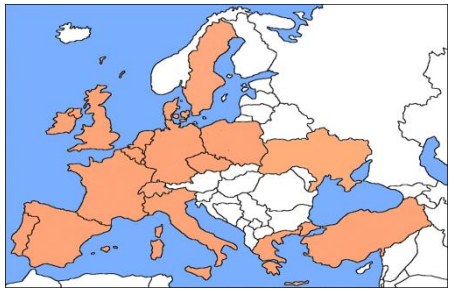
International Day of Clinical Trials

20th May 2014 Warsaw

Dr. Stefano Marini, MD
EUCROF President European Contract Research Organization Federation
Medical Scientific Advisor to TFS Trial Form Support

EUCROF Members

- EUCROF is a non-profit organisation founded on 2005
- Member are legal entities registered in at least one European Country:
  - Associations of CROs, or
  - Private companies working in Clinical Research Services



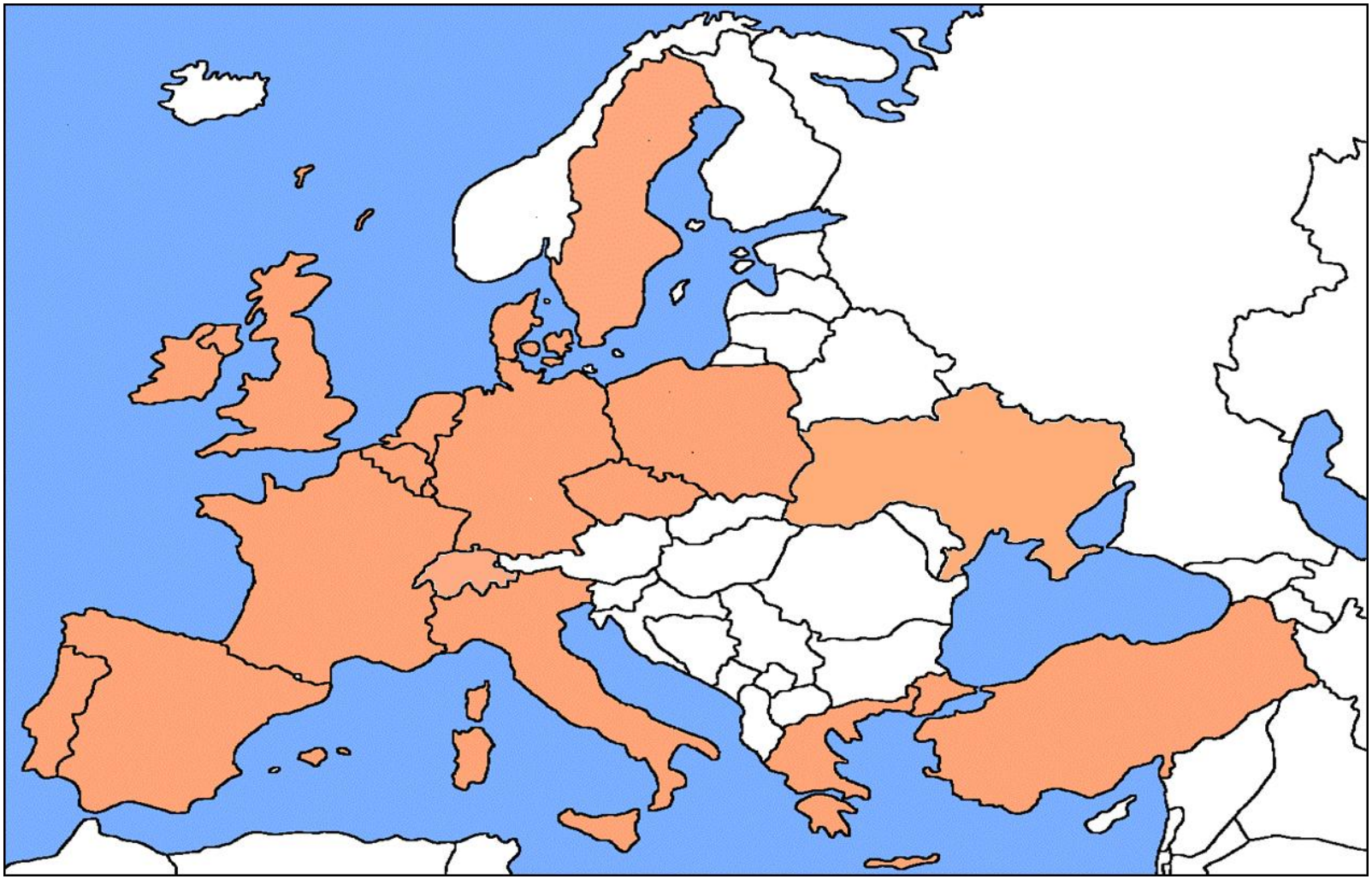
National Association	Country	No. CROs
1. ACRO-CZ	Czech Republic	18
2. ACRON	The Netherlands	40
3. AECIC	Spain	30
4. AFCROS	France	48
5. AICRO	Italy	13
6. ASCRO	Sweden	7
7. BeCRO	Belgium	29
8. BVMA	Germany	39
9. CCRA	United Kingdom	36
10. HACRO	Greece	10
11. SAKDER	Turkey	26

Local CROs

1. Portugal
2. Poland
3. Ireland
4. Denmark
5. Switzerland
6. Ukraine

TOTAL: 293 Companies, 17 Countries , over 16.000 employees

EUCROF Members
Geographic Presence May - 2014



EUCROF

EUCROF Mission

EUCROF is a legal no-profit entity representing the interests of CROs in Europe towards:

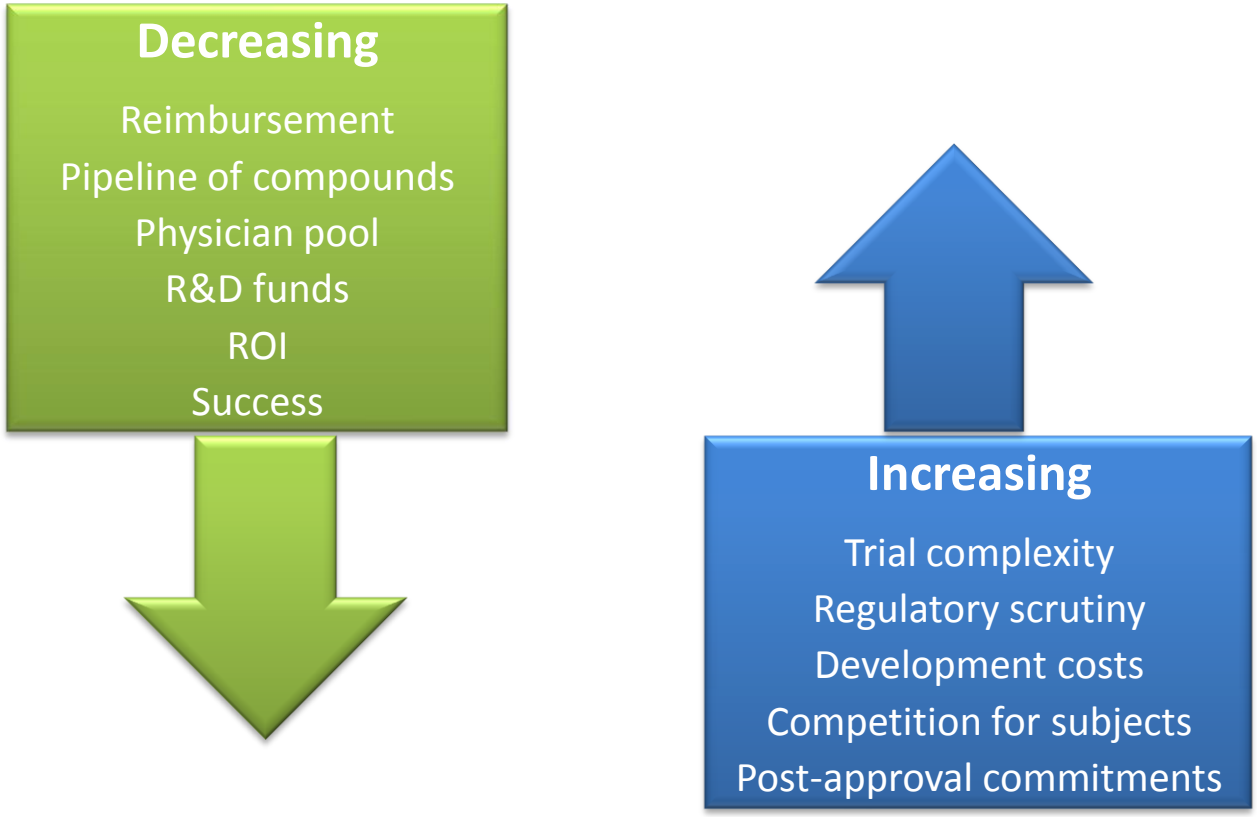
- regulatory bodies
- pharmaceutical, biotech, medical device industry
- healthcare related industry within the field of clinical research
- patients associations

