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SCIENCE MEDICINES HEALTH

GMP Supervision of Medicines Manufacturers in the European Union

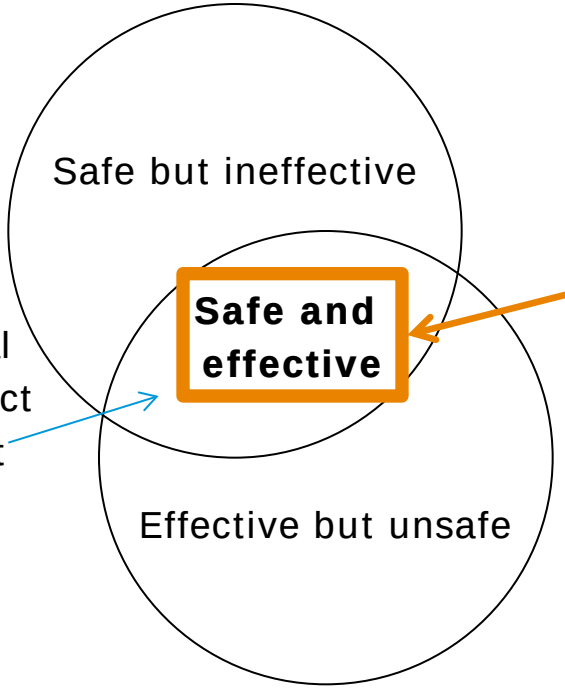
A System of Equivalent Member States and a Coordinating Agency

The EU medicines regulatory system and the European Medicines Agency:
an introduction for international regulators and non-governmental organisations

Brendan Cuddy, Head of Manufacturing and Quality Compliance

An agency of the European Union

Quality, Safety and Efficacy



If safety/clinical studies are correct its **Quality** that defines this boundary

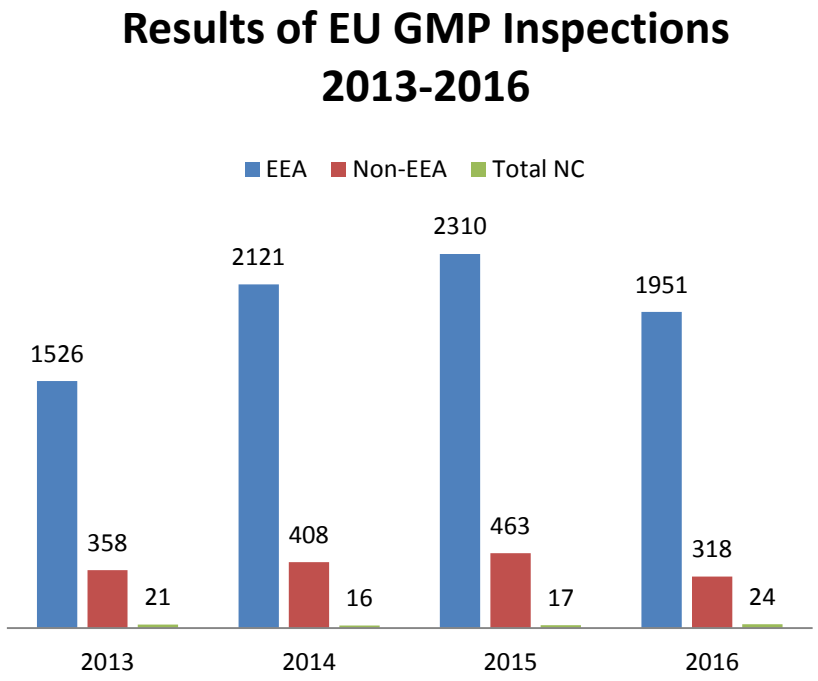
...and its **GMP** that keeps us here...

Guiding Principles

Any medicine manufacturer, no matter where it is located, must comply with GMP if the products manufactured are supplied to the EU

Any medicine manufacturer located in the EU must comply with GMP no matter where the medicines are supplied to.

- Medicines for human use (and their active substances)
- Medicines for veterinary use (and their active substances)
- IMPs (used in clinical trials)



The EU System for GMP Supervision of Manufacturers

A single system throughout all the EU Member States

2 pillars

- Authorisation/registration of operators in the supply chain
- Inspection of those operators to ensure compliance with legal requirements, including compliance with GMP and the requirements in the MA or CTA
- Formal recognition of each others inspections set down in EU law.

Harmonisation achieved through:

- Same legislation
- Same GMP guide
- Same quality manual for inspectorates / procedures
- A common forum
  - The GMP/GDP Inspectors Working Group is a group of senior inspectors appointed by all the EEA competent authorities which meets at EMA premises four times a year
- Joint Audit Programme

EudraLex Vol 4: Today

Principles and Guidelines of GMP
Directives 2003/94/EC and 91/412/EEC

Principles of GMP for Active Substances
Regulation 1252/2014

EU GMP Guide Part 1
Detailed Guidelines for Medicinal Products

EU GMP Guide Part II
Detailed Guidelines for Active substances

Directives 2001/83(2)
Manufacturing Authorisations, QPs and Registration of API manufacturers

Supplementary Guidelines
Annex 1 to 19 (no 18 or 20)

EU GMP Guide Part III
Miscellaneous GMP-related guidance

EudraLex Vol 4: Coming Soon

Principles and Guidelines of GMP
New Directive (Marketed products) and 91/412/EEC

Principles of GMP for Active Substances
Regulation 1252/2014

Principles and Guidelines of GMP
New Regulation (IMPs)

EU GMP Guide Part 1
Detailed Guidelines for Medicinal Products

EU GMP Guide Part II
Detailed Guidelines for Active substances

GMP guidelines for IMPs

Directives 2001/83(2)
Manufacturing Authorisations, QPs and
Registration of API manufacturers

Regulation 1394/2007
ATMPs

Supplementary Guidelines
Annex 1 to 19 (no *13*,18 or 20)

GMP guidelines for ATMPs and ATIMPs

EU GMP Guide Part III
Miscellaneous GMP-related guidance

Manufacturers and Importers of Finished (Drug) Product

Manufacturers and Importers in the EU need to be authorised to carry out their activities

- (Manufacturing/Importation Authorisation (MIA) only granted after inspection
- Applies to IMPs manufacturers

All finished products manufacturers and importers are regularly inspected by an EU authority, unless a Mutual Recognition Agreement is in place

- Irrespective if the site is in or outside of the EU
- Frequency of inspection is based on risk

Manufacturers and Importers of Active (Drug) Substance

Manufacturers and Importers in the EU need to be registered with the National Competent Authority of the Member State where they are located

- Applies to IMPs manufacturers

Inspection of active substance manufacturers in case of suspicion of non-compliance

- Responsibility for using active substance manufactured according to GMP is with the Manufacturing Authorisation Holder (finished product manufacturer or importer)
- Qualified Person declaration in Marketing Authorisation dossiers (based on audit)

Qualified Person

The QP has an important role in the EU system for GMP supervision

- Full time QP in order to obtain MIA (finished products manufacturers/importers)
- Takes responsibility for (among other things)
  - GMP compliance (both finished product and active substance)
  - Compliance with Marketing Authorisation requirements
- Every batch on the EU market is certified by a QP based in the EU before it can be released for market
- EU Member States are empowered to take administrative and disciplinary measures against QPs if they have failed to fulfil their obligations

GMP certificates and EudraGMDP

EudraGMDP is a database which contains (non-exhaustive list) public information on:

- manufacturing/import authorisations (MIA)
- GMP Certificates
- GMP Statements of non-compliance (SNC)

MIA and GMP Certificates uploaded directly by EU National Competent Authorities (NCAs)

EU NCAs can be contacted for clarifications

Allows to verify the GMP status of the manufacturing sites

http://eudragmdp.ema.europa.eu/

Welcome to EudraGMDP

Directives 2004/27/EC on human medicinal products and 2004/28/EC on veterinary medicinal products introduce the legal framework for the Community database.

