



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

The EMA inspections process PhV Inspectors Working Group role and interaction with Stakeholders

AIFA Pharmacovigilance Symposium 2016

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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)



EU Legislation and Guidance

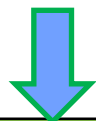


- [Commission Implementing Regulation No 520/2012](#) of 19 June 2012 on the **performance** of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC
 - Legally binding act published by the European Commission
 - Details on the operational aspects for the new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



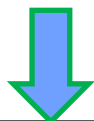
New requirements of 2012 PhV legislation directly affecting PhV inspections

**PhV
system
master
file (PSMF):**



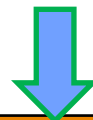
A detailed description of the pharmacovigilance system used by the marketing authorisation holder with respect to one or more authorised medicinal products. **Art 1(28e) of DIR 2001/83/EC**

**Concept of the
Supervisory
Authority (SA)
for CAPs**



Is 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-
authorisation
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**

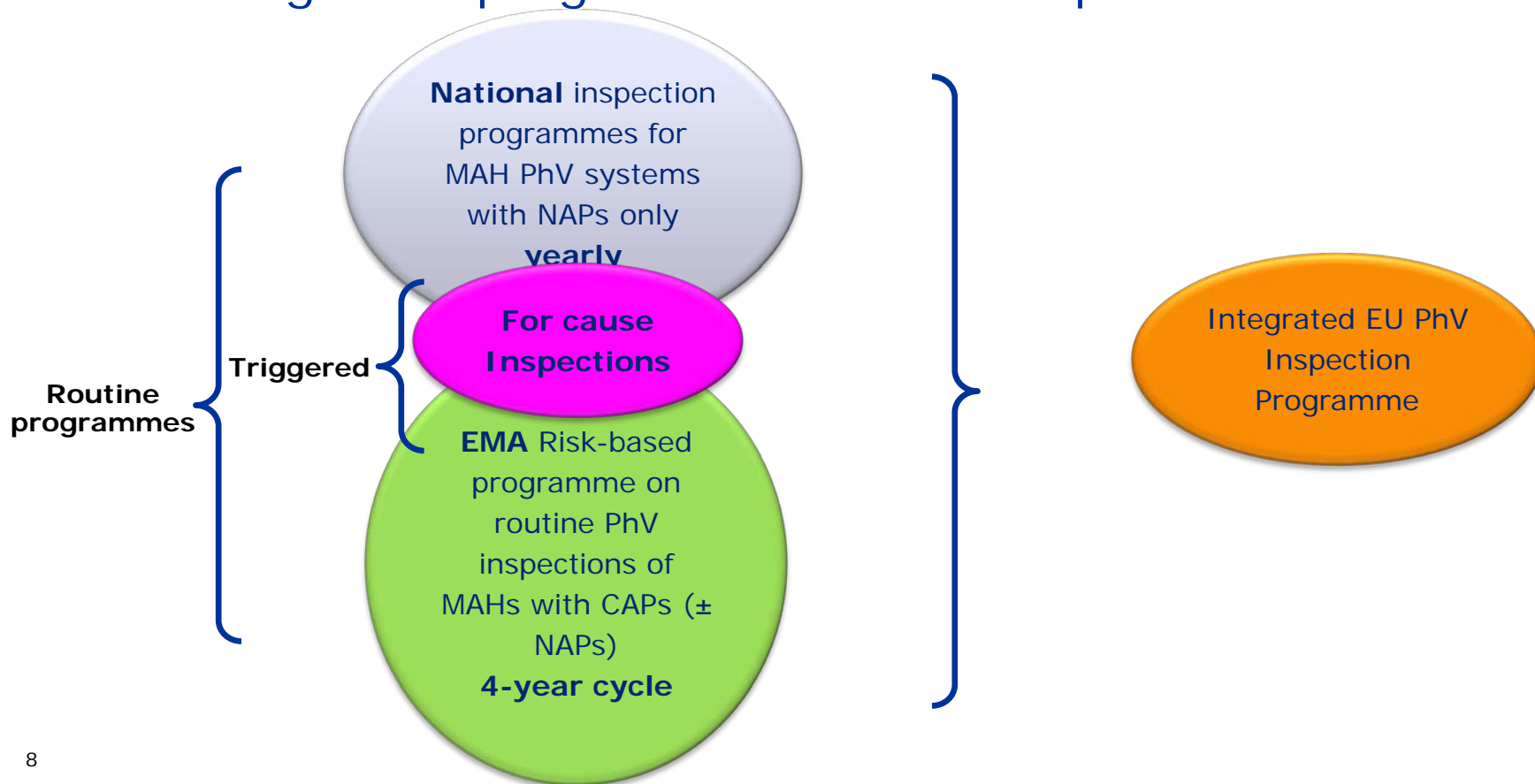


EU PhV Monitoring system of MAHs

- 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 MSs on behalf of EMA (EMA does not have its own inspectors);