- EUCROF's goal is to promote Clinical Research by

Improving the knowledge, competence and skills of CROs in Europe

- **Working groups** (Paediatric, Late Phase, How to start a clinical trial, Early Phase, Medical Device)

The landscape demands change



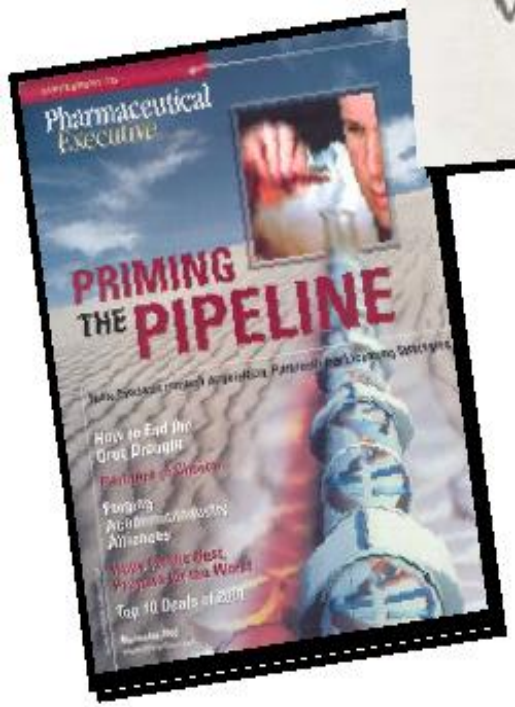
Trial complexity is increasing

Growing clinical trial complexity continues to challenge the ability of companies to contain costs of new drug development

- Greater protocol complexity is associated with lower patients enrollment and retention rates [1]
- Median number of procedures per trial increased 57 % from 2000 to 2011 [2]
- Work burden per protocol increased 54 % [2]
- Eligibility criteria increased 58 % while enrollment rates dropped 21 % and retention rates dropped by 30 % [3]
- The complexity and work burden associated with longer study timelines has shown an even more profound increase at 69-75 % [2]

1. Tufts Center for the Study of Drug Development: Assessing the impact of protocol design changes on clinical trial performance,
2. Tufts Center for Drug Development: Assessing the down stream impact of protocol design complexity
3. Tufts Center for Drug Development: 2012 Protocol Study