The concept of a European Inspections database is included in the above specified legislation to provide EEA National Competent Authorities and the European Medicines Agency (EMA) with an overview of the status of pharmaceutical manufacturers. The legislation provides for an electronic tool containing complete information on all pharmaceutical manufacturers. This includes information on Manufacturing and Importation Authorisations (MIA) and Good Manufacturing Practice (GMP) Certificates for authorised sites in the EEA and information on GMP certificates for manufacturers in third countries.

Compliance with Good Manufacturing Practice:

A certificate of Good Manufacturing Practice (GMP) is issued to a manufacturer by the national competent authority that carried out an inspection if the outcome of the inspection confirms that the manufacturer complies with the principles of Good Manufacturing Practice, as provided by European Union legislation. If the outcome of the inspection is that the manufacturer does not comply a statement of non-compliance may be entered into EudraGMDP. Certificates and statements of non-compliance may be issued to manufacturers of medicinal products and manufacturers of active substances located inside and outside of the European Union.

Manufacturing and Importation Authorisation:

Manufacture of medicinal products in the EU or importation from a third country is subject to the holding of a Manufacturing and Importation Authorisation. The National Competent Authority of the Member State in which the manufacturer or importer operates issues these authorisations.

Compliance with Good Distribution Practice:

A certificate of Good Distribution Practice (GDP) is issued to a wholesale distributor by the national competent authority that carried out an inspection if the outcome of the inspection confirms that the wholesale distributor complies with Good Distribution Practice, as provided by European Union legislation. If the outcome of the inspection is that the wholesale Distributor does not comply a statement of non-compliance may be entered into EudraGMDP. GDP certificates and statements of non-compliance may be issued to wholesale distributors of medicinal products and distributors of active substances.

Wholesale Distribution Authorisation:

The wholesale distribution of medicinal products is subject to the holding of a Wholesale Distribution Authorisation. The National Competent Authority of the Member State in which the wholesale distributor operates these authorisations.

Registration of Active Substance manufacturers, Importers and Distributors:

Manufacturers, importers and distributors of active substances are required to register their activities with the National Competent Authority of the Member State in which they operate.

The Role of EMA

The Agency has a coordinating role for GMP inspections of manufacturing sites for Centrally Authorised Products (CAPs) or as part of a referral procedure

Key role on e.g.:

- Ensuring common interpretation of EU GMP requirements and related technical issues
- Developing EU-wide procedures on GMP inspections and related activities
- Facilitating cooperation between Member States for inspections of manufacturers in third countries
- Developing and maintaining the EudraGMDP database
- Sampling and Testing planning for CAPs
- Coordination of the actions at EU level in case of Quality Defects

Quality Defects & Rapid Alert System

- Rapid Alert: transmission of information when urgent action is required to protect public or animal health e.g. recall of defective/falsified products, draft SNC
- Circulated to Member States, MRA partners, PIC/S, European Commission, international organisations e.g. WHO
- Details in the Compilation of Community Procedures (http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004706.pdf)

Any questions?

Further information

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Web resources

European Medicines Agency (EMA) website

http://www.ema.europa.eu/ema/

Notice to Applicants (EudraLex vol. 2 and 6)

A document aimed at applicants for Marketing Authorization in the EU, where the various procedures for Marketing Authorization and the structure of the dossier are explained in detail.

http://ec.europa.eu/health/documents/eudralex/vol-2/index_en.htm

EudraLex page in the European Commission website

This is the Commission webpage where all the pharmaceutical legislation applicable in the EU can be found.

http://ec.europa.eu/health/documents/eudralex/index_en.htm

Scientific guideline page on the EMA website

All the guidelines in use for assessment of Marketing Authorisation applications can be consulted here.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000043.jsp&mid=WC0b01ac058002402cb

Web resources

EU GMP guide (EudraLex vol. 4)

http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm

EudraGMDP database

http://eudragmdp.ema.europa.eu/inspections/displayWelcome.do;jsessionid=fgh3S2RTppG2tHZZQ6GSJrYsDhMP0lR1YGfzwVyyxJtcQFt6hZDf!899440497

QP declaration in the EMA website

Webpage on the EMA website where a template and guidance on the QP declaration are published.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000696.jsp&mid=

Joint Audit Program page in the EMA website

Extensive information on the JAP is published here.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000160.jsp&mid=WC0b01ac0580029750

Web resources

Compilation of Community Procedure on Inspections and Exchange of Information

The Compilation is a collection of harmonized procedures and templates for EU inspectorates, covering e.g. GMP and GDP inspections, dealing with Quality Defects, recalls and non-compliance.

http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004706.pdf

GMP/GDP Inspectors Working Group page in the EMA website

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000161.jsp&mid=WC0b01ac05800296c9

PIC/S website

https://www.picscheme.org/v

Mutual Recognition Agreements page in the EMA website

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000248.jsp&mid=WC0b01ac058005f8ac

Web resources

EMA publication: GMP Oversight of Medicines Manufacturers in the European Union (2015)

http://www.pda.org/pda-letter-portal/archives/full-article/gmp-oversight-of-medicines-manufacturers-in-the-european-union

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Good Clinical Practice (GCP) and Good Laboratory Practice (GLP) supervision and inspections

The EU medicines regulatory system and the European Medicines Agency:
an introduction for international regulators and non-governmental organisations

Presented by Sophia Mylona on 19 September 2017
Scientific Administrator – Clinical and Non-Clinical Compliance, EMA