Pharmacovigilance programmes and EU inspections coordination





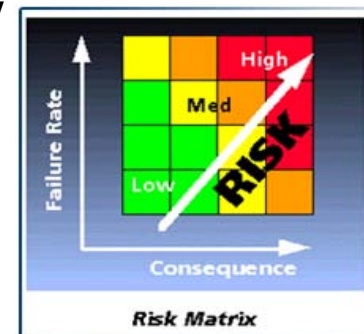
Risk-based *routine* PhV inspections planning & risk factors (1/2)

Product related:

- Product with large patient exposure
- Additional pharmacovigilance activities or risk-minimisation activities
- Marketing authorisation with conditions associated with safety

Marketing Authorisation Holder related:

- MAH has never been inspected
- Number of products on the market
- Negative information and/or safety concerns raised by competent authorities, other bodies outside the EU or other areas (i.e. GCP, GMP, GLP and GDP)
- Changes in the organisation, mergers and acquisitions



Risk-based *routine* PhV inspections planning & risk factors (2/2)

Inspection related:

- Compliance history
- Previous inspection outcome



Pharmacovigilance system related:

- Subcontracted pharmacovigilance activities and changes in the service providers
- Changes to pharmacovigilance safety database(s)
- QPPV changes and /or delegation or transfer of pharmacovigilance system master file (PSMF) management

Non-routine, “*for cause*” inspections : triggers (1/2)

- **Delays or omissions in reporting obligations** (expedited and periodic), poor quality or incomplete reports or inconsistencies between reports and other information sources
- **Failure to respond** or poor quality / inadequate provision of data to requests from the National Competent Authorities
- **Delays or failure to carry out specific obligations** relating to the monitoring of product safety; concerns about the status or fulfilment of risk management plan (RMP) commitments

Non-routine, “*for cause*” inspections : triggers (2/2)