Industry Headlines

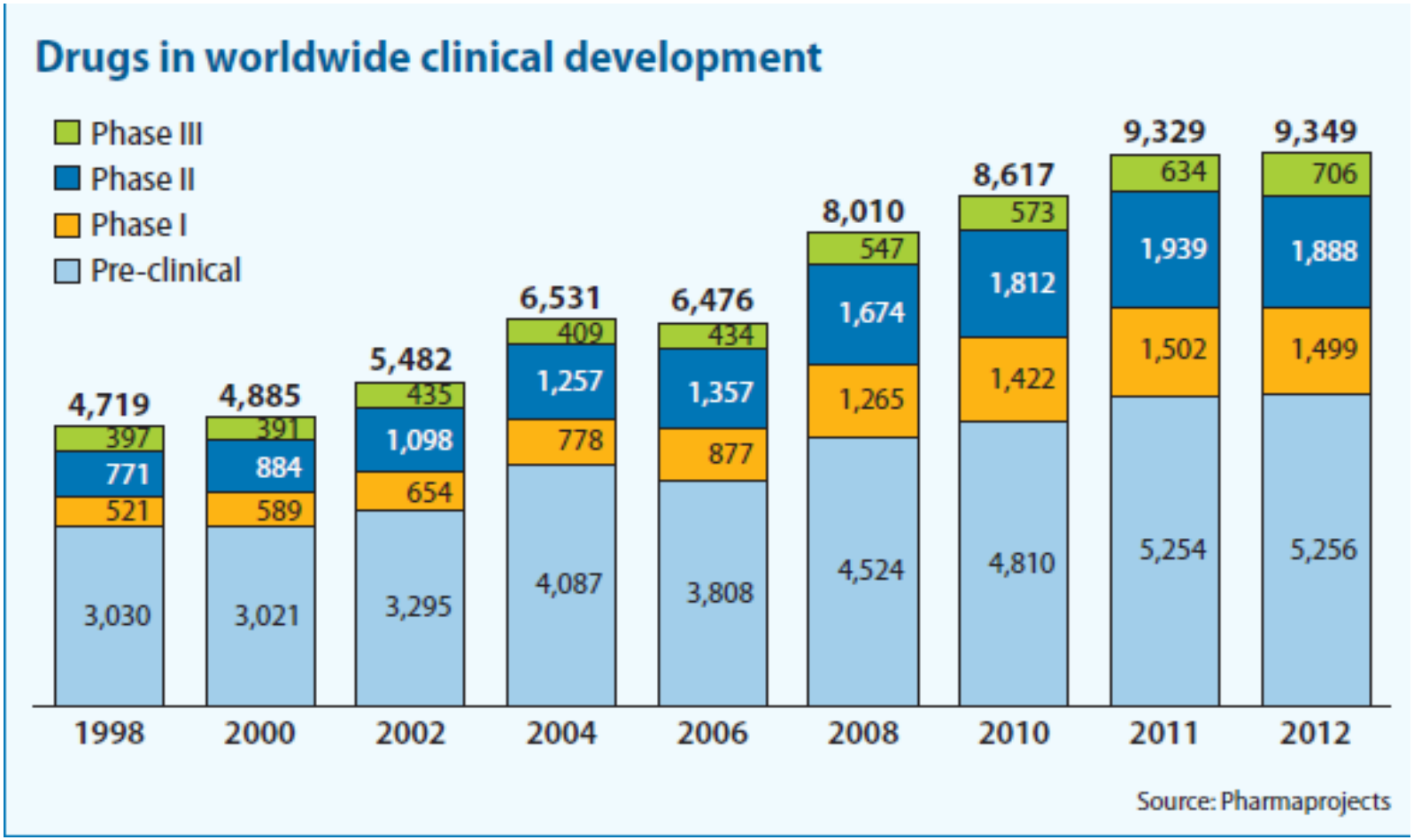


The New York Times
Money&Business
Section 3

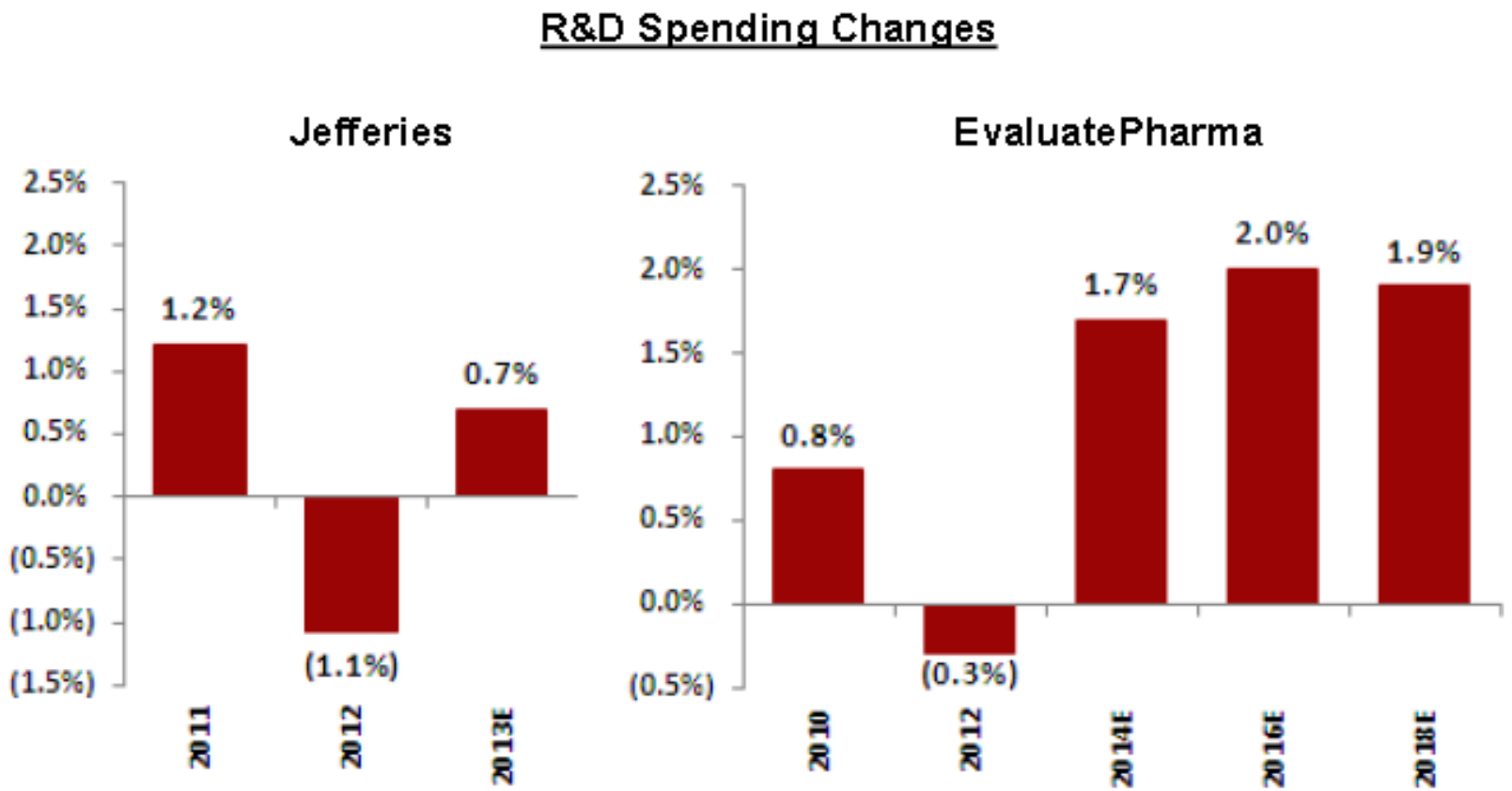
Where Are All the New Drugs?

Critics Blame Mergers for Lab Drought at Glaxo

Increasing costs, complexity and competition coupled with decreasing return on investment is forcing to do more with less

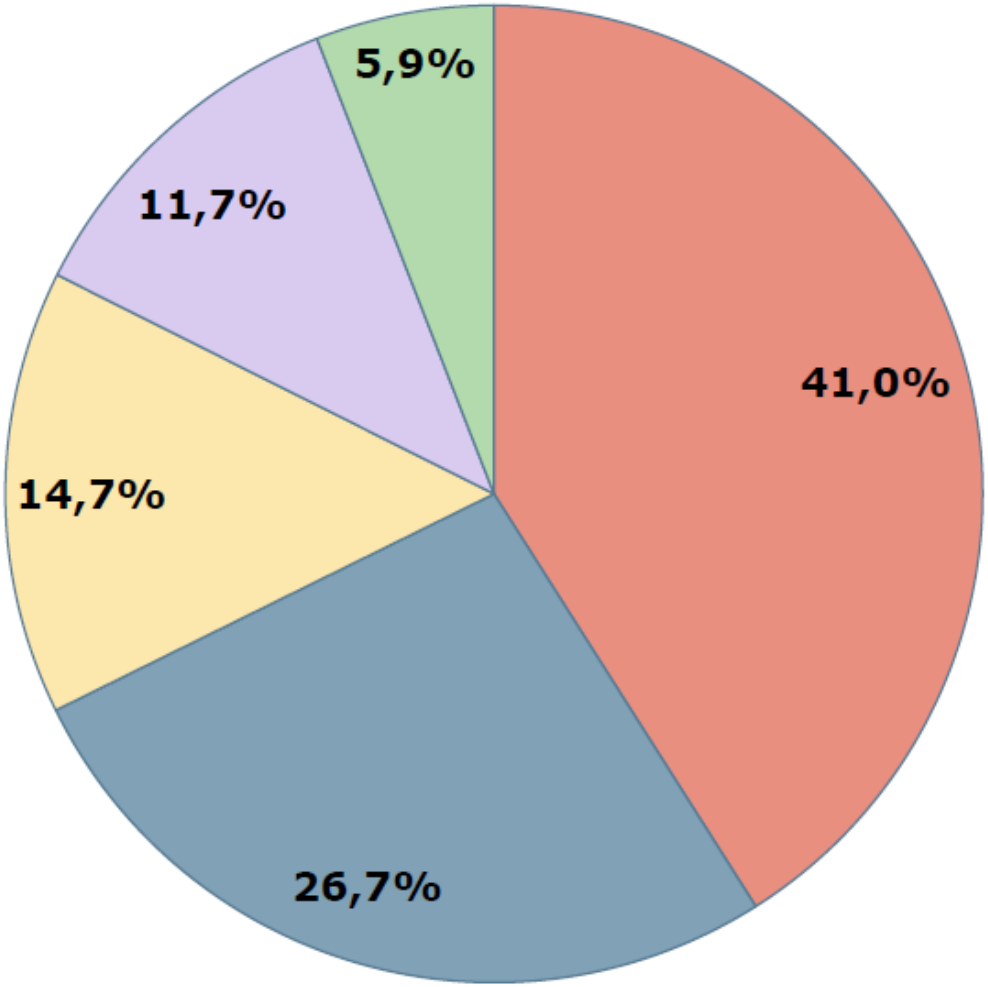


Investment Preview in R & D Up to 2018



Source: Company Data, Capital IQ, EvaluatePharma, and Jefferies LLC

World Pharmaceutical Market 2013



- North America
- Europe
- Africa, Asia (Ex-Japan) Australia
- Japan
- Latin America

Source: EFPIA 'The Pharmaceutical Industry in Figures 2013'