An agency of the European Union

EU GCP/GLP Regulatory Framework

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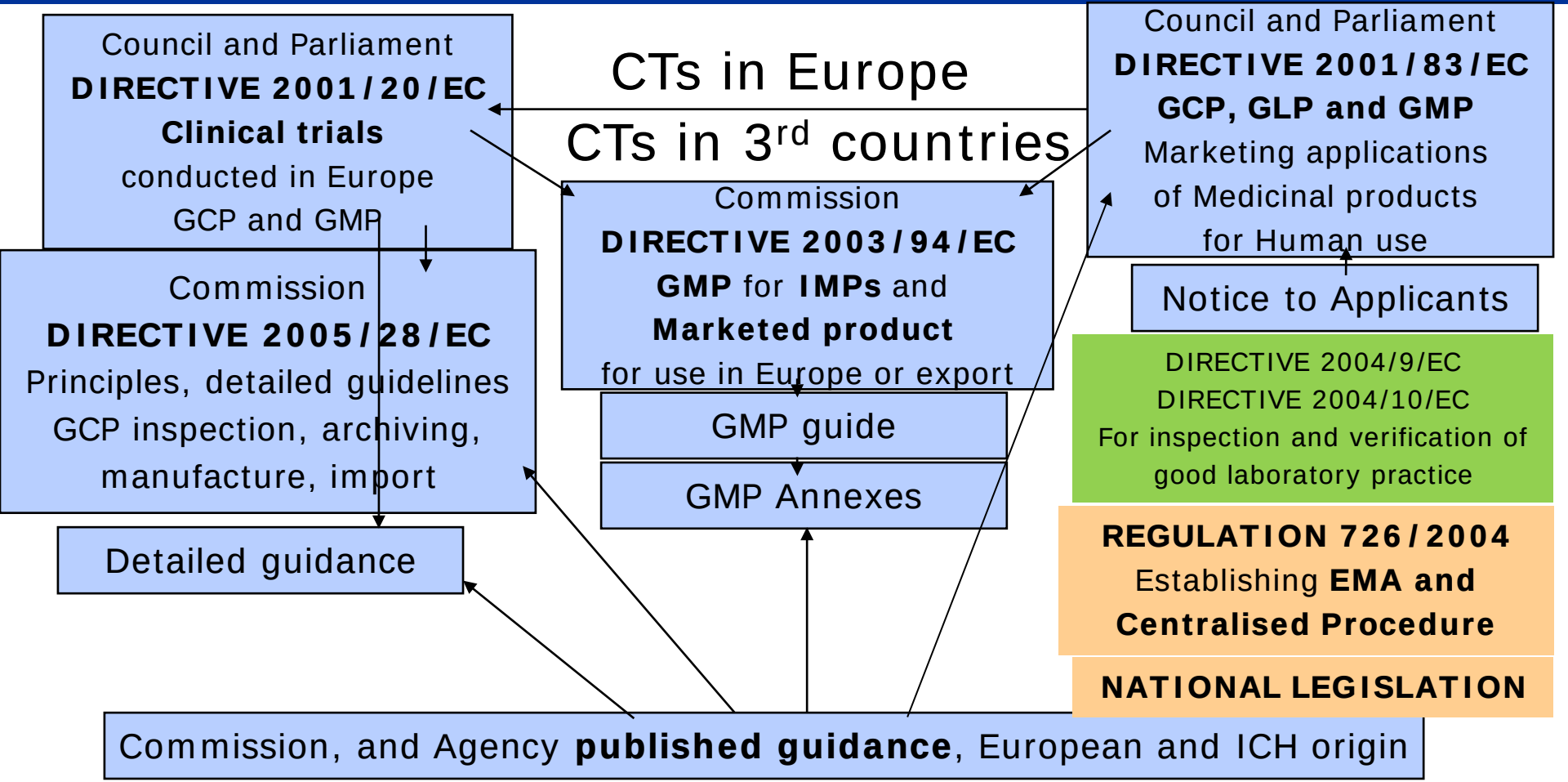

GCP inspections in the EU – current legal framework

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Directive 2001/20/EC

GCP Directive 2005/28/EC

repealed by

new Clinical Trial Regulation EU no 536/2014

For GCP inspections conducted in the context of a Marketing Authorisation procedure

Directive 2001/83/EC

REGULATION 726/2004

EudraLex - Volume 10 - Clinical trials guidelines

GCP Inspections conducted by EU inspectors

- *Article 2 of Directive 2001/20/EC Definitions 2(l) inspection*

*"**Inspection:** the act by a **competent authority** of conducting an **official review** of, documents, facilities, records, quality assurance arrangements, and **any other resources** that are deemed by the competent authority to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's site and/or contract research organisation's facilities, **or at other establishments** which the competent authority sees fit to inspect."*

- *Article 11* EudraCT Database (include inspection records)
- *Article 15* Verification of compliance of IMPs with GCP and GMP

Legal Basis for GCP inspections

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Directive 2001/20/EC: Article 15

• Member States (MS) shall appoint inspectors to inspect sites concerned by any clinical trial conducted to verify compliance with the provisions on good clinical and manufacturing practice.

Directive 2005/28/EC: Articles 21 – 30

• Covers requirements for inspectors, the team and inspection procedures.

Regulation (EC) No 726/2004: Article 57(i)

• The Agency shall coordinate the verification of compliance with the principles of good manufacturing practice, good laboratory practice, good clinical practice and the verification of compliance with pharmacovigilance obligations.

Inspections coordinated by EMA vs National inspections

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Inspections coordinated by EMA:

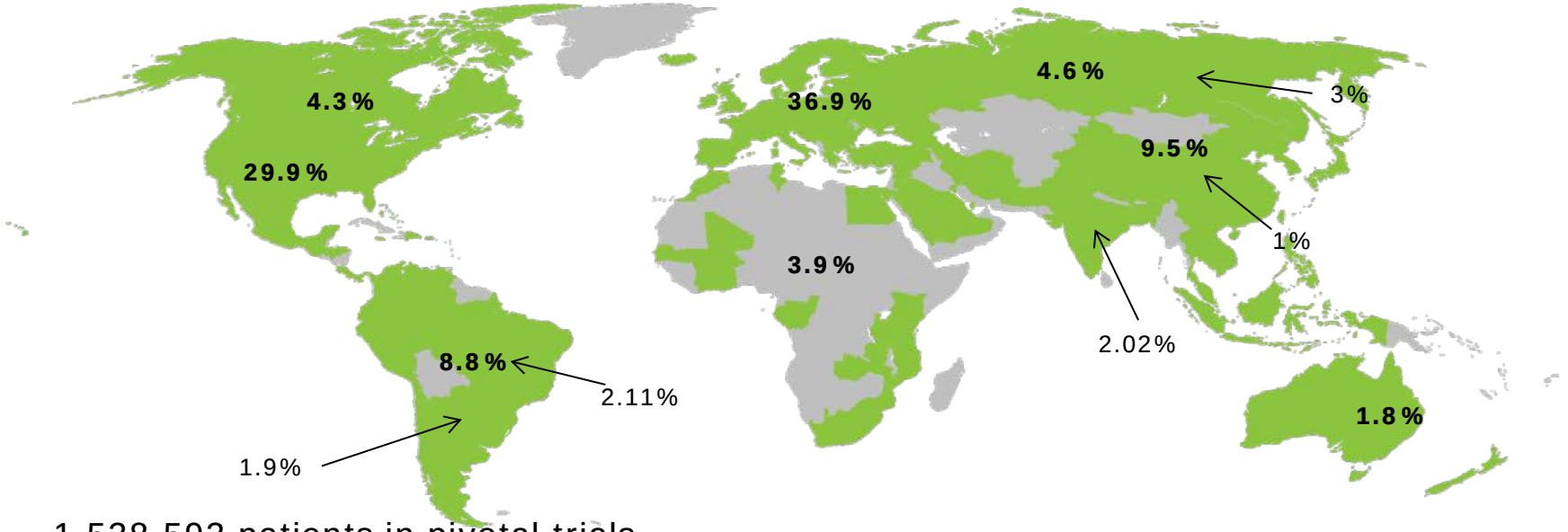
- Part of Marketing Authorisation Applications (MAA) for centralised products
- Most clinical trials have been completed
- Requested by CHMP
- Conducted by EU inspectors on behalf of EMA
- EMA website: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000140.jsp&mid=WC0b01ac05800296c6

National inspections:

