European Union (EU) Regulatory Trends in GMP

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Presentation Topics

- EU Background
- Inspections outside the EU
- EMEA Inspection Outcomes
- Dedicated Facilities
- Qualification of Suppliers
- Computerized Systems
- ICH Q10 impact
- Counterfeit Product

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EU Background

The European Paradox - one entity but many parts

EU Background - Size and Complexity

- Size
  - 27 member states
    - 3 more countries in negotiation
  - 495 million inhabitants
    - world's 3rd largest population (after India and China)
- Complexity
  - 23 official languages

EU Background - Legislation

- Directives
  - › requires member states to achieve a certain result
  - › does not dictate the means of achieving the result
  - › requires member states to transpose into national legislation
  - › example: Commission Directive 2003/94/EC on the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use

EU Background - Legislation

- Regulation
  - › legal instrument that is immediately enforceable
  - › example: Council Regulation (EEC) No 2309/93 on Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products

EU Background - GMP Regulatory Oversight

- Licensing and control of manufacturers is done by member states
  - › each member state grants manufacturer's authorisations
  - › each member state carries out its own inspections of manufacturing sites
- European Medicines Evaluation Agency (EMEA)
  - › includes an Inspections Sector
  - › co-ordinates inspections required for products under centralized procedure
  - › includes a GMP/GDP Inspectors Working Group
    - meets 4 times per year
    - has senior inspectors from member states
    - publishes a work plan each year
    - mandated to provide input on all GMP/GDP matters

EU Background - GMP Guidelines

- GMP guidelines defined in Volume 4 of “The rules governing medicinal products in the European Union”
  - › available on-line at http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/
  - › guidelines are organized as
    - Part I - Basic Requirements for Medicinal Products
    - Part II - Basic Requirements for Active Substances used as Starting Materials (equivalent to ICH Q7A)
    - Annexes 1-20
  - › guidelines apply not only to the EU but also the European Economic Area countries
    - includes Switzerland

Inspections outside of the EU

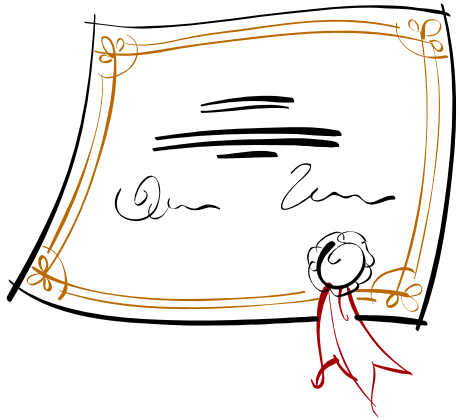
Inspections outside of the EU

- EMEA Inspectors Working Group
  - working to co-ordinate inspections for…
    - sites listed on a centralized marketing authorization application if…
      - site is located in a third country
      - no mutual recognition agreement (MRA) is in place
- So for sites outside EU there are three possibilities
  - inspection by local authority accepted if there is an MRA
  - inspection by EU national authority (for EU national applications)
  - inspection by EU national authority 'team' agreed with EMEA (for centralized applications)
    - normally 2-3 inspectors from different authorities
- Inspection standard is EU GMP