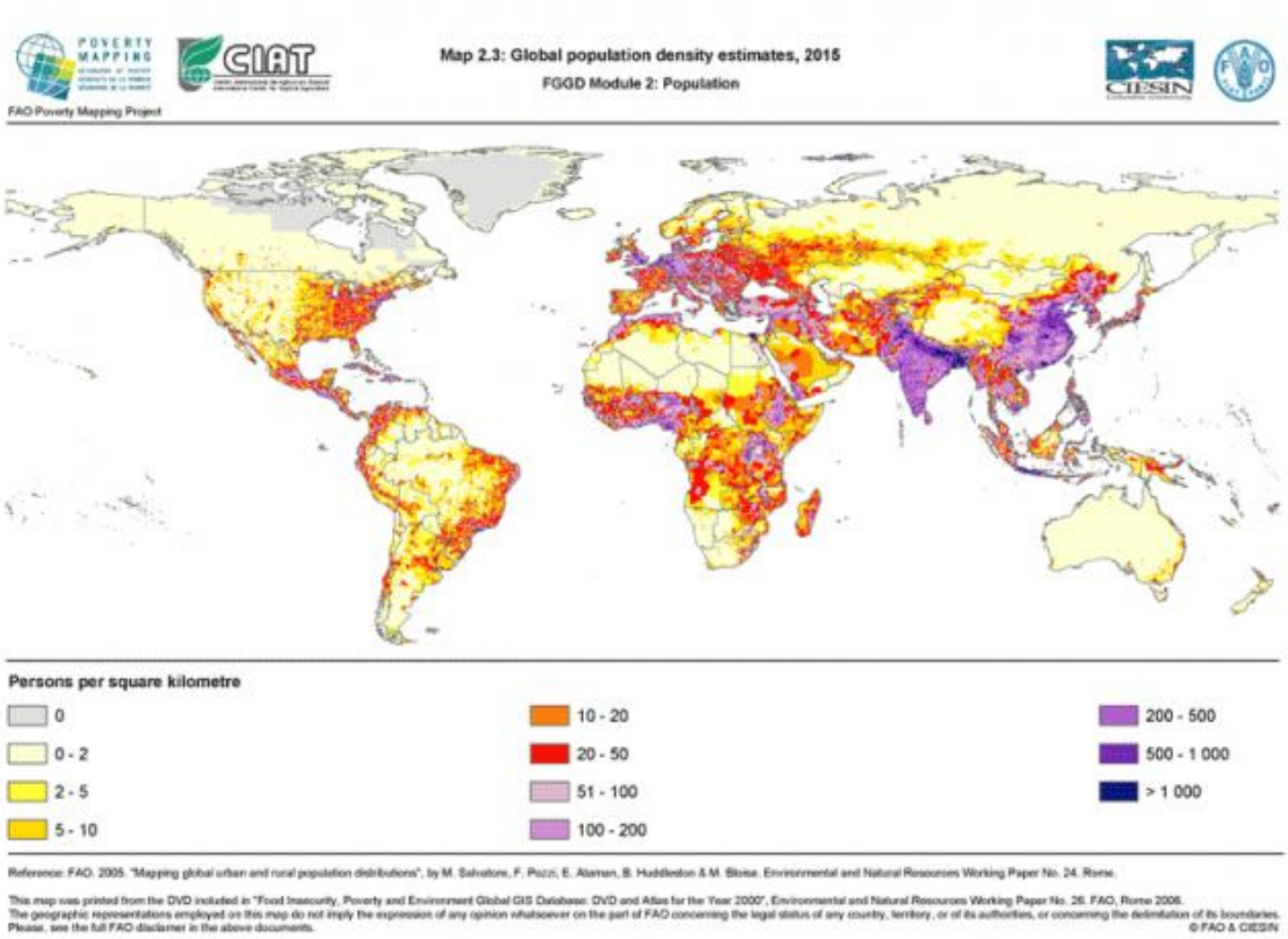
Global Pharmaceutical Sales 2012

	Sales ($billion)	% growth
North America	349	-1.0
Europe	224	-0.8
Asia	168	12.8
Japan	111	0
Latin America	69	10.9
Total	959	2.4

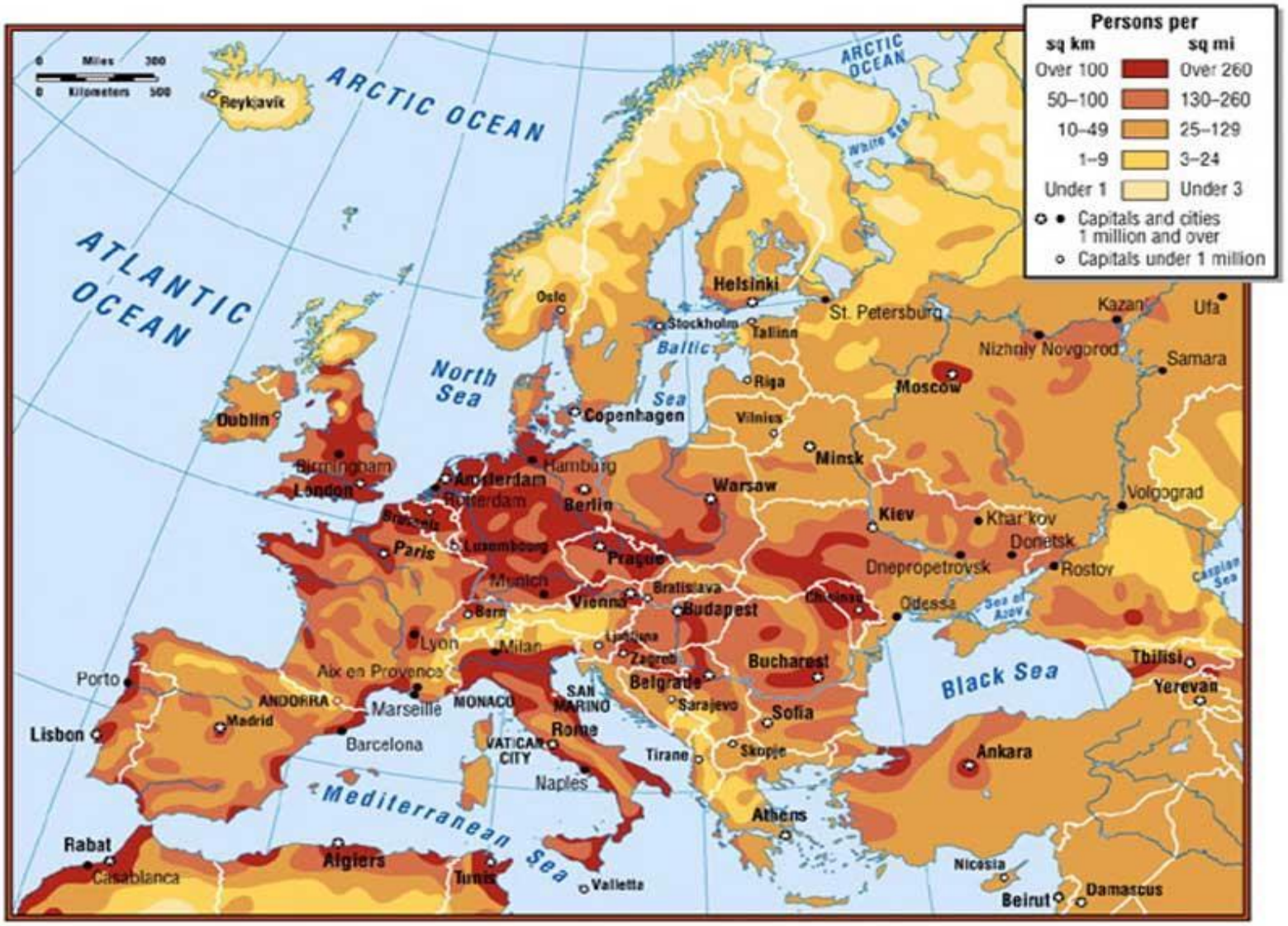
- EMEA has 5 countries in global top 10
- Europe's market share is shrinking but so is that of North America

Source: Imshealth.com

World Population density



Europe Population density



European Population compared to Rest of the World (ROW)

The European Union makes up over 500 million people, which accounts for over 7% of the world's population.