- Part of a national MAA
- Oversight of clinical trials conducted in Member State territory
- National inspection programmes
- Own inspectors

- EudraLex Volume 10, Chapter IV: http://ec.europa.eu/health/documents/eudralex/vol-10/

Patient recruitment in Clinical Trials included in Marketing Authorisation Applications submitted to EMA (2005 and 2015)

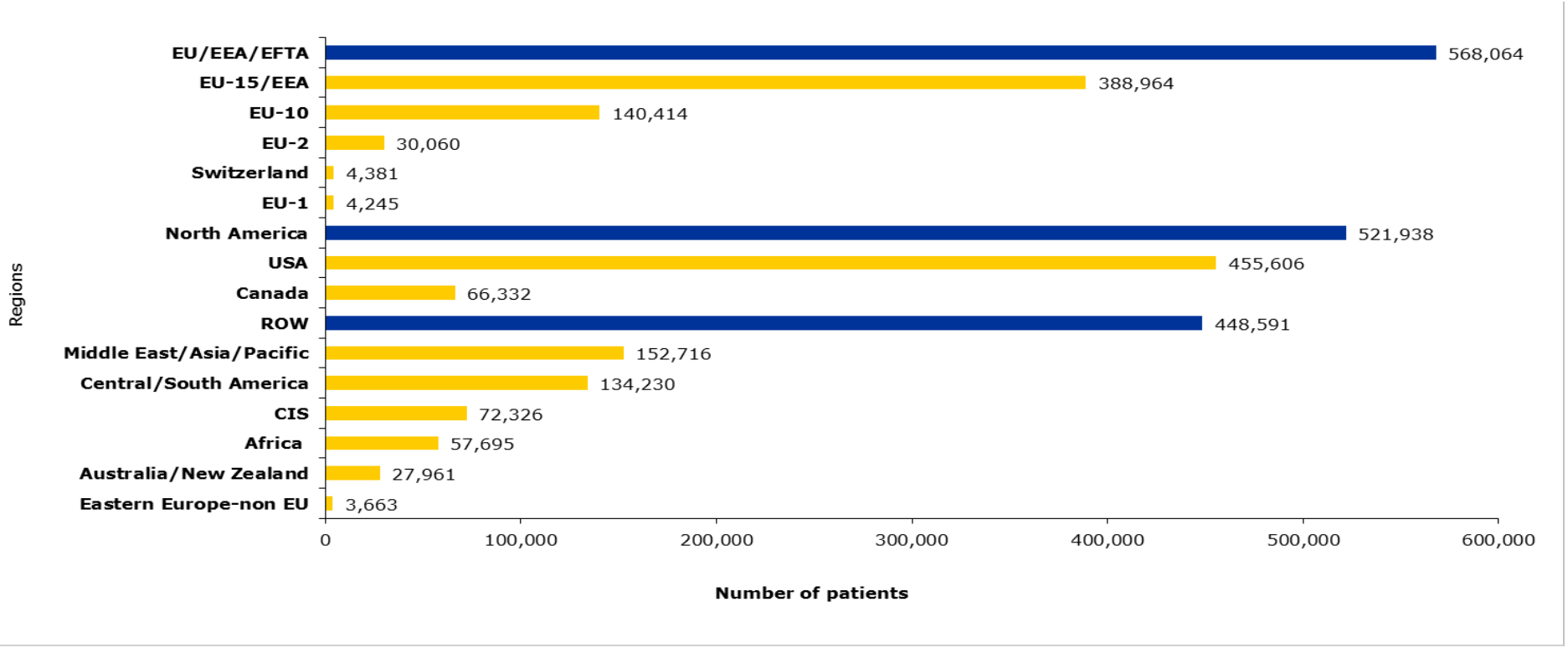


1,538,593 patients in pivotal trials

138,312 clinical trial sites in 107 countries

1,298 including new Marketing authorisation applications, line extensions and variations

Number of patients in pivotal trials (2005-2015)



GCP Inspections coordinated by EMA

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All clinical trials that are part of a marketing application dossier can be subject to a GCP inspection. Not all applications would necessarily give rise to a GCP inspection

Routine inspections

Routine GCP inspections are inspections carried out as a routine surveillance of GCP compliance, in the absence of a specific trigger or concern.

Suggested by the Inspection service

Triggered inspections

These are triggered inspections, which are requested by assessors because there is a concern about deviation from GCP in relation to the overall trial conduct or to the conduct at a particular site.

Suggested by Rapporters/Assessors

*Priority of triggered inspections **vs.** routine inspections*

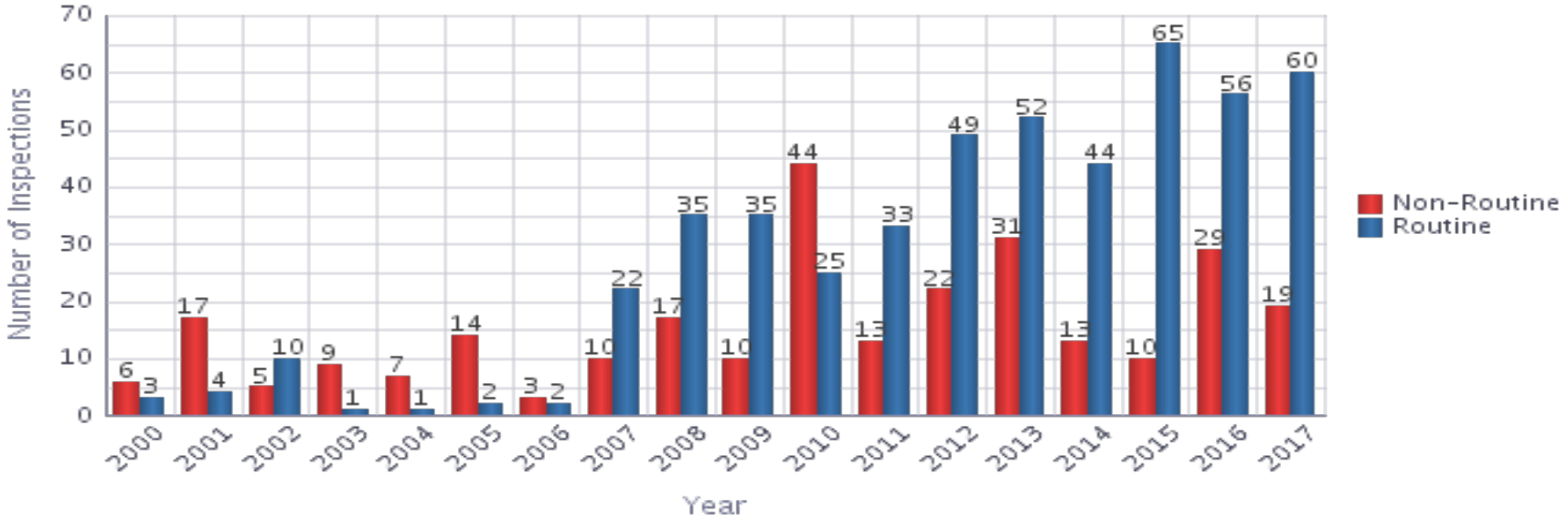
How does the EMA/CHMP select the trials and sites to be inspected?

