Trends in pharmacovigilance inspection deviations

8th Scandinavian SARQA/DKG Quality Assurance Conference

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Disclaimer

This presentation does not represent the views of LEO Pharma or the Danish Medicines Agency.

It is solely the view of the presenter.

All examples are fictive unless references are stated on the slides

Pharmacovigilance inspections

- The number of competent authorities that perform Pharmacovigilance inspections are increasing – but at a slow rate
- Countries with Pharmacovigilance inspections:

  EU/EEA

  Switzerland

  USA

  Canada

  Japan

  Brazil

  Arab League (not fully implemented)

  Australia

  China?

  Mexico?

Regular reporting on Pharmacovigilance inspections

- EMA on CHMP (and CVMP inspections)
- MHRA
- Health Canada
- (FDA)

EMA

- EU Marketing authorisation holders with Centrally Approved Products are subject to pharmacovigilance inspections from EMA. The national supervisory authority may however choose to perform a national inspection and report the results to EMA

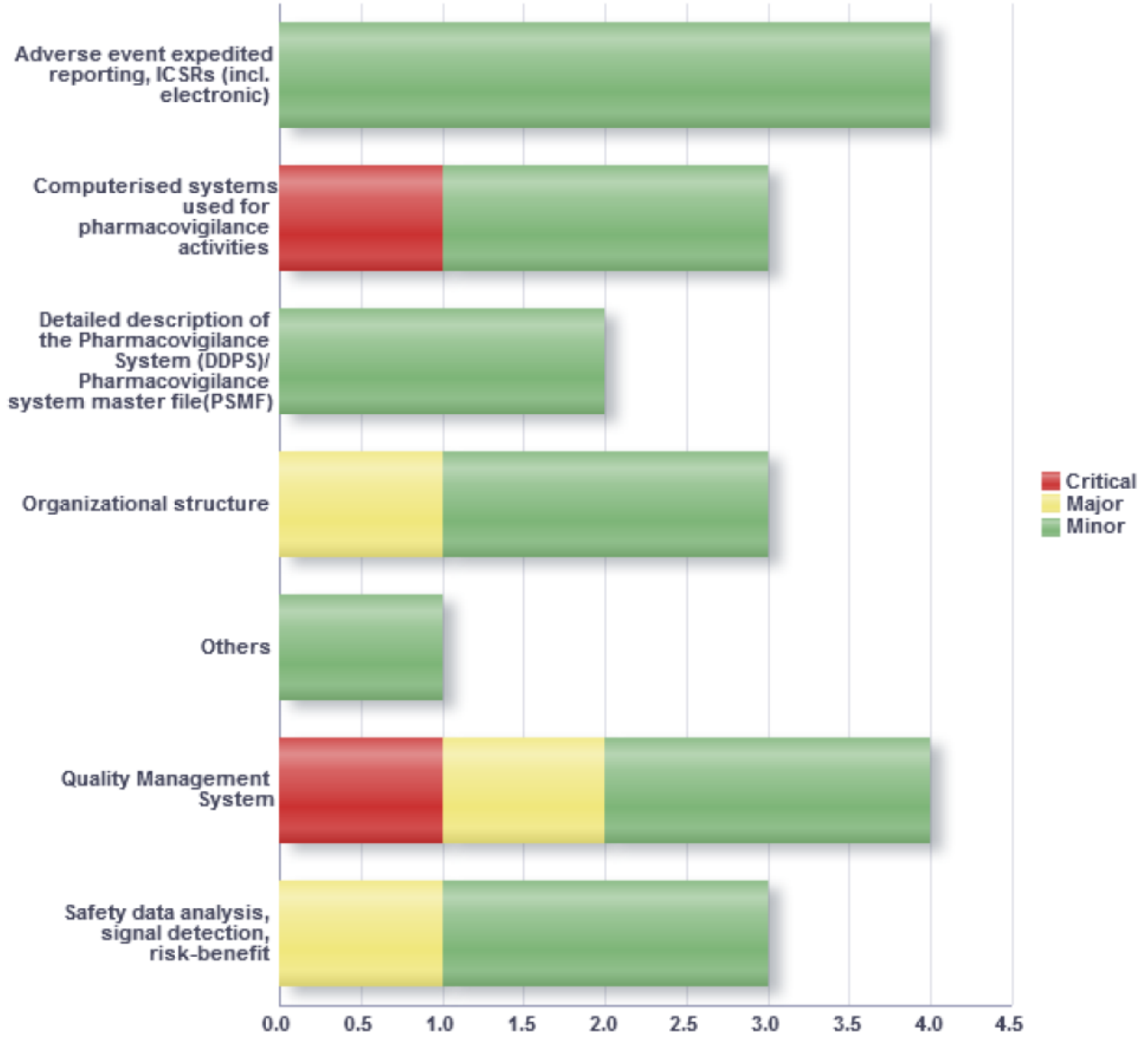
Table 1 - Human pharmacovigilance inspections requested in 2016 in the context of the programme for pharmacovigilance inspection of companies with CAPs