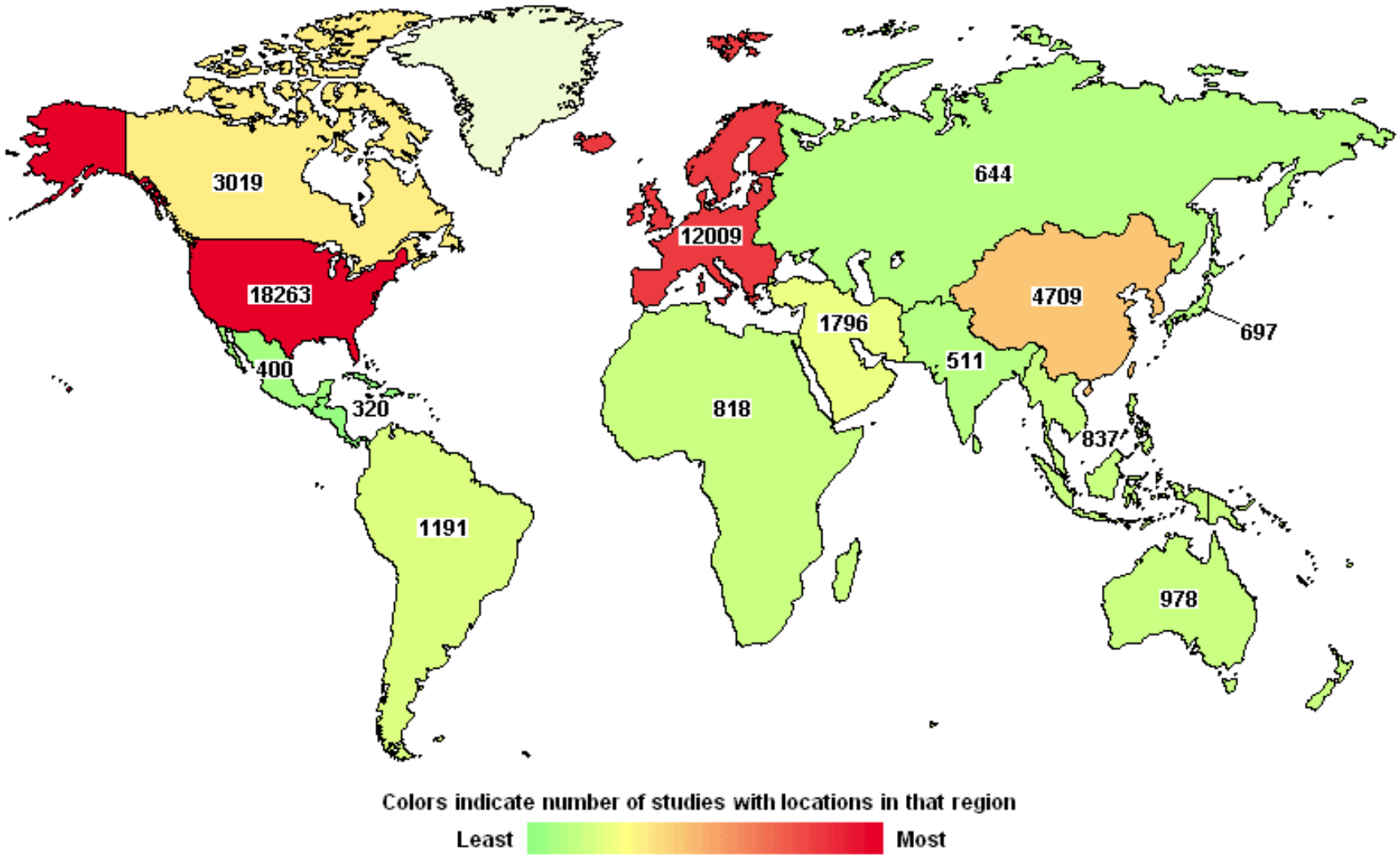
US population in 2014 is of 317 million people

China has 1,35 billion people in 2013

India has 1,23 billion people in 2013

Clinical Trials Registered in ClinicalTrials.gov

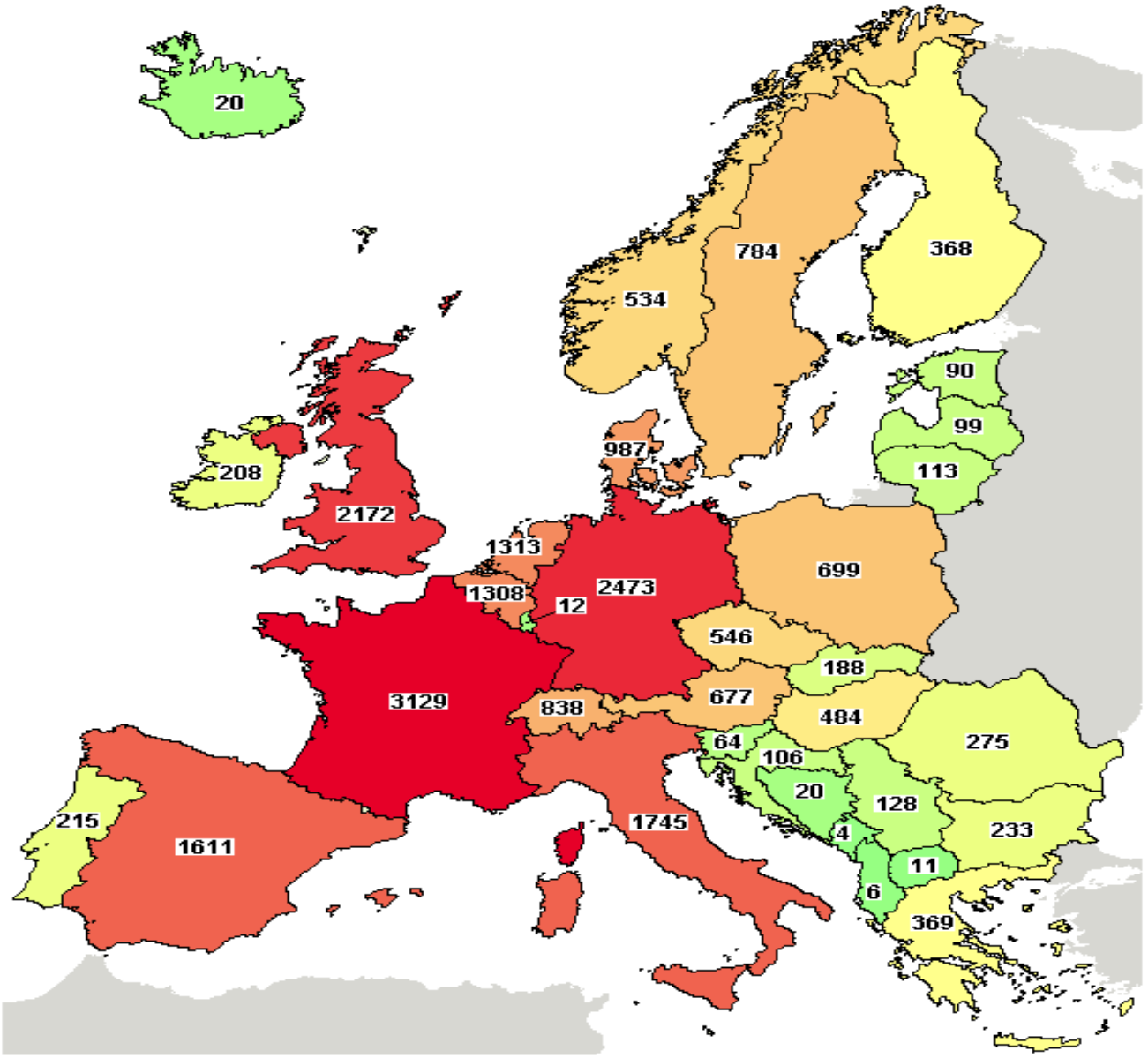
(May 10, 2013)



Clinical Trials Registered in ClinicalTrials.gov

Region/Country	N. of Studies
World	39453
Africa [map]	818
Central America [map]	320
East Asia [map]	4709
Japan	697
Europe [map]	12009
Middle East [map]	1796
North America	20359
Canada [map]	3019
Mexico	400
United States [map]	18263
North Asia [map]	644
Pacifica [map]	978
South America [map]	1191
South Asia [map]	511
Southeast Asia [map]	837