Points to consider for assessors, inspectors and EMA inspection coordinators on the identification of triggers for the selection of applications for “routine” and/or “for cause” inspections, their investigation and scope of such inspections

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/08/WC500148220.pdf

Inspections coordinated by EMA - Overall number of sites inspected by type of inspection *(Routine vs triggered inspections) per year (period 2004-2017*)*

(**data up to 10/08/17*)- ***total 778 sites inspected***



CHMP Requested Inspections

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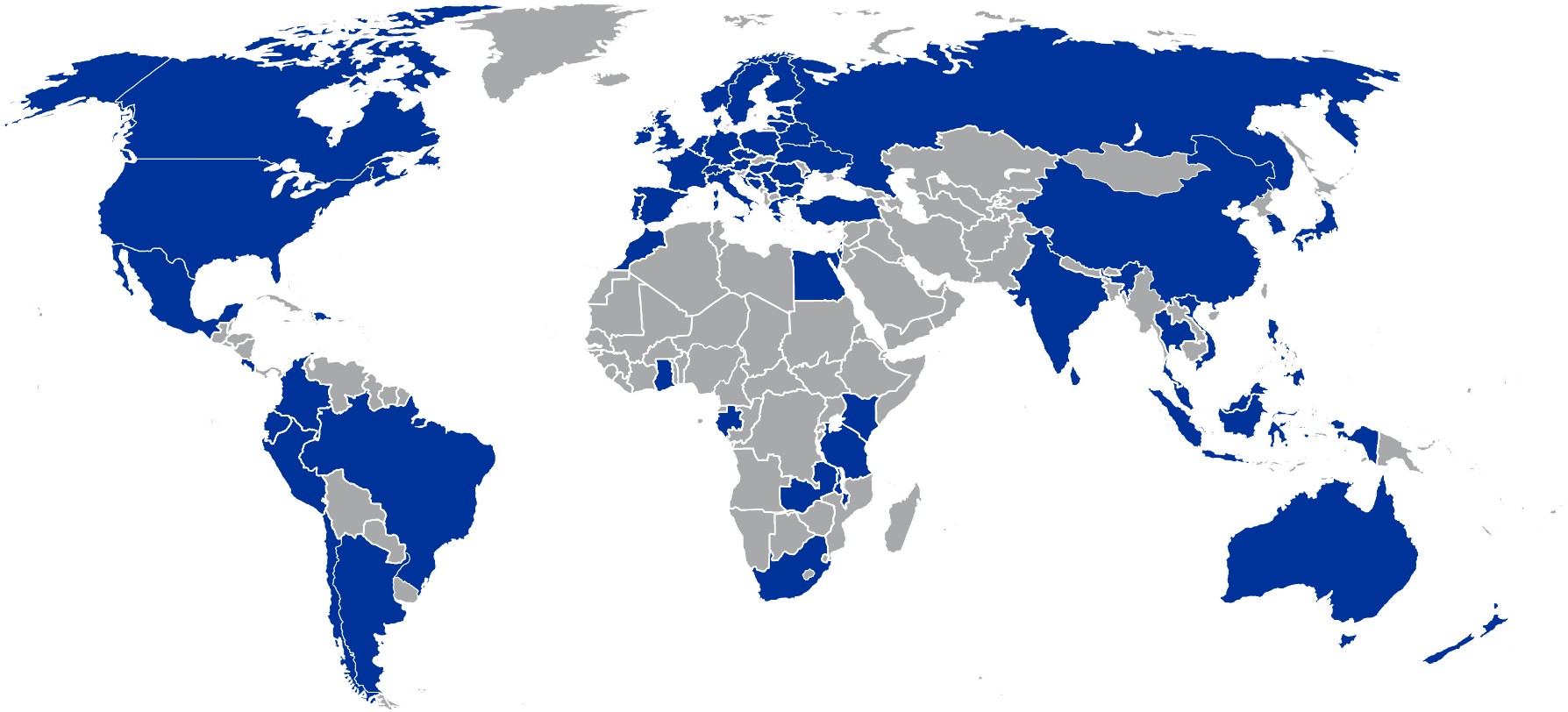

GCP inspections coordinated by EMA
Number of sites inspected by year and region

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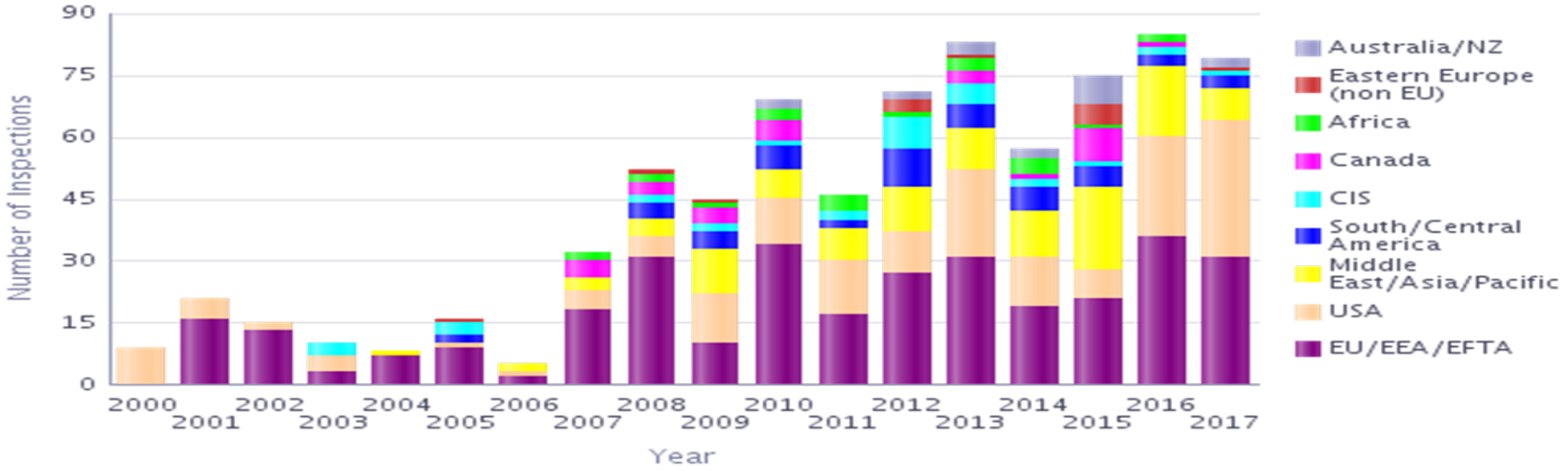

	Number of Inspections/year																	
Region	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
EU/EEA/EFTA		16	13	3	7	9	2	18	31	10	34	17	27	31	19	21	36	31
USA	9	5	2	4		1	1	5	5	12	11	13	10	21	12	7	24	33
Middle East/Asia/Pacific					1		2	3	4	11	7	8	11	10	11	20	17	8
South/Central America						2			4	4	6	2	9	6	6	5	3	3
CIS				3		3			2	2	1	2	8	5	2	1	2	1
Canada								4	3	4	5			3	1	8	1	
Africa								2	2	1	3	4	1	3	4	1	2	
Eastern Europe (non EU)						1			1	1			3	1		5		1
Australia/NZ											2		2	3	2	7		2
Grand Total	**9**	**21**	**15**	**10**	**8**	**16**	**5**	**32**	**52**	**45**	**69**	**46**	**71**	**83**	**57**	**75**	**85**	**79**

Inspection Report : Definition of inspection findings

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• **Critical**: Conditions, practices or processes that adversely affect the rights, safety or well-being of the subjects and/or the quality and integrity of data.