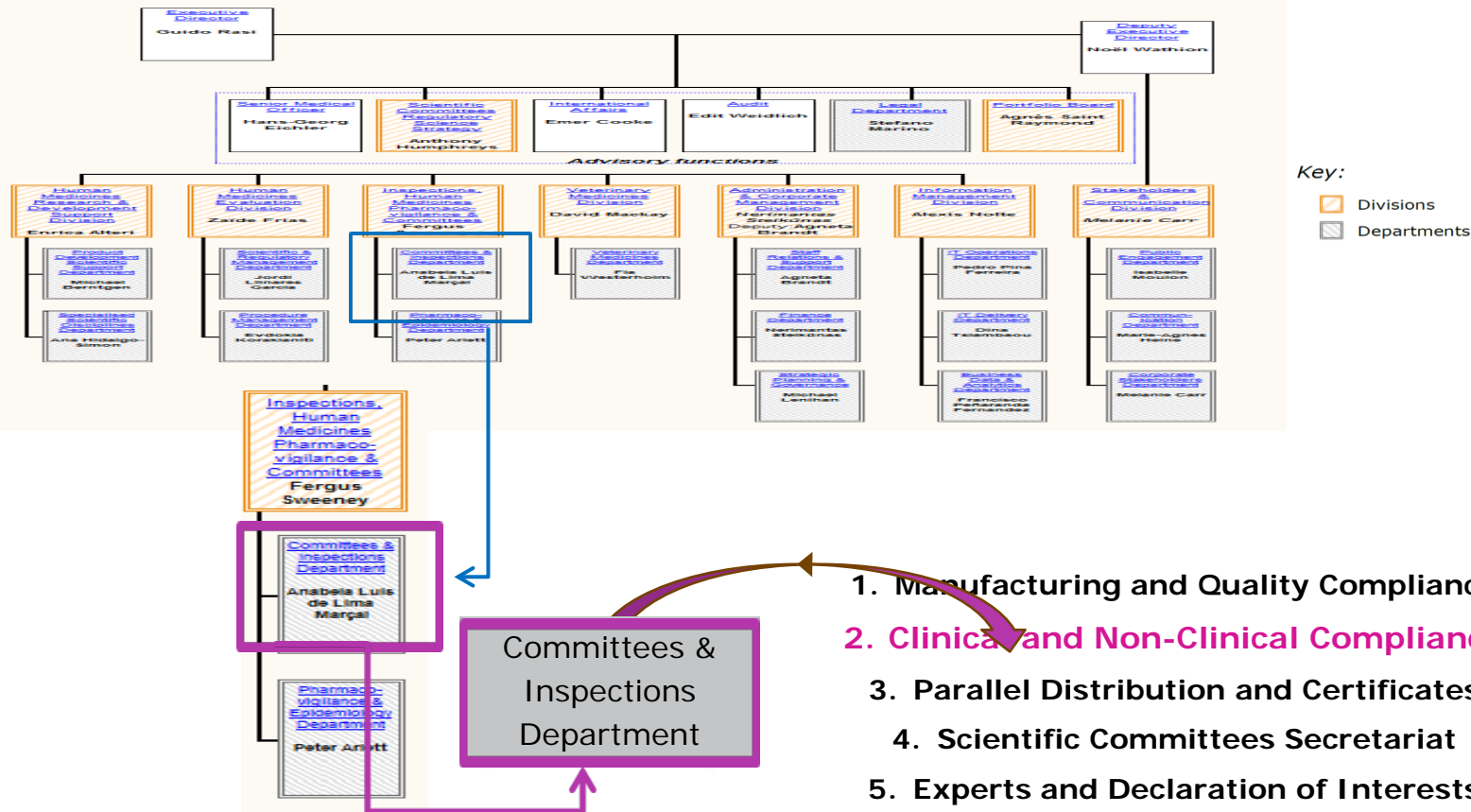
- **Inspection information** that may highlight issues of non-compliance or product safety issues; delays in corrective and preventive action plan (CAPA) implementation / **inappropriate CAPA implementation**
- **Change in B-R balance** of the product where further examination through an inspection is considered appropriate; delays or failure to identify or communicate a risk or a change in the risk-benefit balance to the National Competent Authorities
- As part of assessment (e.g. as part of **PSURs assessment**)



The EMA role - EMA Organisational structure



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Number of PhV inspections requests

	Total Inspections	All CAPs*	CHMP
2014	165	58	10
2013	195	43	6
2012	207	35	9
2011	226	33	5
2010	201	37	4

* CHMP requested inspections + National Inspections for CAPs

PhV inspections requested by CHMP and coordinated by EMA for CAPs

A small proportion of the inspections within the EMA risk-based programme is requested by **EMA Committees** and coordinated by EMA:

- 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



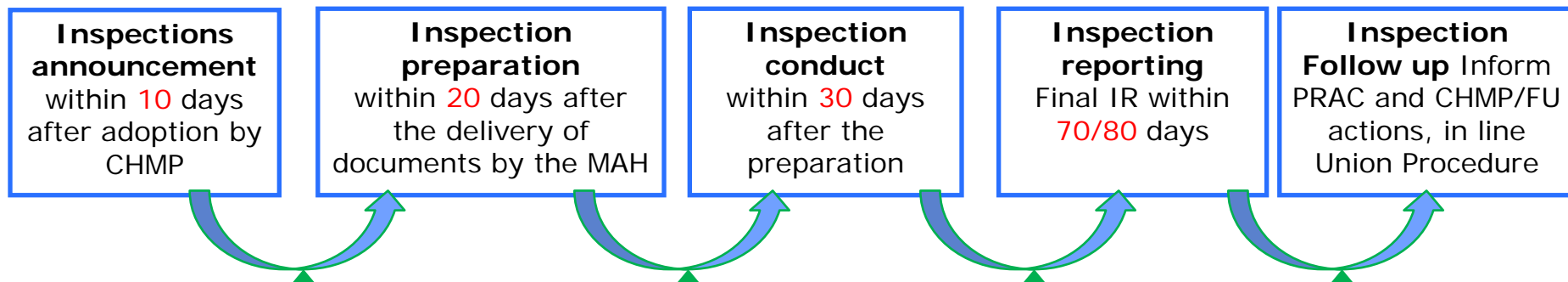
Type of sites inspected during PhV inspections coordinated by EMA