Clinical Trials Registered in ClinicalTrials.gov



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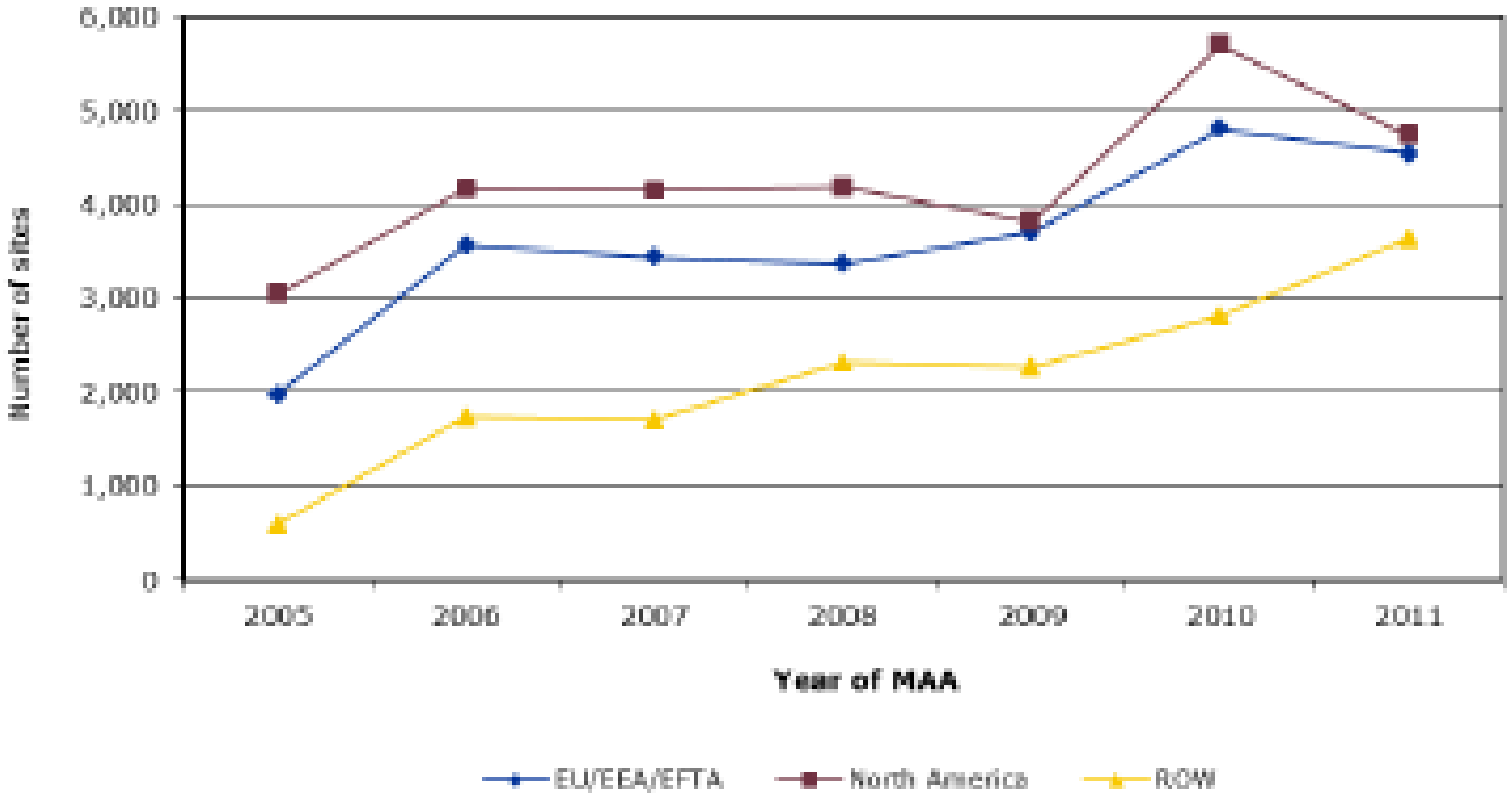
New Studies registered in Clinicaltrials.gov between January 1st and December 31st of each year

New Studies registered in Clinicaltrials.gov					
	2009	**2010**	**2011**	**2012**	**2013**
Total	1413	2524	4433	9200	13822
Europe	361	737	1472	2928	4310
USA	887	1364	2193	3980	5884
East Asia	113	247	493	1218	1880
Africa	14	43	99	200	303
South America	82	58	172	343	411

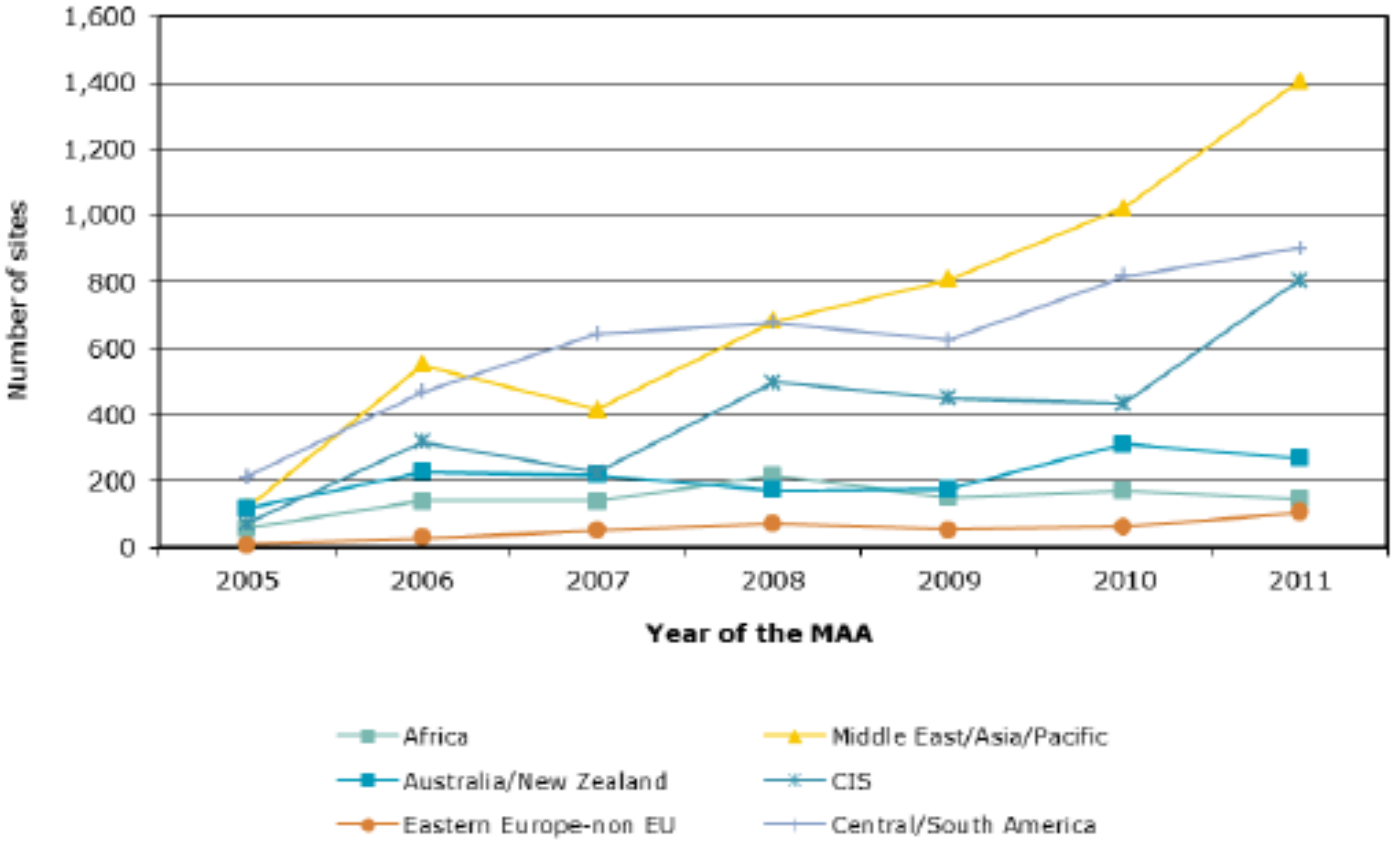
Investigator Sites per Region

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



Investigator Sites per ROW sub-Regions

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



Agency EMA/INS/GCP/676319/2012

What could threaten Europe's future?