	QPPV/PSMF (MAH) site	Global PhV site	Subcontractor/ Licensing partner/affiliate site	Total
CHMP requested	1	0	1	2**
National inspection programmes	31	0	18	49
Total	**32**	**0**	**19**	**51**

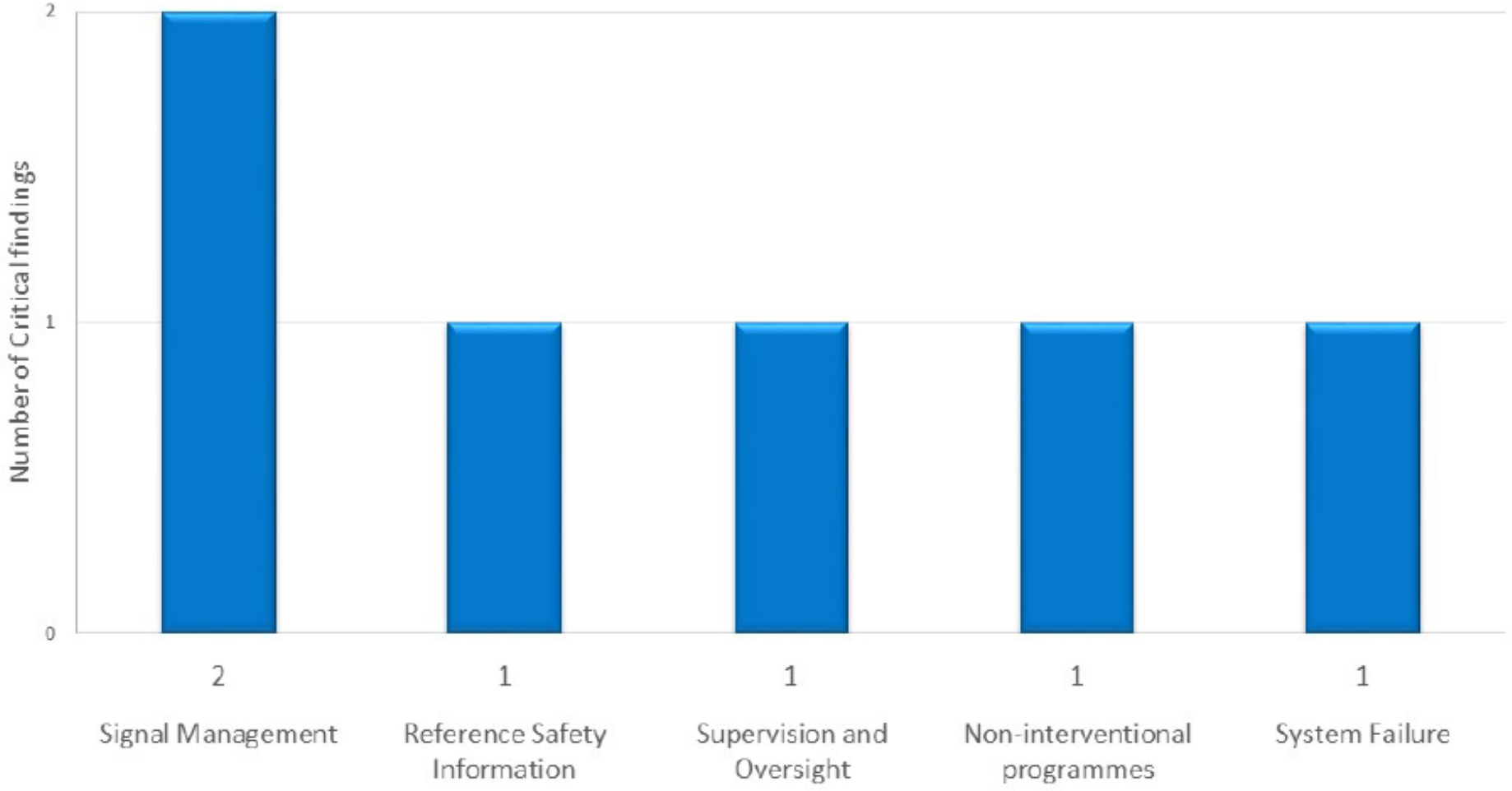
Annual report of the Pharmacovigilance Inspectors Working Group 2016