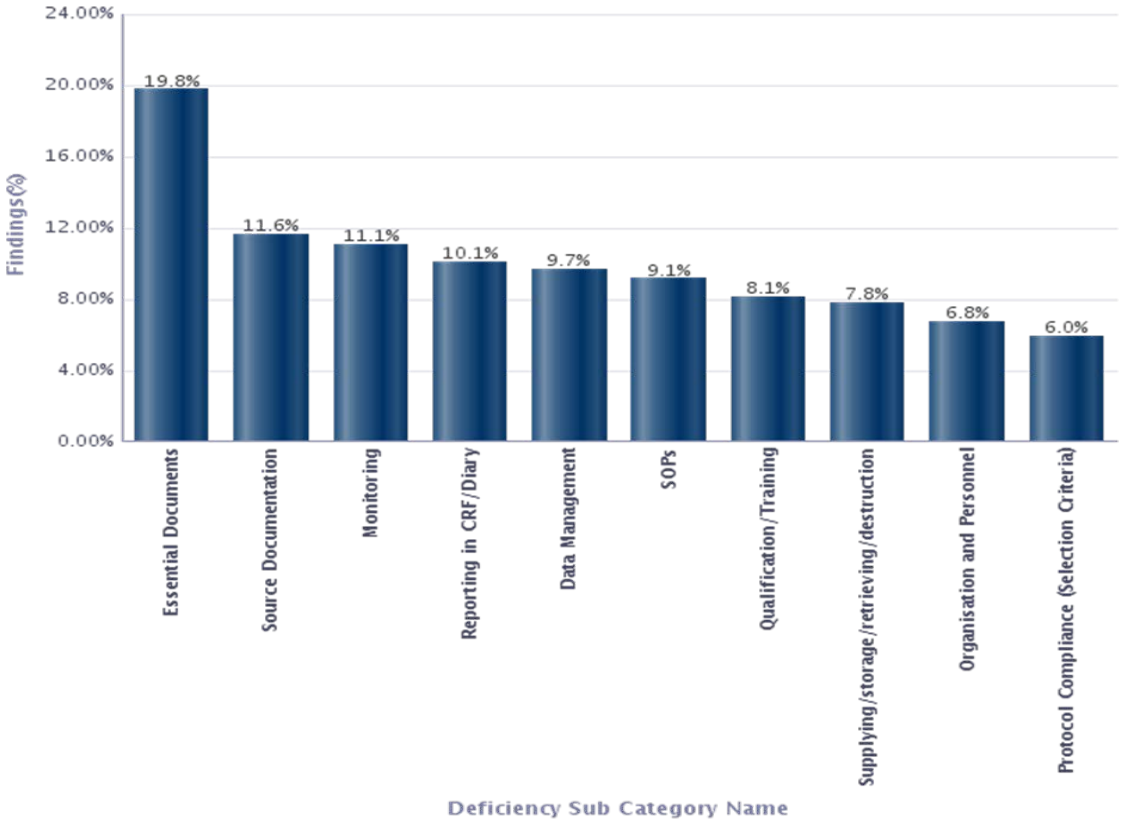
-Critical observations are considered totally unacceptable.

• **Major**: Conditions, practices or processes that might adversely affect the rights, safety or well-being of the subjects and/or the quality and integrity of data.

-Major observations are serious findings and are direct violations of GCP principles.

Minor: Conditions, practices or processes that would not be expected to adversely affect the right, safety or well-being of the subjects and/or the quality and integrity of data.

Ranking of the top 10 critical findings



Deficiency Sub Category Name	Findings	Findings (%)
Essential Documents	1,092	19.8%
Source Documentation	642	11.6%
Monitoring	611	11.1%
Reporting in CRF/Diary	556	10.1%
Data Management	535	9.7%
SOPs	505	9.1%
Qualification/Training	448	8.1%
Supplying/storage/retrieving/destruction	432	7.8%
Organisation and Personnel	374	6.8%
Protocol Compliance (Selection Criteria)	329	6.0%
Grand Total	**5,524**	**100.0%**

Points to consider on GCP inspection findings and the benefit-risk balance

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EMA document on points to be considered on GCP inspection findings

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/01/WC500137945.pdf

Three categories are used:*

- Inspection findings which are likely to influence the benefit-risk evaluation;
- Inspection findings which may influence the benefit-risk evaluation;
- Inspection findings which are less likely to influence the benefit-risk evaluation.

The potential **impact of the findings on the benefit-risk assessment should be analysed and discussed case by case**

** terminology used for the three categories is not to be viewed as a formal grading system*

Impact of GCP inspections in the decision making

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Possible consequences following a GCP inspection:

- Data accepted, no consequence
- Inspection of new sites / trials
- Rejection of data from selected site, re-analysis of remaining data
- Correction of data (e.g. re-monitoring), re-analysis, new clinical study report
- Rejection of the whole trial

➔ **Possible delay or rejection of the application**

Possible corrective / preventive actions (CAPA)

- Often too late for the trial itself, unless still ongoing
- CAPA may be needed for other trials performed at the same trial site / by the same sponsor or CRO
- Follow up of non compliance clear in the revised ICH E6 text (5.20.1)
- May require follow-up inspections of other trials

Pivotal non-clinical studies submitted in **Marketing Authorisation Applications** (MAAs) and **Clinical Trial Applications** (CTAs)*:*

- ***must be conducted in, or inspected by, a country that has implemented the Organisation for Economic Co-operation and Development (OECD) Mutual Acceptance of Data (MAD) system.***
- *Studies conducted at a facility located in a non-MAD adherent country may be accepted if the facility* ***has been subject to a full monitoring inspection conducted in the last three years by a monitoring authority from a country which is a signatory to the MAD agreement.***

Marketing Authorisation application – GLP information *(1)*

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- **The dossier should include a comment on the GLP status of the studies submitted in the application in the Marketing Authorisation dossier**
- ***Additional information to be provided by the Applicants (cover letter annexes):***

A summary table, listing the non-clinical studies and indicating for each study:

- study title /study code (Unique identifier assigned to the study)
- date of completion of the Final Report
- test facility and test sites in which the study was conducted
- complete address of the test facility (and test sites where applicable)
- **period in which the test facility(ies) and/or test site(s) was(were) used, indicating if in that period they were part of an European Union (EU) or an Organisation for Economic Co-operation and Development (OECD) Mutual Acceptance of Data (MAD) accepted GLP monitoring programme.**

Marketing Authorisation application – GLP information *(2)*

- The information provided is checked at the dossier validation time by the validation team (EMA).
- If data from non OECD MAD country(ies) are included in the dossier, this is flagged to EMA Committees and Inspections Department.
- Rapporteurs, non - clinical assessors and GLP inspectors are informed and requested to discuss further.
- The final decision on the need for a GLP audit is taken by the Committee for Medicinal Products for Human Use (CHMP).

The goal

- Protect the rights, integrity and well-being of patients
- Helping each other, building expertise and systems
- Using inspection findings as lessons learned to avoid repetition of mistakes
- Reducing duplication of effort
- Filling the gaps in the global network
- Ensure the quality of non-clinical and clinical trial data
- Ensure that decisions to authorise and use medicines are based on robust non-clinical and clinical trial data

Any questions?