Inspections outside of the EU - EudraGMP

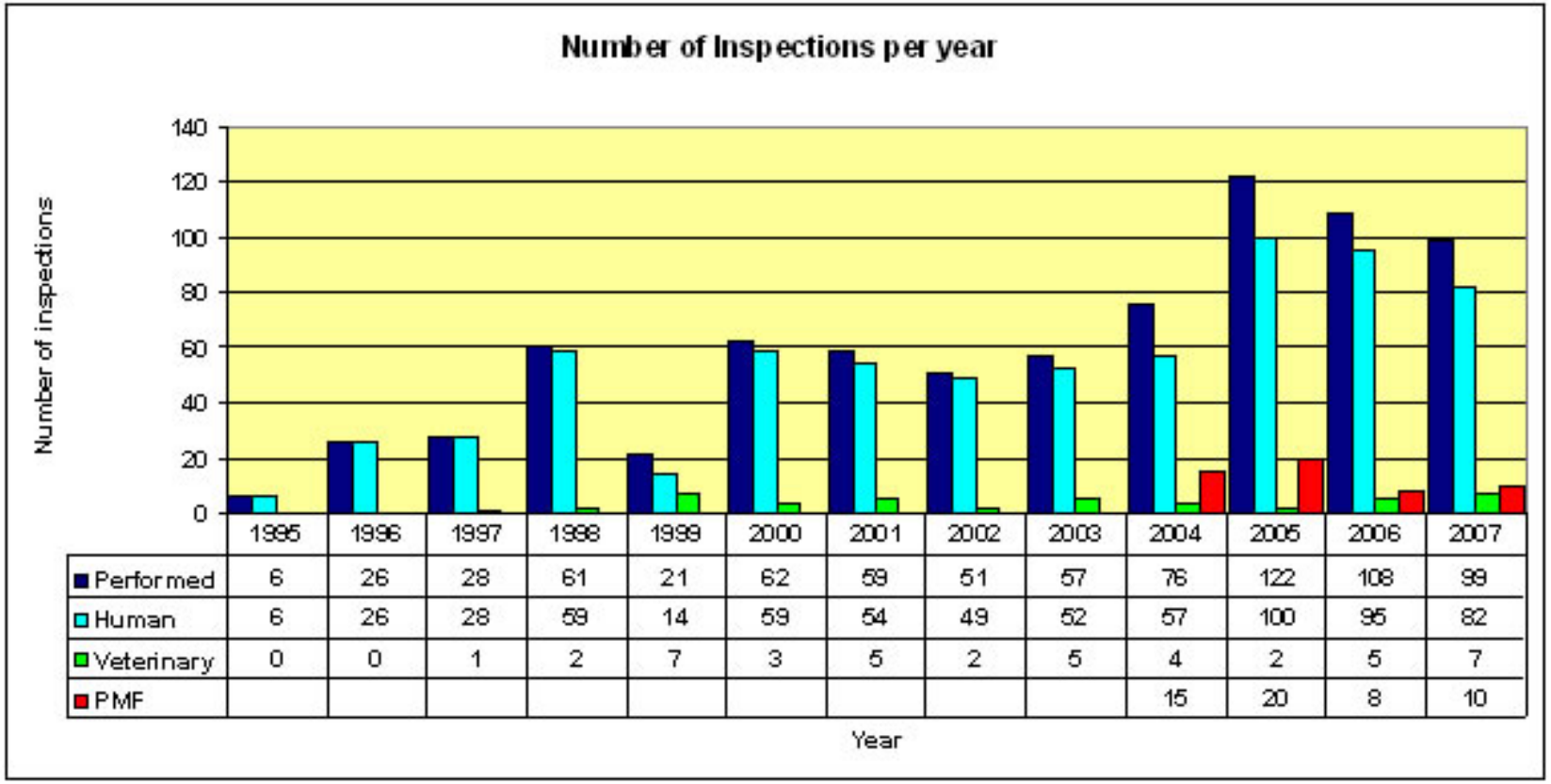
- EudraGMP
  - On-line database
  - Cover manufacturers and importers into EU
  - Provides access to both authorities and public
  - Public information limited currently
  - website - http://eudragmp.emea.europa.eu

EMEA Inspection Outcomes



EMEA Inspection Outcomes

- Number of EMEA inspections performed
  - › for centralized products / applications only



	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007
Performed	6	26	28	61	21	62	59	51	57	76	122	108	99
Human	6	26	28	59	14	59	54	49	52	57	100	95	82
Veterinary	0	0	1	2	7	3	5	2	5	4	2	5	7
PMF										15	20	8	10

EMEA Inspection Outcomes

- Two reports published on inspection findings carried out as part of centralized procedure applications
  - 1995 - 2005, published in January 2006
  - 2006, published in April 2008
  - both reports available on EMEA Inspections website