EMA

Figure 1 - Number of findings with regard to the main categories graded by critical, major and minor for CHMP inspections requested

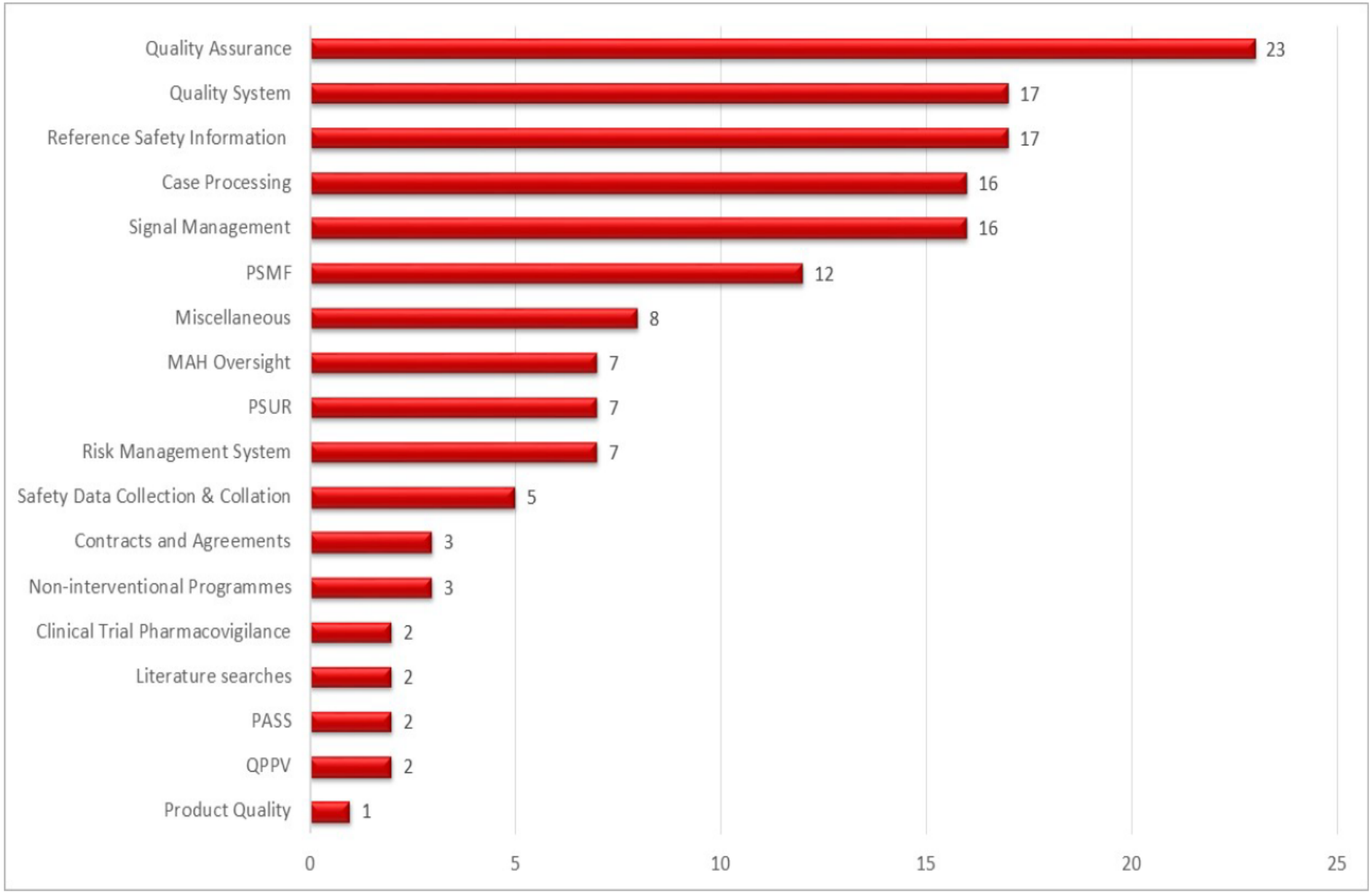


MHRA Critical Non-conformities