Disadvantages

- Population fragmented across multiple countries
  – inefficiency in cost, time and manpower
- Western Europe high cost region
- Multiple regulatory approvals needed:
  – Lack of harmonised central process
  – Other approvals needed eg (Radiology board, Biobank Law)
  – Bureaucratic procedures
- Strict data protection legislation (eg Italy, Germany)
- Protracted site contract negotiation
- High proportion of saturated sites

What could threaten Europe's future?

Disadvantages

- Pharmaceutical pricing pressures and market dynamics
- Perceived economic instability of 'Euro zone'
- Shift of sponsor decision making to North America
- Attitude - history of failing to value or encourage Clinical research – particularly Western Europe

What does Europe offer?

- **Flexibility:**
  - Variety of healthcare systems
  - Variety of treatment & referral pathways
  - Availability of treated and treatment naïve patients
  - Both low and high cost centres for Clinical Research

- **Clinical research practise pedigree**
  - Key player in development of GCP guidelines
  - Most European countries have conducted trials to GCP standards since early to mid 1990s
  - GCP training is widely available for site staff

What does Europe offer?

- English widely spoken and *de facto* common language for clinical research
- New legislation and government action aimed at promoting clinical research eg Spain, UK, Romania
- R&D tax credits in growing number of countries
- Concentration of key opinion leaders
- Remains a key territory for:
  - ✓ Pharmaceutical sales
  - ✓ Pharmaceutical R&D investment
  - ✓ Pharmaceutical employment (700,000 with 116,000 in R&D)

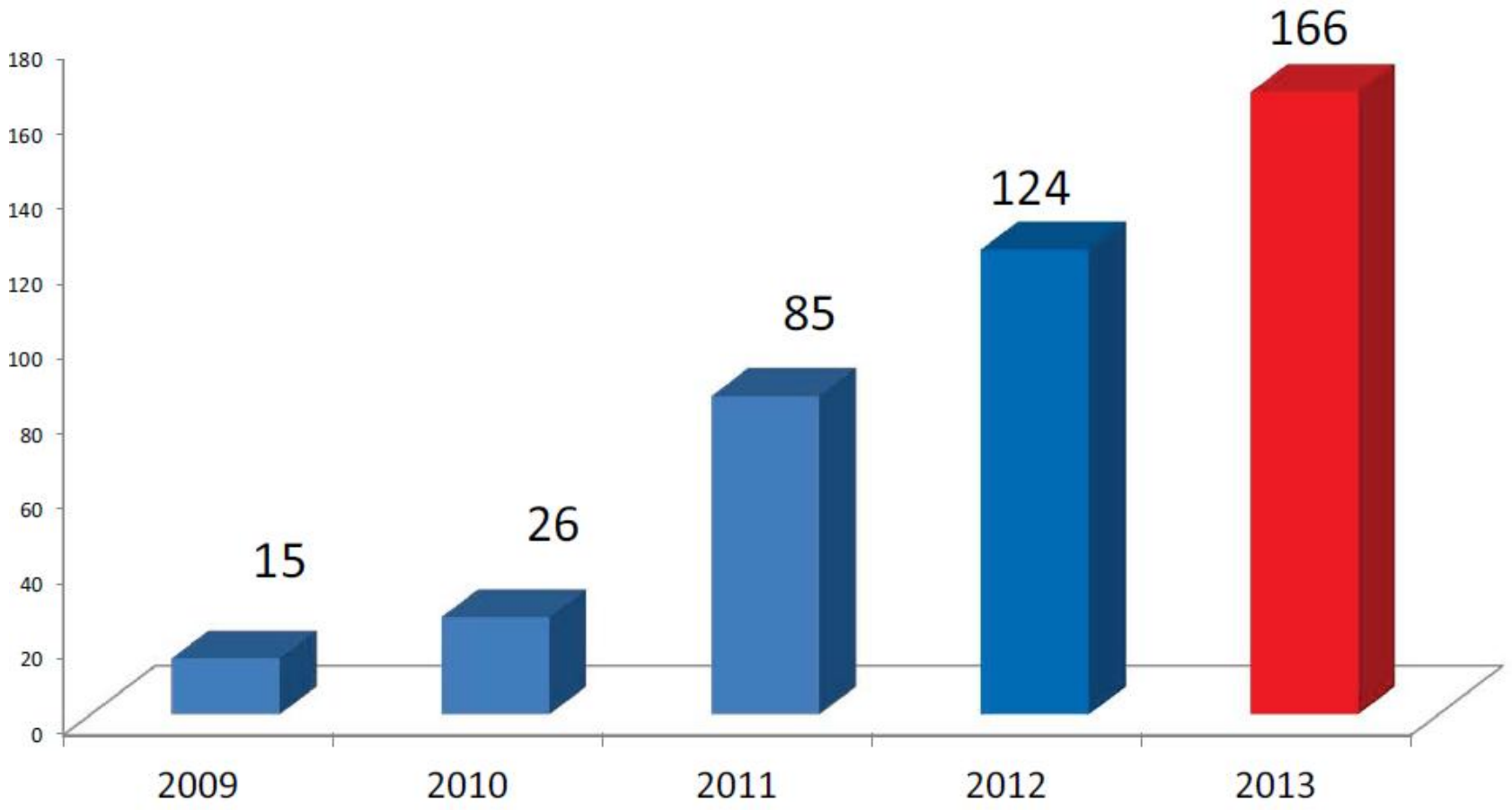
HMA
Heads of Medicines Agencies

Clinical Trials Facilitation Groups

Guidance document for sponsors for a Voluntary Harmonisation Procedure (VHP) for the assessment of multinational Clinical Trial Applications

