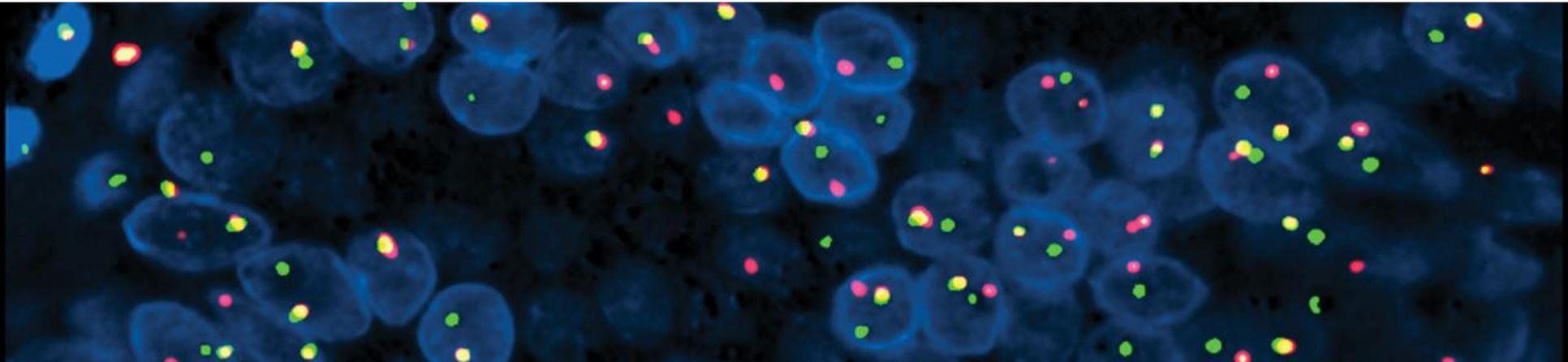


# PIC/S

Risk based approach to  
scheduling Inspections



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*ROCHE - PTQG – External Relations Europe*

*Washington, September 2014*

# CONTENTS

- References
- PIC/S updated information
- PIC/S Risk based model described
- How EU has adopted this recommendation

# References

**from European Union (EU), PIC/S, ISO standards etc.**

- PIC/S 002-3/25.09.2007 ***“Recommendation on Quality System Requirements for Pharmaceutical Inspectorate”***
- PIC/S SOP PI 031-1/29.07.2009 on ***“TEAM Inspections”***
- PIC/S Recommendation PI-037-1/01.01.2012 on ***“A Recommended Model for Risk-Based Inspection Planning in the GMP Environment”*** (for routine and follow-up inspections)
- ISO 17020:2012 ***“Requirements for the operation of various types of bodies performing inspection”***
- ISO 9001:2008 ***“Quality Management Systems”***
- ***EU Compilation of community procedures in inspections*** ([www.ema.europa.eu](http://www.ema.europa.eu)) (July 2013)
- Various ***Quality Systems of EU and PIC/S*** Inspectorates
- Collective ***experience of GMP Inspectors within PIC/S***

# PIC/S- Main features



**PIC/S' mission is:**

**"to lead the international development, implementation and maintenance of harmonised Good Manufacturing Practice (GMP) standards and quality systems of inspectorates in the field of medicinal products."**