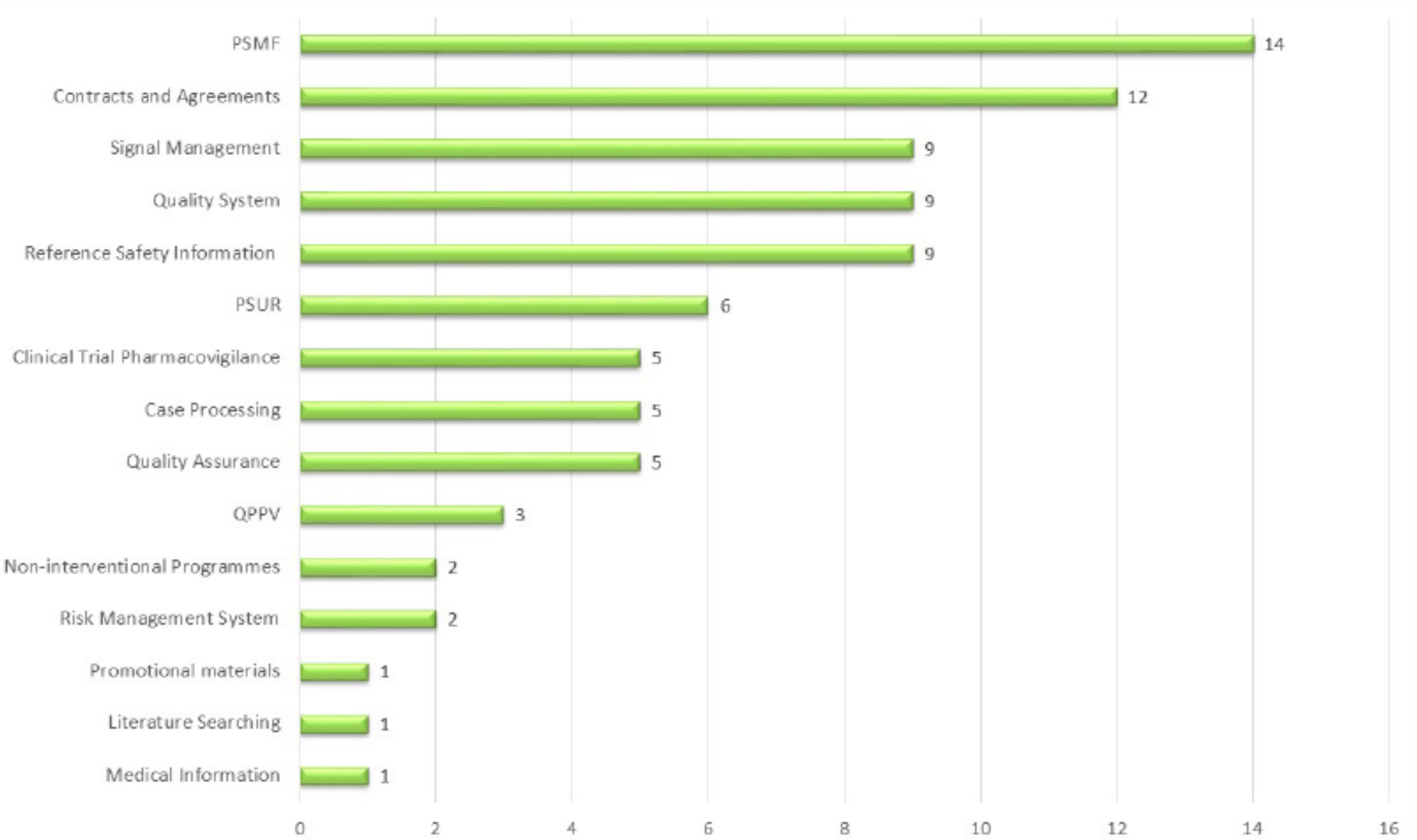
- MHRA: Pharmacovigilance Inspection Metrics Report, April 2016 - March 2017
- Distribution of 6 critical Non-conformities from 36 inspections in the UK