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



EMA coordination activities for CHMP requested inspections

- Preparation of the inspection request (product, sites, scope) with input from PRAC (as applicable)
- Adoption by the CHMP
- Designation of the inspection team (Reporting Inspector, Lead Inspectors, expert, trainee)





Announcement, preparation and conduct of EMA PhV Inspections

- Standard EMA announcement letters are sent to the inspectee(s) within 10 working days since adoption of inspection request
- Inspectees are requested to:
 - ensure cooperation
 - confirm in writing that the sites **accept** to be inspected
 - make all required **documents available**, for direct access by the inspectors
 - provide copies of an initial set of documents before the inspection (PSMF + other ***ad hoc*** documents)
- More than one site can be inspected in one EMA inspection



Reporting of EMA PhV Inspections

- **Initial Inspection Reports (IRs)** for each site ---→ prepared within **30* days** after end of inspection
- MAHs are invited to provide their comments to the inspection findings directly inside the IRs
- **Final Inspection Reports** for each site --→ prepared within **70* days** after end of inspection (include feedback from inspectees)
- For multi-site inspections an **Inspection Overview (IO)** is prepared taking into account the outcome of the inspections at all sites
- The IO --→ sent to the Agency within 80* days after the inspection and according to the deadline agreed with CHMP

Escalation of PhV inspections outcome to PRAC

- 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

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000164.jsp&mid=WC0b01ac0580029754



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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 (H+V)
- Composition: **PhV Inspectors** of EEA countries
+ Observers from candidate accessing countries
+ Switzerland






The PhV Inspectors Working Group

- Objectives:
 - To discuss PhV inspections findings
 - To develop/update guidance and procedures
 - To share experience and views
 - Training and development
 - Collaboration with other groups
 - International cooperation
- Collaboration with PRAC: PhVIWG-PRAC subgroup



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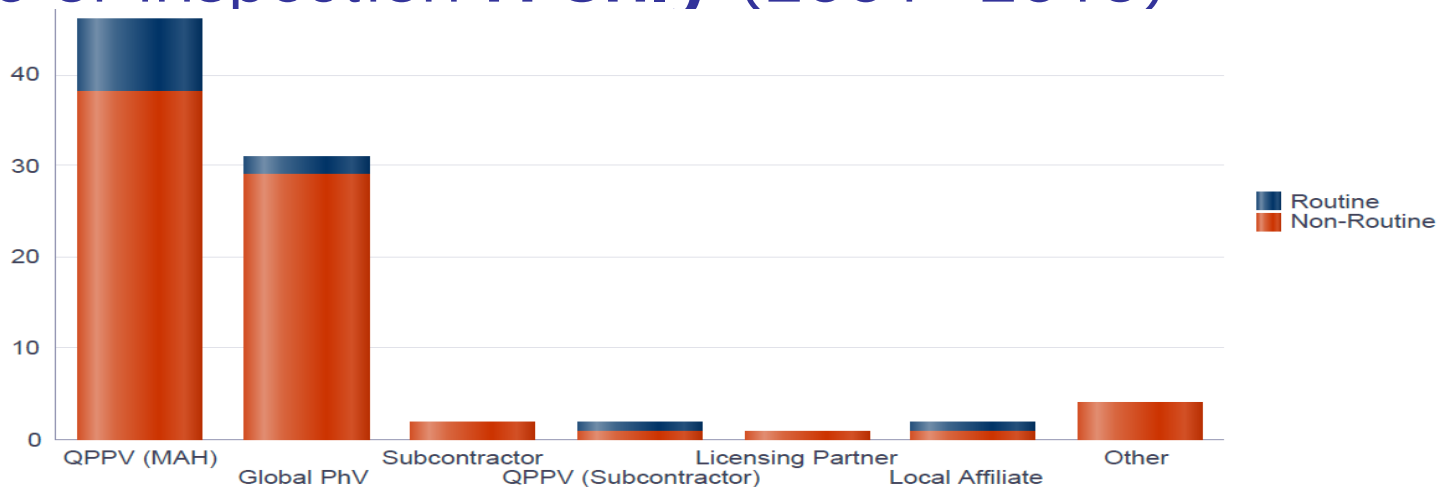
Number of conducted PhV inspections by type of inspection and year **H only** (2001- 2015)