Further information

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References

- EudraLex - Volume 1 - Pharmaceutical legislation for medicinal products for human use [https://ec.europa.eu/health/documents/eudralex/vol-1_en]
- EudraLex - Volume 10 Clinical trials guidelines [https://ec.europa.eu/health/documents/eudralex/vol-10_en]
- Annual report of activities of the EMA GCP inspectors working group for 2015, including more information on the findings detected, can be found at: [http://www.ema.europa.eu/docs/en_GB/document_library/Annual_report/2016/08/WC500211479.pdf]
- Clinical trials submitted in marketing-authorisation applications to the European Medicines Agency Overview of patient recruitment and the geographical location of investigator sites (Containing data from 2005 to 2011) [http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/12/WC500016819.pdf
- More information on GCP inspections coordinated by EMA can be found on EMA website: [http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000136.jsp&mid=WC0b01ac05800296c4]
- Points to consider on GCP inspection findings and benefit-risk http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/01/WC500137945.pdf
- Non-acceptability of replacement of pivotal clinical trials during the assessment of an application in the context of a marketing authorisation application in cases of GCP non-compliance http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/11/WC500
- Pre-submission guidance questions http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000023.jsp&mid=WC0b01ac0580022714

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Good Vigilance Practice (GVP) supervision and inspections

The EU medicines regulatory system and the European Medicines Agency:
an introduction for international regulators and non-governmental organisations

Presented by Sophia Mylona on 19 September 2017
Scientific Administrator – Clinical and Non-Clinical Compliance, EMA

An agency of the European Union

Table of content:

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Pharmacovigilance system

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- Pharmacovigilance system: a system used by the marketing authorisation holder (MAH) and by Member States to fulfil the tasks and responsibilities listed in Title IX of Directive 2001/83/EC and designed to monitor the safety of authorised medicinal products and detect any change to their risk-benefit balance.
- As part of the pharmacovigilance system, the marketing authorisation holder shall:

(a) have permanently and continuously at his disposal an appropriately **qualified person responsible for pharmacovigilance (QPPV);** The QPPV shall reside and operate in the Union and shall be responsible for the establishment and maintenance of the pharmacovigilance system.

(b) maintain and make available on request a **pharmacovigilance system master file;**

(c) operate a **risk management system for each medicinal product;**

Legal framework for PhV inspections

- **Art 111 (1)(d)** of **Directive 2001/83/EC** as amended by Directives 2010/84/EU and 2012/26/EU
- **Art 19(1)** of **Regulation (EC) No. 726/2004** as amended by Regulation (EU) No 1235/2010 and No 1027/2012 (for PhV inspections of CAPs)
- **Art 57(1)(d)** of **Regulation (EC) No. 726/2004** as amended by Regulation (EU) No 1235/2010 and No 1027/2012 (for PhV inspections of CAPs)

New requirements of 2012 PhV legislation affecting PhV inspections

PhV system master file (PSMF):

A detailed description of the pharmacovigilance system used by the marketing authorisation holder with respect to one or more authorised medicinal products. **Art 1(28e) of DIR 2001/83/EC**

Concept of the Supervisory Authority (SA) for CAPs

The Competent Authority of the Member State in which the pharmacovigilance system master file is located. **Article 18 (3) of Regulation (EC) No 726/2004**

Pre-authorization inspections

To examine the existing or proposed PhV system as it has been described by the applicant in support of the MA Application. **Article 19(1) of Regulation 726/2004 and IR 15(1)f**

Cooperation in the coordination of third country inspections

Member States and Agency cooperation in the coordination of third country inspections. **Art 111 of DIR 2001/83/EC**

EU Legislation and Guidance

- **Commission Implementing Regulation No 520/2012** of 19 June 2012 on the **performance** of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC
  - Legally binding act published by the European Commission
  - Details on the operational aspects for the new legislation

- **Guidelines on good pharmacovigilance practices (GVP)**:
  - GVP modules are practical measures to facilitate the performance of pharmacovigilance in accordance with the legislation (Art 108(a) of Directive 2001/83/EC)

Table of content:

EU procedures for marketing authorisation

Centralised Procedure (via EMA)

Mutual Recognition procedure

De-centralised Procedure

National Procedure

EMA

National Authorities

Good vigilance Practice (GVP) supervision and inspections

EU PhV Monitoring system of MAHs

- EU PhV inspectors conduct a variety of MAH pharmacovigilance system specific/product specific inspections that are **not** coordinated by EMA. This is valid for MAHs with **Nationally Authorised Products (NAPs) only** or MAHs with **Centrally Authorised Products (CAPs) + NAPs;**

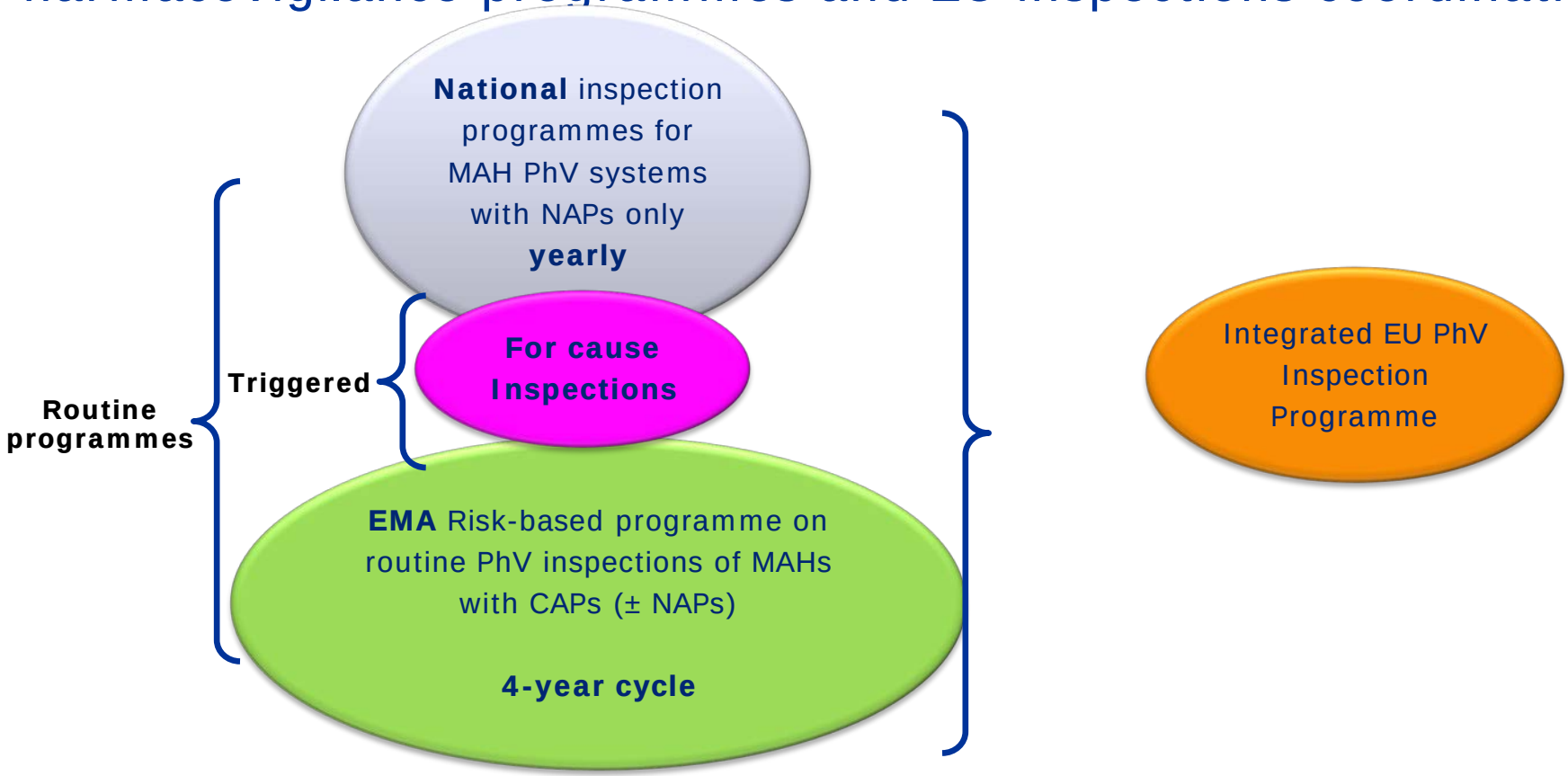
- Some of the Pharmacovigilance inspections of MAHs with CAPs are coordinated by EMA and are conducted by EU Member States on behalf of EMA (EMA does not have its own inspectors);