Version 3

No. of VHPs per submission year



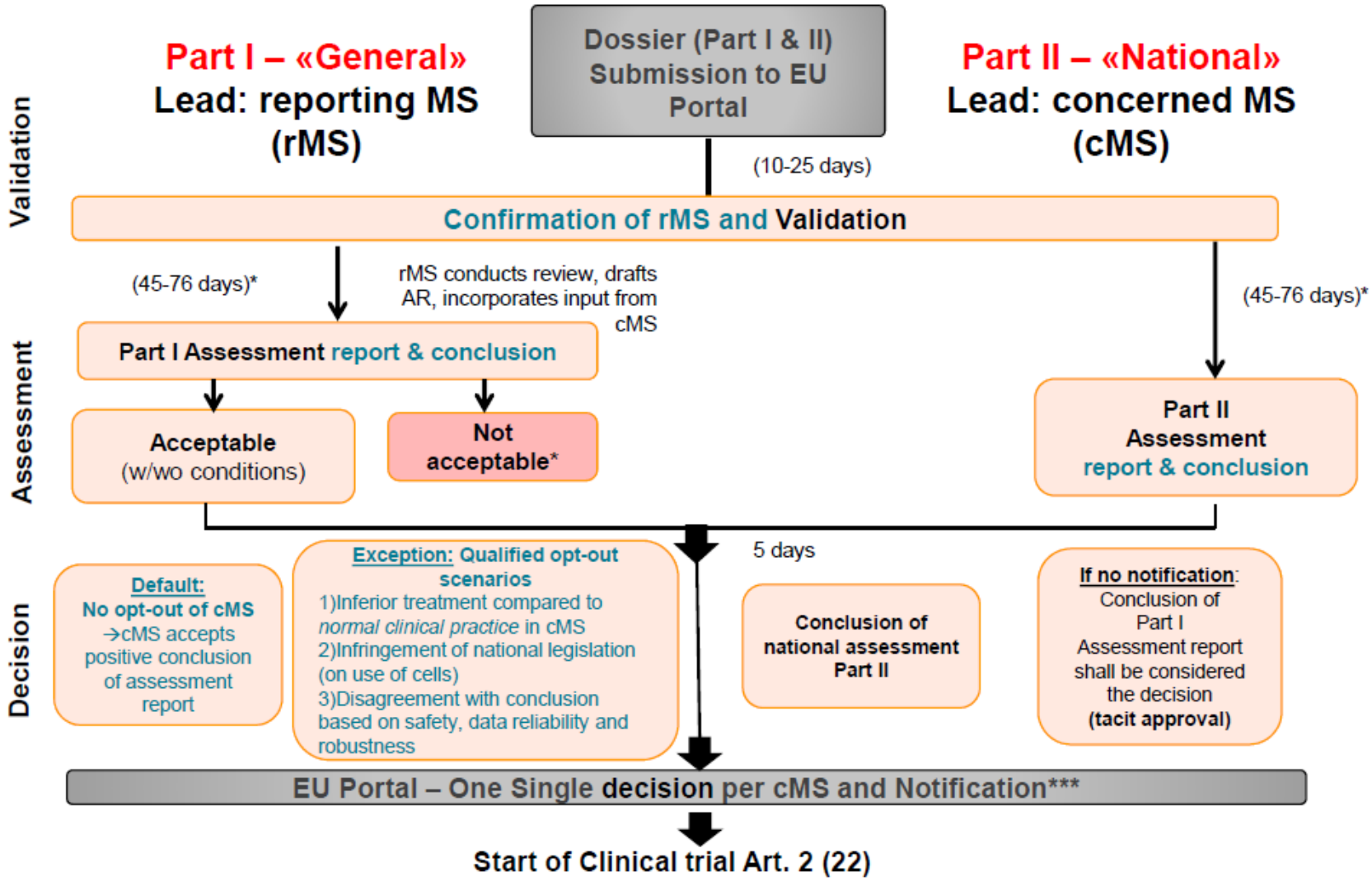
Times for a VHP Decision

	Days
mean time from start VHP until the end (without open / withdrawn, Christmas special and accelerated VHPs but including the time for response to GNA for Sponsors)	53,1
Minimum in days	0
Maximum in days	75
STD in days	13,2

New European Clinical Research Regulation Timelines

- Legislative text approved: 20 Dec 2013
- Vote in EU Parliament: 2-3 April 2014
- Health Council approval: 2-3 Jun 2014 (tbc)
- Entry into force: 20th day after publication in
- Official Journal of the European Union
- Application
  - 6 months after functionality of EU portal, but
  - No earlier than 2 years after publication

CT Authorisation Concept (simplified)



Presented by Nick Sykes at DIA Vienna 2014

UK initiative

UK clinical research network restructures as trial numbers climb

By Zachary Brennan, 09-Apr-2014

Related topics: Phase I-II, Phase III-IV, Clinical Development

The National Institute for Health Research (NIHR) Clinical Research Network, which provides more than £284m ($475m) a year to support the delivery of clinical research studies, has reconfigured to become 15 local clinical research networks across England.

European Clinical Research Infrastructures Network (ECRIN)

ECRIN is a sustainable, not-for-profit infrastructure supporting multinational clinical research projects in Europe.
ECRIN provides information, consulting and services to investigators and sponsors in the preparation and in the conduct of multinational clinical studies, for any category of clinical research and in any disease area.
Relevant for investigator-initiated or small and medium enterprise-sponsored clinical trials, and for clinical research on rare diseases where international cooperation is a key success factor.
ECRIN is based on the connection of coordinating centres for national networks of clinical research centres and clinical trials units, able to provide support and services to multinational clinical research.
Relevant tools for clinical researchers involved in multinational clinical trials are available on the website.
http://www.ecrin.org/

Turkey initiative

	Regulations
1. **Basic, Clinical Research Competency and Services Export**	1. Government adoption of a central research policy on life sciences in alignment with the strategy put forth by the Turkish Pharmaceutical Industry 2. Developing a road map for life science clusters 3. Implementing clinical research regulations in order to improve Turkey's competitive position

4. Increasing the variety of R&D financing resources to encourage & support an increase in life sciences R&D
5. Strengthening collaboration between universities and pharmaceutical industry
6. Developing infrastructure to motivate & improve the level of research of universities and research hospitals, and to enable the integration of this research within global R&D networks
7. Standardizing clinical trials procedures to match international standards

Action Plan
Basic and Clinical Research

6. Developing infrastructure to motivate & improve the level of research of universities and research hospitals, and to enable the integration of this research within global R&D networks

Actions	Rel. Stakeholder	Follow-up Ind.	Duration
6.1. Develop a road map aimed at integrating a qualified labor force in Turkey into global R&D studies **a.** Assess research capabilities & interests of Turkish scientists & Turkish expatriates scientists, and implement mechanism for continuous monitoring **b.** Organize workshops aimed at developing or enhancing collaboration with Turkish scientists in successful R&D centers around the world	SI, PC, NGO, MoSIT, CoHE, Univ.	Taking inventory of scientists and integration of them into a database. Number of workshops organized	2012 -2014

Members of TransCelerate BioPharma Inc.: the industry move

Objectives of TransCelerate BioPharma Inc.

Our Vision, Mission and Core Values

Launched in September 2012, TransCelerate Biopharma Inc. aims to simplify and accelerating the delivery of innovative medicines to patients. With so much progress and so much future opportunity, we have continued to refine our focus. The new statements below reflect our organization's continued commitment:

Our Vision

To improve the health of people around the world by accelerating and simplifying the research and development of innovative new therapies.

Our Mission

To collaborate across the global biopharmaceutical R&D community to identify, prioritize, design and facilitate implementation of solutions designed to drive the efficient, effective and high quality delivery of new medicines.

Our Core Values

Quality
Transparency & Openness
Trust & Integrity
Collaboration
Courage

EUCRO
European CRO Fede

What does this tell us?

- Although numbers of trials are falling globally, CRO revenues are increasing probably due to :
  – CROs conducting a larger proportion of studies
  – Cost of trials is increasing
  – Probably both size and complexity of studies increasing
- North America was decreasing in share of number of trials and revenue BUT has seen an uptick over past 18 months
- European share has at best remained flat but decreased in both measures over past 18 months

What does Central and Eastern Europe have to offer?

- Availability of treatment naïve subjects in some country
- Centralised healthcare systems with concentrated populations of patients
- Faster recruitment rates with less mobile patients
- Relatively high proportion of medically qualified monitoring staff
- Investigators and site staff are eager to participate and more compliant with protocol and GCP
- The high regard for doctors in society translates into patients who are more compliant with study protocols and taking medication.
- Patient treatment in a clinical trial is often superior to local standard of care which leads to high enrolment and patient compliance.

What hurdles does Central and Eastern Europe still have to overcome?

- Volatile legislative environment eg Russia, Turkey, Bulgaria (although not just CEE eg Italy, Greece, Middle East)
- Site contracts needed prior to regulatory review eg Bulgaria, (Poland)
- Importation/Exportation challenges
- Perception of 'non-western' business practises or relationships
- Variability in infrastructure and facilities at investigator sites
- Site Quality?

Summary and Conclusions

Positive aspects

- Crisis has impacted investments in R&D, but the trend has changed
- Europe is the second market of the world
- Europe has a population of over 500 millions
- New legislation has been approved

Negative aspects

- New R&D investments may be directed to Asia Pacific
- Europe is fragmented (still many different rules in many areas)
- MSs are and will demonstrate different speed for approvals
- New legislation will take 2 years to be implemented

Summary and Conclusions

Ideally, all stakeholders should contribute:

- EU parliament representatives
- Regulatory Bodies
- Academia
- Ethics Committees
- Pharmaceutical Industry
- Contract Research Organizations
- Patients Associations
- Non- profit Research Consortia
- Hospitals-Universities Administrations
- Who ever else is involved

A permanent Working Group should be set up

Thank you

Very Much

for your attention

Dziękuję bardzo za uwagę

Stefano Marini

Acknowledgment:
part of this presentation is based on slides prepared by
Roger Newbery - VP CM EMEA, PPD

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