Global GMP inspection landscape: industry point of view and the way forward

Dr.-Ing. Stephan Rönninger, F. Hoffmann-La Roche
Dr. Georges France, Pfizer

The International Federation of Pharmaceutical Manufacturers & Associations
IFPMA in brief

- Non-profit, non governmental organization (NGO) founded in 1968
- Represents R&D-based pharmaceutical industry in Geneva
- Official observer status with UN in Geneva, including the World Health Organization, also WIPO, WTO, etc.
- Advocates policies favouring innovation, high quality standards, and sustainable access to medicines for patients around the world
- IFPMA Membership:
  - 26 R&D-based leading biopharmaceutical companies
  - 46 national Industry Associations, from all 5 continents
- Provides secretariat for International Conference on Harmonisation (ICH)
Regulatory inspections are important to ensure pharmaceutical industry’s compliance with GMP regulations

This presentation will

• Explore the current situation for research-based innovative companies with respect to inspections

• Discuss opportunities for improved utilization of resources for better compliance, based on data gathered
Topics for today

Data basis

Results and Key points

Towards risk-based approaches

Challenges and Opportunities
Topics for today

Data basis

Results and Key points

Towards risk-based approaches

Challenges and Opportunities
Scope:

- An inspection undertaken by a regulatory body at a research-based company’s manufacturing site:
  - Within regulatory body’s own country: “domestic inspection”
  - Outside of regulatory body’s own country: “foreign inspection”
Regulatory GMP inspection surveys

- **How data were generated**
  - Questionnaire to EFPIA, JPMA and PhRMA member companies

- **Response rate**
  - Surveys had a high response rate e.g.
    - EFPIA: 24 responses representing 641 facilities
    - JPMA: 31 responses representing 134 facilities
    - PhRMA: 20 responses representing 181 facilities

(numbers from 2008)
Topics for today

Data basis

Results and Key points

Towards risk-based approaches

Challenges and Opportunities
Outcome of the surveys

- Data are consistent across regions
- Trend towards increasing global inspection activity
- Increasing number of inspections per health authority
- Most active inspectorates: Brazil, USA, EU, and Japan (2008 data)
- Many additional inspectorates now performing foreign inspections, usually targeting the same manufacturing sites
Countries performing foreign inspections

49 countries have performed foreign inspections from 2003 to 2009;

37 countries performed foreign inspections in 2009 (reported by EFPIA in 2009)

- Algeria
- Argentina
- Australia
- Belarus
- Botswana
- Brazil
- Canada
- Chile
- China
- Chinese Taipei
- Columbia
- Costa Rica
- Croatia
- Ethiopia
- EU-countries
- Ghana
- Gulf States (GCG)
- Iran
- Iraq
- Ivory Coast*
- Japan
- Jordan
- Kazakhstan
- Libya
- Malaysia*
- Mexico
- Morocco
- New Zealand
- Nigeria
- Oman
- Pakistan
- Russia
- South Africa
- Saudi Arabia
- Serbia
- Singapore
- South Korea
- Sudan
- Switzerland
- Tanzania
- Thailand
- Tunisia
- Turkey*
- Uganda
- Ukraine
- USA
- WHO
- Yemen
- Zimbabwe

* new in 2009
1 EU countries as one inspectorate only

italics: active in previous years; no reports in 2009
Consequence of increased number of inspections, driven by globalization:

Significant increase in regulatory and industry resources, needed to manage multiple inspections
Inspectorates performing highest number of foreign inspections, 2003 - 2009 (EU as 1)

EFPIA data
Inspectorates performing middle number of foreign inspections, 2003 - 2009 (EU as 1)

EFPIA data
Number of foreign inspections ordered by countries

- Brazil
- USA
- EU (EU as 1)
- Japan
- South Korea
- Colombia
- Mexico
- Uganda
- Saudi Arabia
- Canada
- Russia
- Libya
- WHO
- Chinese Taipei
- Australia
- Gulf States
- Argentina
- Nigeria
- Iran
- Belarus
- China
- Croatia

EFPIA data, top 5 countries consistent with JPMA & PhRMA

Source: EFPIA 2008 data
Manufacturing sites for global supply are priorities for domestic AND foreign regulatory inspections
Even if there is a mature regulatory inspection activity by the domestic authorities, many foreign inspections still occur.

Data suggests opportunities for efficiencies via mutual acceptance processes between regulatory authorities.
Reported number of inspections per site

- ≥ 2 inspections: 34%
- 1 inspection: 38%
- 0 inspection: 28%

Greatest number of inspections at one site: 16

EFPIA 2009 data
Similar focus of inspections

- Resources are focused on the same product categories

- Similar focus results in similar observations by different regulatory authorities inspecting the same site

Sterile drug product  API  Non sterile drug product

Authority evaluation Japan
Translation from the MHLW study report, July 2010
Review of the data

For regulators:

- Can there be more
  - Joint inspections
  - Sharing of inspection results
  - Use of other data (e.g. compliance history, MRA, MoU, Eudra/WHO database)
  
  to ensure manufacturing site acceptability?