MHRA Major Non-conformities



- MHRA: Pharmacovigilance Inspection Metrics Report, April 2016 - March 2017
- Distribution of 150 major Non-conformities from 36 inspections in the UK

MHRA Minor Non-conformities



- MHRA: Pharmacovigilance Inspection Metrics Report, April 2016 - March 2017
- Distribution of 84 minor Non-conformities from 36 inspections in the UK

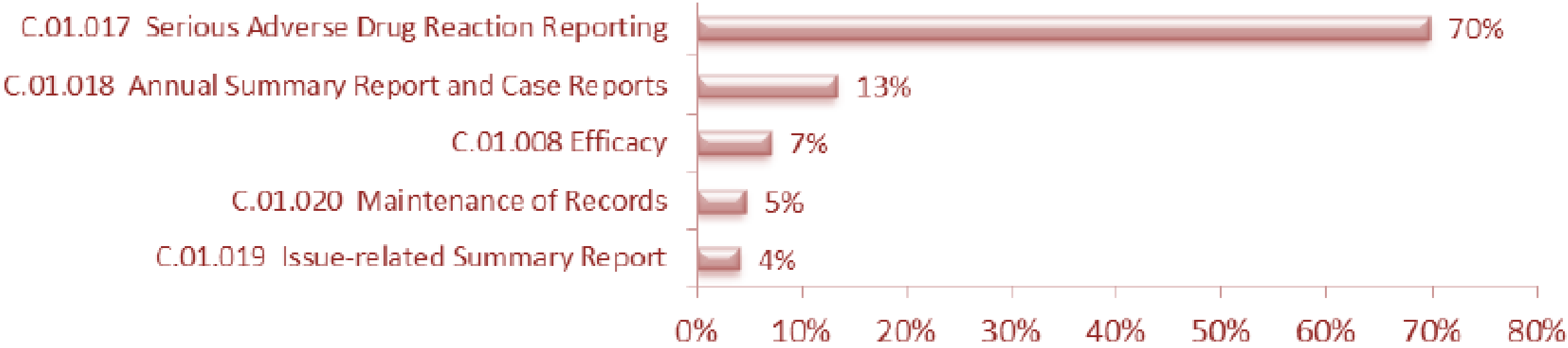
Health Canada

Health Canada
Annual Inspection Summary
Report 2015 – 2016

- 9 inspectors
- 42 inspections conducted
- 172 observations made
  - 0% critical risks
  - 51% major risks
  - 49% minor risks
- Top observations:
  - serious adverse drug reaction reporting
  - annual summary report and case report
- 98% compliance rate