Request Type	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Total
Non-Routine	1	1	2	2	3	3	5	12	13	6	4	7	4	10	3	76
Routine		1										2	1	4	4	12
Grand Total	1	2	2	2	3	3	5	12	13	6	4	9	5	14	7	88

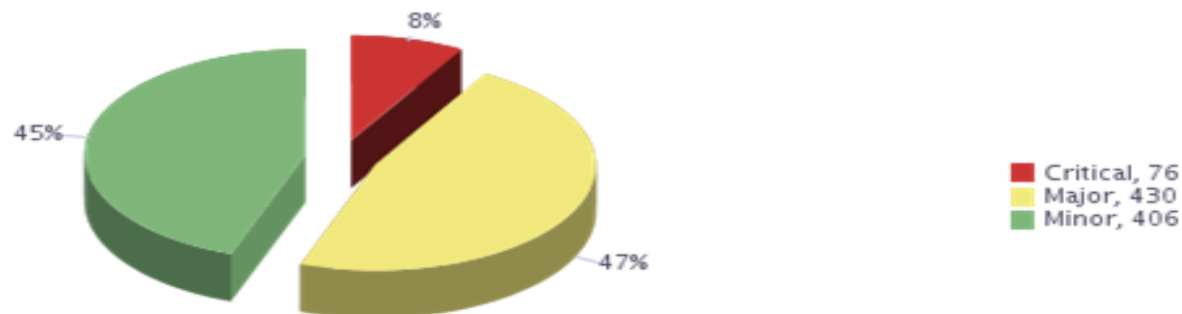


Number of conducted PhV Inspections per type of site and type of inspection **H only** (2001- 2015)



	# Inspections		# Inspections Total
Inspection Site Type	Non-Routine	Routine	
QPPV (MAH)	38	8	46
Global PhV	29	2	31
Subcontractor	2		2
QPPV (Subcontractor)	1	1	2
Licensing Partner	1		1
Local Affiliate	1	1	2
Other	4		4
Grand Total	76	12	88

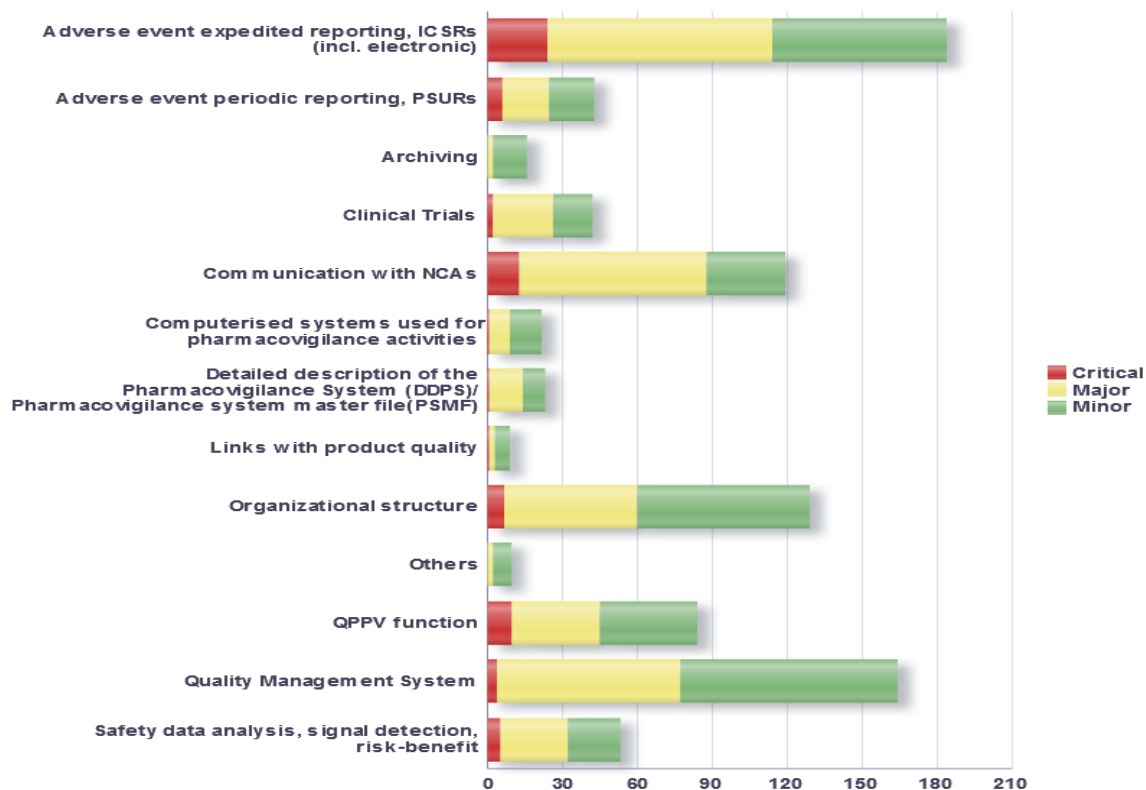
Number of findings by grading (2001- 2015)