- Will implementation of more confidentiality agreements be forthcoming? e.g.
  - Accession of more authorities into PIC/S
  - Recognition of other requirements to be equivalent
  - Harmonized guidance such as ICH Q7, Q8, Q9, Q10

ICH Q7 (GMP for APIs), ICH Q8 (Pharmaceutical Development),
ICH Q9 (Quality Risk Management), ICH Q10 (Pharmaceutical Quality System)
Inspection scheduling could be even more risk-based, providing broader coverage with cooperative arrangements among trusted regulatory authorities.
Topics for today

Data basis

Results and Key points

Towards risk-based approaches

Challenges and Opportunities
How can we move towards a more global risk-based approach for management of foreign inspections?
Model for risk-based scheduling of inspections

Different suppliers
- Availability of drugs
- Public health
- Product portfolio
- Compliance requirement
- Audit history

An agency

Selection process

Perform / Delay Inspections

Risk-based scheduling of inspections
Principles on risk-based scheduling of audits: An industry approach

Qualitative assessment of suppliers for inspection / audit planning

- Purpose
  - Contribute to overall aim of ensuring supply of quality medicines
  - Obtain knowledge of a manufacturing site’s compliance and operations
  - Assure that the quality is fit for intended purpose

- Targeted risk-based inspections linked to protection of the patient
  - Focus on
    - Compliance (safety & efficacy)
    - Availability
    - Complexity of products / processes
    - Audit / inspection history


© IFPMA 2010
Determine frequency of on-site inspections

- On-site inspection is decided based on risk-based approaches allowed by law and considering the risk factors such as (translation from PMDA presentation:)

<table>
<thead>
<tr>
<th>Low risk</th>
<th>Product</th>
<th>Process</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- General</td>
<td>- Packaging/Labeling/Storage/Laboratory</td>
<td>- MRA</td>
</tr>
<tr>
<td></td>
<td>- General generic</td>
<td></td>
<td>- MoU</td>
</tr>
<tr>
<td></td>
<td>- Sterile generic</td>
<td></td>
<td>- PIC/S</td>
</tr>
<tr>
<td></td>
<td>- New entity</td>
<td></td>
<td>- Dosage form</td>
</tr>
<tr>
<td></td>
<td>- Sterile, new entity</td>
<td></td>
<td>- Information from other inspectorates</td>
</tr>
<tr>
<td></td>
<td>- Radioactive</td>
<td>- General</td>
<td>- Compliance history</td>
</tr>
<tr>
<td></td>
<td>- Biological</td>
<td>- Sterile</td>
<td>- Others</td>
</tr>
</tbody>
</table>

Others published or presented by PIC/S, US FDA, EMA, MHRA (UK)
Topics for today

Data basis

Results and Key points

Towards risk-based approaches

Challenges and Opportunities
Review of the data: Key points

- Industry favours regulatory inspections
  - To address challenges of globalisation
  - To facilitate independent evaluation of their facilities

- Many governments and regulators have established foreign inspection work plans
  - To inspect sites located worldwide that supply their country or region

- Conducting and receiving these inspections involve considerable use of regulatory and industry resources
  - Up to 16 inspections per manufacturing site in a year in some cases, but
  - A significant number of sites do not receive any inspection
Potential barriers

- **Local legal requirement**
  - Local drug laws require mandatory foreign inspection to protect public health

- **IP challenges**
  - Lack of, or uncertain, arrangements for the protection of confidential commercial and trade secret information between authorities

- **Mutual acceptance processes**
  - GMP-certificates are not accepted if issued by other inspectorates
  - Insufficient Mutual Recognition Agreements (MRA) between national/regional authorities
Practical opportunities now

- Continued and enhanced focus on risk-based approaches for scheduling and conducting inspections
- Information sharing and communication between regulatory agencies
- Work towards a global regulatory inspection framework
- Dialogue between parties involved
Alternatives to an on-site/desktop inspection

- **Sharing information and building trust**
  - Joining the Pharmaceutical Inspection Cooperation Scheme (PIC/S)
  - Confidentiality agreements
  - Stringent Regulatory Authorities showing the way
    - Transatlantic simplification initiative

- **Governmental agreements**
  - Mutual Recognition Agreement (MRA)
  - Memorandum of Understanding (MoU)

- **Accepting GMP-certificates based on legal formats**
  - GMP-certificates
  - Certificate of Pharmaceutical Product (CPP) according to WHO
  - Maintaining a list of ‘Countries of reference’: GMP-certificates issued by these countries are accepted, no bilateral agreements (e.g. MoU, MRA) needed

- **Using common document format**
  - For information about the sites e.g. PIC/S ‘Site Master File’ form
How to go forward?

- **Industry:**
  - Willingness to support agreements with health authorities e.g. joint inspections
  - Share knowledge regarding quality performance (e.g. audit, GMP inspection)
  - Continual support for harmonised approaches for GMP e.g. WHO, PIC/S, ICH Q7, Q9, Q10

- **Regulators:**
  - Continued cooperation efforts, agreements and advancement of risk based efforts on scheduling and conducting inspections
  - Recognition of harmonised approaches (e.g. PIC/S)

- **Regulators and Industry:**
  - Exchange information and facilitate communication

ICH Q7 (GMP for APIs), ICH Q8 (Pharmaceutical development), ICH Q9 (Quality Risk Management), ICH Q10 (Pharmaceutical Quality System)
Desired results

- Facilitate the best utilization of industry and regulator resources by
  - An appropriate level of regulatory oversight and international cooperation
  - Harmonization and mutual acceptance processes

- Enhance focus on risk-management approaches for inspections and related processes
Conclusion

- In summary, avoid major quality gaps in the supply chain by a risk-management approach associated to an optimized use of resources, in respect of local legal requirement.

- Keep the Patient Protection as the primary focus target.
Thank You!

Ch. Louis-Dunant 15
P.O. Box 195
121211 Geneva 20
Switzerland

Tel: +41-22-338 32 00
Fax: +41-22-338 32 99
Email: info@ifpma.org
Web: www.ifpma.org