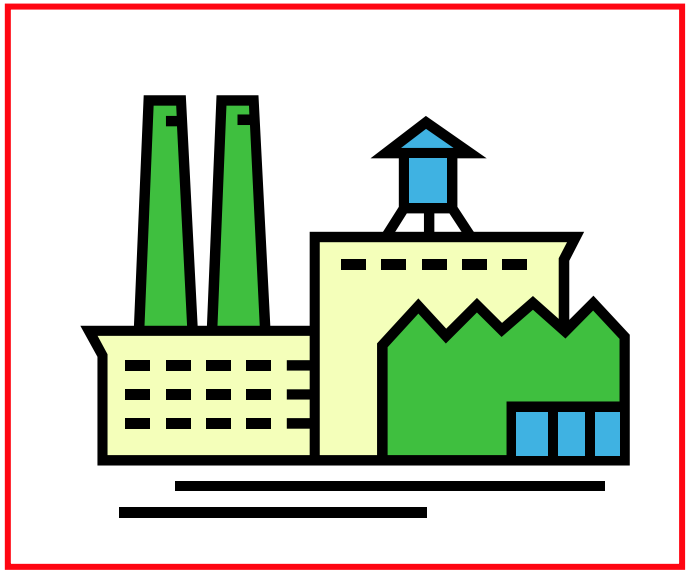
	Active ingredient	Finished Product	EEA	Third country
Number of inspections	119	316	35	400
Number of critical deficiencies	34 (1.65%)	159 (2.13%)	55 (7.50%)	138 (1.57%)
Number of major deficiencies	321 (15.52%)	682 (9.15%)	26 (3.54%)	977 (11.12%)
Number of other significant deficiencies	1712 (82.83%)	6611 (88.71%)	653 (88.96%)	7670 (87.31%)
Total deficiencies	2067	7452	734	8785
Average deficiencies per inspection	17	23	21	22

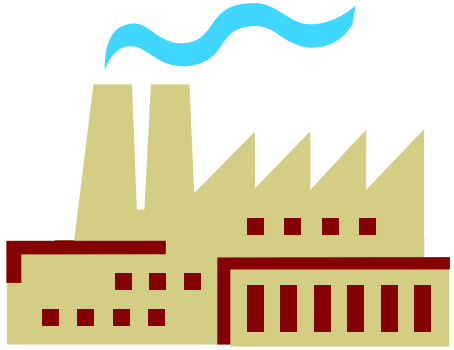
Table 2. Deficiencies found in 1995/2005 by different categories (active ingredient vs. finished product, and EEA vs. third country).

EMEA Inspection Outcomes - Top 10 issues from total GMP deficiencies

Rank	1995 - 2005		2006	
	Issue	Incidence (%)	Issue	Incidence (%)
1	Documentation - quality system	14.1	Documentation - quality system	10.9
2	Design & maintenance of premises	6.7	Documentation - manufacturing	10.2
3	Design & maintenance of equipment	6.2	Design & maintenance of premises	6.5
4	Documentation - manufacturing	5.5	Documentation - specification & testing	5.2
5	Potential microbiological contamination	4.9	Status labelling	4.7
6	Documentation - specification & testing	4.5	Potential microbiological contamination	4.7
7	Status labelling	3.9	Supplier and contractor audit & TA	4.5
8	Environmental monitoring	3.4	In-process controls	4.3
9	Process validation	3.3	Housekeeping (cleanliness etc.)	4.1
10	Sampling - procedures & facilities	3.1	Environmental monitoring	3.7

Dedicated Facilities





Dedicated Facilities

- EMEA Inspectors Working Group are reviewing the concept and requirements for dedicated facilities
- Current EU GMP wording (chapter 3.6) is imprecise and open to interpretation:
  - "In order to minimise the risk of a serious medical hazard due to cross-contamination, dedicated and self contained facilities must be available for the production of particular medicinal products, such as highly sensitising materials (e.g. penicillins) or biological preparations (e.g. from live micro-organisms). The production of certain additional products, such as certain antibiotics, certain hormones, certain cytotoxics, certain highly active drugs and non-medicinal products should not be conducted in the same facilities. For those products, in exceptional cases, the principle of campaign working in the same facilities can be accepted provided that specific precautions are taken and the necessary validations are made."