Health Canada

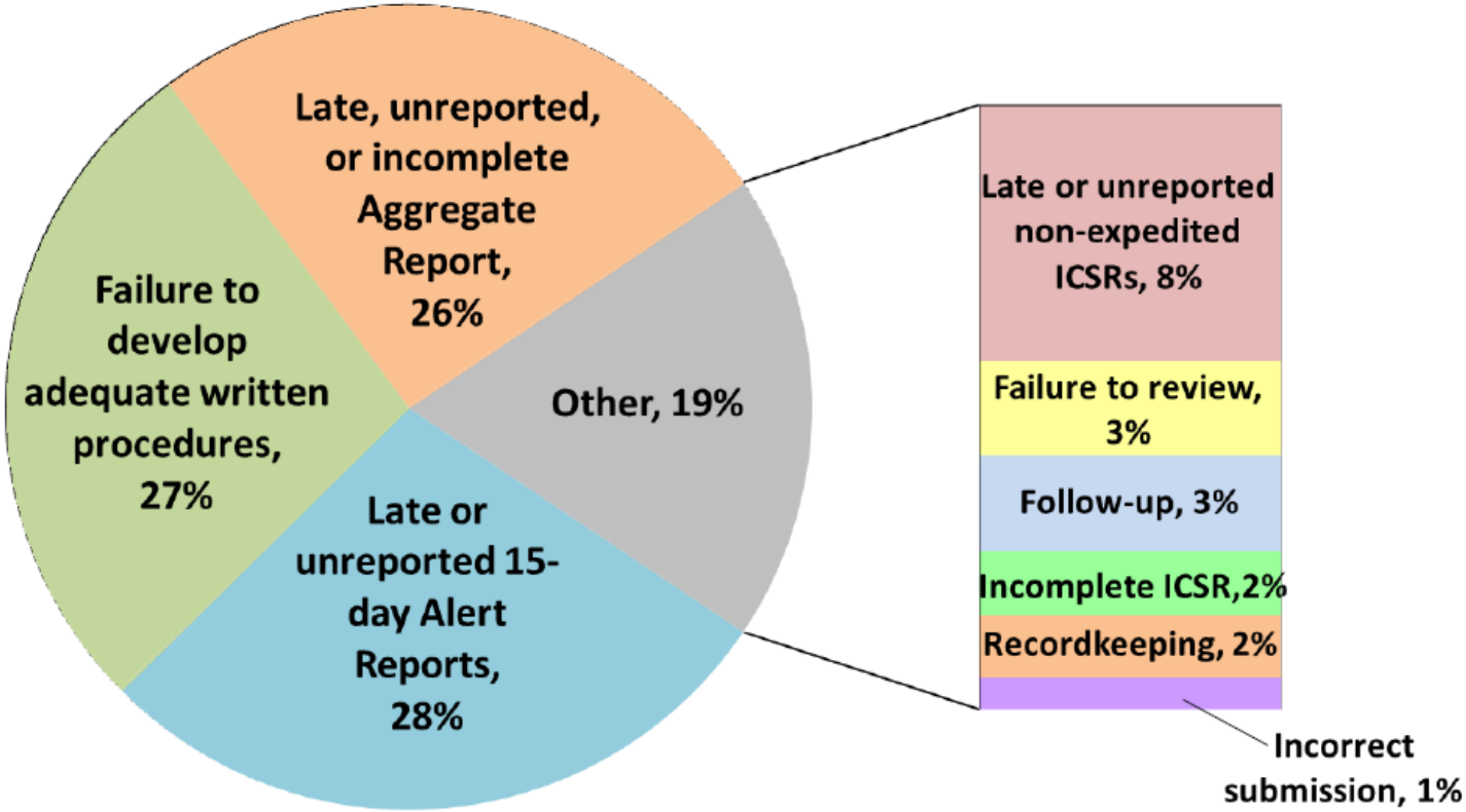
Health Canada
Annual Inspection Summary
Report 2015 – 2016



FDA

PADE Inspection Trends: PADE Citations on Form FDA 483 (FY2015-FY2017)

June 19, 2018
Center for Drug Evaluation and Research (CDER) Small Business and Industry Assistance (SBIA) Webinar



DKMA: Pharmacovigilance System Master File (PSMF)

- Documents are lacking or incomplete
- The document does not reflect the actual pharmacovigilance system
- Annexes to PSMF are incomplete, not updated or not delivered. This applies to e.g. annexes about distributors, partners, system performance etc.