PhV inspections requested by CHMP and coordinated by EMA for CAPs

A small proportion of the inspections (routine/triggered) within the EMA risk-based programme is coordinated by EMA and requested by the **EMA Committees** (CHMP and PRAC). Selection is based on specific criteria :

- When global pharmacovigilance sites in third countries are inspected
- When additional sites within EU are identified for inspection and require joint Member State inspections
- In the case of a “for cause” inspection requested during assessment or following PRAC recommendation
- When the Member State supervisory authority prefers this route

Pharmacovigilance programmes and EU inspections coordination



Type of sites inspected during PhV inspections coordinated by EMA

- PSMF location
- QPPV location (if different)
- Global PhV site
- Local affiliate
- Licensing partner
- Subcontractor
- Other

The PhV Inspectors Working Group

- Year of establishment: 2008
- Frequency meetings: 4 times per year at EMA
- Remit: to focus on harmonisation and co-ordination of PhV-related activities at the European Union level
- Composition: **PhV Inspectors** of EEA countries
  + Observers from candidate accessing countries
  + Switzerland
- Objectives of the meetings:

o To discuss PhV inspections findings
o To develop guidance and procedures
o To share experience and views

Escalation of PhV inspections outcome to PRAC

- PRAC (Pharmacovigilance Risk Assessment Committee) created in 2012 according to Regulation (EC) No 726/2004 Art 56 (1)(aa)
- Deals with PhV related topics
- All the Inspection Reports for EMA PhV inspections are circulated to PRAC

- Discussion during **PRAC plenary meetings** in cases of detected critical/major findings as part of routine/triggered inspections of wide interest (EU level)
- More info in the Union Procedure:

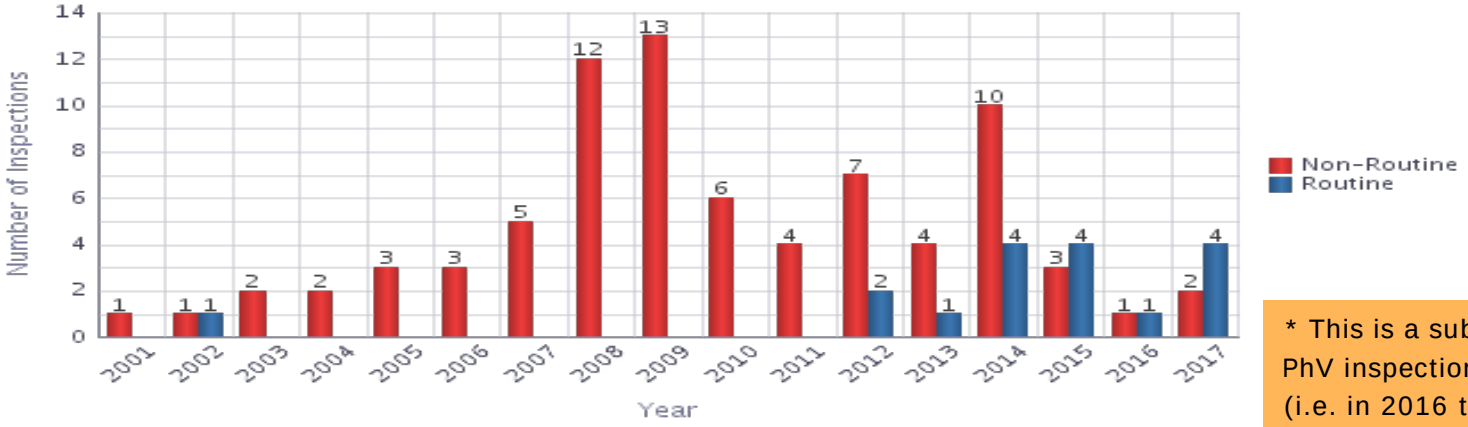
http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2014/06/WC500168519.pdf

Union Procedures on PhV inspections

- Coordination of EU pharmacovigilance inspections
- Preparation, conduct and reporting of EU pharmacovigilance inspections, including templates as appendices
- Management of pharmacovigilance inspection findings which may impact the robustness of the benefit-risk profile of the concerned medicinal products
- Sharing of pharmacovigilance inspection information
- Union recommendations on training and experience of inspectors performing pharmacovigilance inspections

Table of content:

Number of EMA coordinated conducted PhV inspections by type of inspection and year *(Jan 2001- Aug 2017)*



* This is a subset of the total number of PhV inspections conducted in EU/EEA (i.e. in 2016 the total was 217).

Request Type	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	**Total**
Non-Routine	1	1	2	2	3	3	5	12	13	6	4	7	4	10	3	1	2	**79**
Routine		1										2	1	4	4	1	4	**17**
	1	**2**	**2**	**2**	**3**	**3**	**5**	**12**	**13**	**6**	**4**	**9**	**5**	**14**	**7**	**2***	**6**	**96***

Top 5 Pharmacovigilance inspections findings-

- Adverse event expedited reporting, Individual Case Safety Reports (ICSRs), incl. electronic
- Quality management system
- Organisational structure
- Communication with National Competent Authorities (NCAs)
- QPPV functions

Table of content :

Sharing of information within the EU network on Pharmacovigilance inspections

Good Vigilance Practice (GVP) guidance Module III, section III C.1., states that the Agency and the EU Member States shall cooperate to facilitate the exchange of information on:

- **inspections planned and conducted** to optimise the inspection resources.
- the **scope of the inspections** in order to focus future inspections.
- the **outcome of the inspection**, in particular when MAH does not comply with the requirements laid down in legislation and relevant guidance.

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Session 7: Good Practice and Inspections

GMP, supervision of manufacturers and inspections and dealing with quality defects

GCP and GLP supervision and inspections

GVP supervision and inspections

Structure: 3 presentations followed by 20 minutes for exchange and discussion