Dedicated Facilities

- Potential changes to EU GMP guide
  - chapter 3.6 (Premises and Equipment)
  - chapter 5.18 / 5.19 (Prevention of cross-contamination in production)
  - annex 2 (Biological products)
  - annex 3 (Radiopharmaceuticals)
  - annex 4 (Veterinary products)
- EU Inspectors Working Group are collaborating with the US FDA on this issue
  - Concept paper issued in February 2005
  - Status updated published in January 2008
    - final text was expected to be submitted to the European Commission at the end of 2008 / beginning of 2009

Dedicated Facilities

- Expected outcome
  - GMP guidelines to define two categories of product
    - Category 1 would be specific products / product types that require mandatory dedicated facilities
    - Category 2 would be products where campaign working may be possible after a positive risk assessment
- Issue has caused much debate both amongst regulators and with industry
  - interest in use of risk management approaches (example Risk-MaPP from ISPE)

Qualification of Suppliers

Qualification of Suppliers

- Planned updated to EU GMP chapter 5 (qualification of suppliers and testing of starting materials)
  - Guidelines to include new obligations on manufacturing authorization holders to use only active substances manufactured in compliance with GMP
  - This follows requirement for the Qualified Person (QP) to have to provide a supporting GMP compliance statements as part of regulatory submissions
- EMEA has made it clear that active substance supplier qualification should include physical audit
  - "The EEA inspectorates are not generally in favour of "paper-based audits" per se as they do not provide the same level of assurance as on-site assessments, but do accept that they have a part to play in a risk-based strategy. They may be particularly applicable when recent positive inspection information is available and where satisfactory audits have been concluded in the past. They cannot replace on-site audits of active substance suppliers but can be a useful interim and temporary measure within the manufacturers audit programme." (EMEA Inspectors Working Group - Questions & Answers)

Computerized Systems

Computerized Systems

- EMEA Inspectors Working Group have published in February 2008 proposed revisions to the following parts of the EU GMP guidelines:
  - › Chapter 4 (Documentation)
    - this has been updated to more clearly reflect the use of, and requirements for, computerized systems
    - Changes mainly to the Principles and General requirements of chapter 4
  - › Annex 11 (Computerized Systems)
    - this has been re-drafted and significantly extended
      - risk management
      - validation
      - software
      - security
      - accuracy checks
      - signatures
      - back-up
      - suppliers

Final text was expected by Quarter 2, 2009

ICH Q10 Impact

ICH Q10 Impact

- EMEA Inspectors Working Group published in February 2009 a concept paper on the implementation of ICH Q10 (pharmaceutical quality system)
  - › problem statement
    - how to incorporate ICH Q10 into chapters 1 (quality management) and 2 (personnel)
    - how to avoid confusion in terminology between current EU guidelines and ICH Q10
  - › Recommendation
    - revision by EMEA Inspectors Working Group of EU GMP guidelines
      - chapters 1,2 and 7 (chapter 7 covers contract manufacture and analysis)
    - points to be addressed
      - alignment of terminology and concepts
      - emphasis on the role of senior management in ensuring an effective quality system is in place
      - clearer guidance on handling and investigations of deviations, corrective and preventative actions and change control

Draft text was expected for comments in July 2009

Counterfeit Product

Counterfeit Product

- Counterfeit pharmaceutical products are seen as a major issue for the EU
- European Commission launched a public consultation on this topic in March 2008
- Following this consultation a proposal for amendments to Directive 2001/83/EC was published in December 2008, including:
  - legal basis for application of safety feature (example serialization number or seal) to the packaging of medicines
  - obligatory audits of wholesale distributors
  - strengthened requirements for imports of API from outside the EU
  - requirement for Marketing Authorization holder to inform the authorities if finding proven or suspected counterfeit products
  - strengthened GMP / GDP inspections and increased visibility of results via EudraGMP database

Thank you!

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