DKMA website: dkma.dk accessed November 2018

DKMA: Contracts and agreements

- Missing contracts/agreements
- Contracts did not comprise exchange of information about adverse reactions and/or time frames for exchange of information
- Unclear distribution of responsibilities
- Exchange of information on adverse reactions does not ensure timely reporting
- Reconciliation of information about adverse reactions had not been made
- Contracts did not secure possibility of audits

DKMA website: dkma.dk accessed November 2018

DKMA: Organisation and Staff

- The qualified person responsible for pharmacovigilance (QPPV) is not adequately qualified and/or has insufficient overview
- The qualified person responsible for pharmacovigilance (QPPV) does not have access to consult medically trained staff
- Inadequate resources to ensure compliance with current legislation
- Not all employees have been trained in pharmacovigilance
- Training not documented
- Job descriptions and areas of responsibility were not clearly defined
- No cover for critical functions in connection with holidays

DKMA website: dkma.dk accessed November 2018

DKMA: Documentation of adverse reactions

- Adverse reaction reports are not processed and submitted on time (all levels)
- Under-reporting, excess reporting, erroneous reporting
- No follow-up on adverse reaction reports or follow-up made at a very late stage
- Insufficient checking for duplicates
- Inadequate evaluation of adverse reaction reports
- Adverse reaction reports were not submitted electronically
- Adverse reaction reports were not submitted to all the relevant parties
- Inexplicable reclassification of adverse reaction reports
- Wrong day 0, wrong reporting type etc.
- No screening of the company's websites
- No quality control of various pharmacovigilance activities, including e.g. translations

DKMA website: dkma.dk accessed November 2018

DKMA: Literature searching

- Literature searching was not made in accordance with legislative requirements
- Applied search criteria were not validated
- A literature search must comprise both international and national scientific journals.
- A journal is considered relevant if its audience includes persons who are authorised to prescribe medicines and its content is scientifically relevant. Journals included in university library collections would normally be considered as scientifically relevant.

DKMA website: dkma.dk accessed November 2018

DKMA: Periodic Safety Update Reports (PSURs)

- PSURs were not submitted on time
- The contents of PSURs were not in accordance with legislation, for example there was no conclusion that new adverse reactions require a change to the summary of product characteristics.

DKMA website: dkma.dk accessed November 2018

DKMA: Maintenance of reference documentation

- No procedures and deadlines for submission of safety variations
- Safety variations were not submitted within the acceptable deadlines

DKMA website: dkma.dk accessed November 2018

DKMA: Electronic systems

- Systems with no possibility of tracing changes (audit trail) are used for critical processes
- Audit trail was not or only partly readable
- Systems were not validated or documentation for validation was missing
- Differences between source data and data entered in the database
- Inadequate reconciliation of information about adverse reactions between the pharmacovigilance database and other databases (for example about complaints, medical information, clinical trials)
- Insufficient quality control of data entered
- Insufficient access control to the electronic systems

DKMA website: dkma.dk accessed November 2018

DKMA: Quality management systems

- Lacking, incomplete, incorrect and outdated standard operation procedures (SOPs)
- Lack of all types of documentation, including the documentation for important decisions
- Deviations were not handled in accordance with the description in the deviation system
- Inadequate follow-up on the causes for adverse reaction report submitted too late
- Auditors do not have sufficient experience in pharmacovigilance and subsidiaries have not been audited

DKMA website: dkma.dk accessed November 2018

DKMA: Audits

- Contract organisations/collaboration partners were not audited
- Conducted audits did not focus on the monitoring of adverse reactions
- Pharmacovigilance was not comprised by the procedure for audits

DKMA website: dkma.dk accessed November 2018

DKMA: Facilities

- Inadequate access control to archives
- The filing period is not described in procedures or is too short
- The MAH cannot receive reporting of adverse reactions etc. 24/7
- Cases that were not filed in the MAH's archives/database

DKMA website: dkma.dk accessed November 2018

Any Questions?