Grade	# Deficiencies	% Inspected Deficiencies
Critical	76	8.33%
Major	430	47.15%
Minor	406	44.52%
Grand Total	912	100.00%



Number of findings by category and grade (2001- 2015)



Top 5 Pharmacovigilance inspections findings

- Adverse event expedited reporting, ICSRs (incl. electronic)
- Quality management system
- Organisational structure
- Communication with NCAs
- QPPV functions



Top 5 List

- 1.
- 2.
- 3.
- 4.
- 5.

Top 5 **critical** findings

- Adverse event expedited reporting, ICSRs (incl. electronic)
- Communication with NCAs
- QPPV function
- Organisational structure
- Adverse event periodic reporting, PSURs



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Sharing of information within the EU network on Pharmacovigilance inspections

Directive 2001/83/EC Art 111 (1) requires:

- **Cooperation between the EU MSs and the Agency** through the means of sharing information for both inspections that are planned and those that have been conducted
- EU Member States and the Agency are also required to **cooperate** in the **coordination of inspections in third countries**

Directive 2001/83/EC Art 111 (8) states that in case of non compliance the Member State concerned **shall inform** the other Member States, the Agency and the Commission

Sharing of information within the EU network on Pharmacovigilance inspections

GVP 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.



22 September 2016 - PhV IWG Meeting with Stakeholders an initial 'listening meeting'

- Industry provided feedback regarding:
 - PSMF implementation;
 - Inspection and Harmonisation;
 - Transparency & education;
 - Shared PV systems and licensing agreements.



22 September 2016 - PhV IWG Meeting with Stakeholders

Feedback: PSMF implementation

- Clarifications on the level of detail to be included in PSMF:
 - Lists of procedural documents which should be included in the PSMF, global only or local;
 - Audit findings and CAPAs, level of detail and position in the PSMF
 - Clarification on whether audit findings outside EU/EEA should be in the PSMF.
 - Clarification on whether CAPAs from audits performed by vendors themselves should also be included.
 - Clarify that it is necessary to include in PSMF audit findings and CAPAs until resolved even if there is a different practice in a company that demonstrates that a QPPV is informed of audit findings regularly.
 - Deviations from the quality system and from pharmacovigilance procedures, their impact and management until resolved.
- Sharing PSMF when working with business partners; EU and ex-EU partners
- Scope of 'Service Providers', 'Computerised Systems', 'Studies and Programmes' (further clarity as to what is expected)
- PSMF maintenance and submission of the PSMF within 7 days



22 September 2016 - PhV IWG Meeting with Stakeholders

Feedback: Inspection & Harmonisation

- **National vs Supervisory Authority Inspections:** GVP Module III and inspection procedures provide limited guidance on what can be included in the scope of National Inspections. The PhV IWG clarified that topics included in the Supervisory Authority scope can also be included, if needed, in the Agenda of a national inspection. Inspectors agreed to provide information on what should typically be reviewed on National Authority inspections and to ensure that the National requirements are provided clearly in the scope/Agenda of national inspections.
- **Transparency and Education:** Industry representatives requested additional details on the most common categories of inspection findings and real examples of inspection findings. Consider possibilities to educate MAHs outside inspections, i.e. organise future stakeholder meetings and events such as pharmacovigilance symposium and focus on pharmacovigilance inspection topics.



22 September 2016 - PhV IWG Meeting with Stakeholders an initial 'listening meeting'

- Final remarks:
 - Industry recognised improvements in the area of inspections and noted that GVP is helpful.
 - There are still areas for clarification and additional guidance and feedback from industry is key to focus on those areas;
 - The Agency and the PhV IWG work towards further harmonisation and coordination of activities and this is very welcome by the industry;
 - Transparency, education and communication is a common goal for Industry and regulators and the PhV IWG will look into the proposals made by the industry.





Thank you for your attention

Further information

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