# PIC/S- Main features

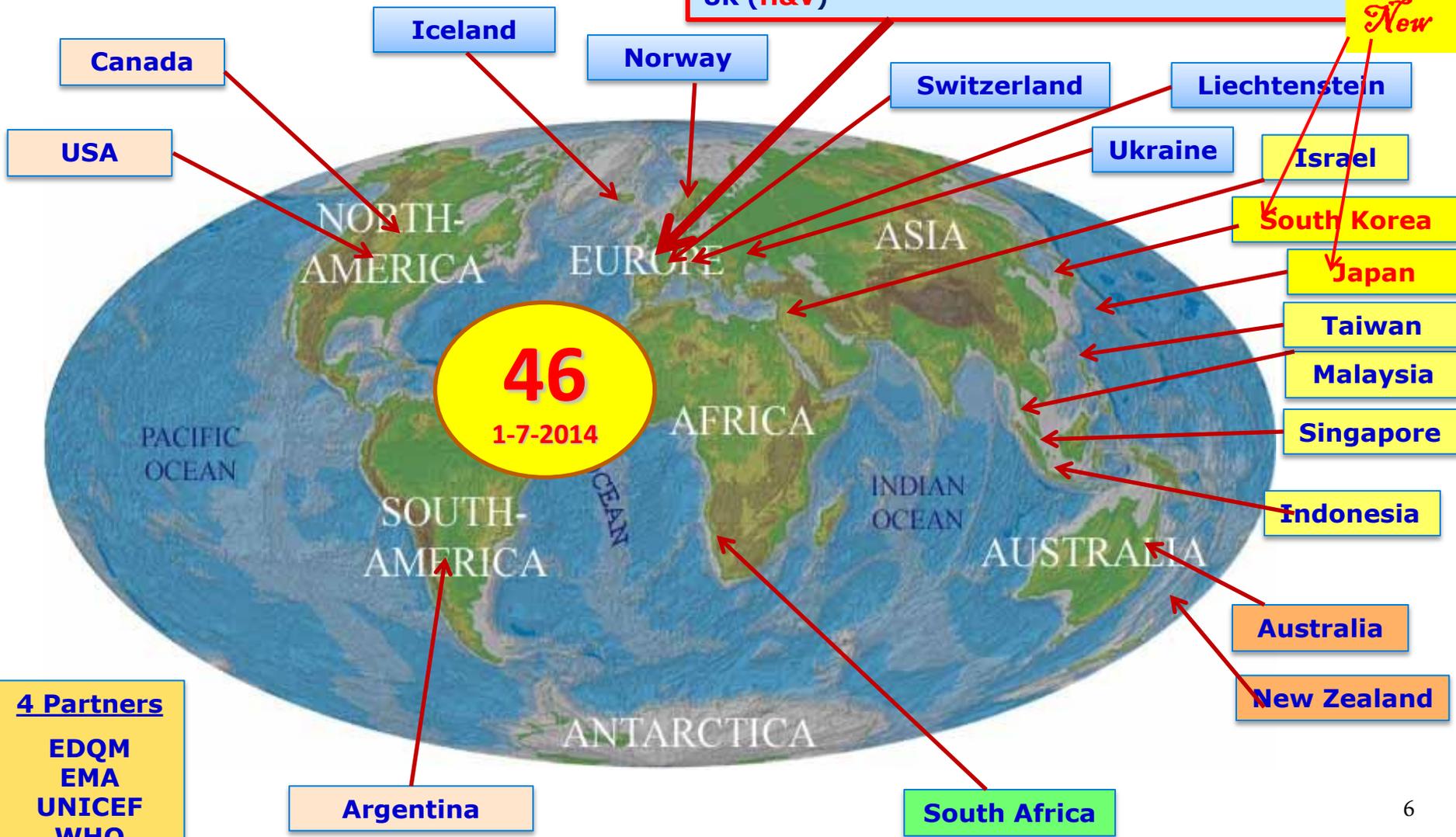
- Commenced operating in **November 1995**
  - It existed as “PIC” (Pharmaceutical Inspection Convention) since **1971**, a legal treaty between 10 countries. After EU completeness (1995) EU Member States could not sign treaties on their own, so it changed to PIC/S.
  - Is an **informal “Cooperative Arrangement”** between GMP regulatory authorities;
  - **NOT** a legal treaty between Countries / States
- A **forum of Inspectors** for:
  - **Networking and confidence building**
  - **Exchange of information and experience on GMP & GDP**
  - **Focus on Quality Systems for Inspectorates**
  - **Focus on training of GMDP inspectors**
  - **International harmonisation of GMDP**
- No obligation for member authorities to accept **inspection reports** of other members. But they share them and decide on the use.



September 2014

# PIC/S Member Authorities

EUROPEAN UNION Member States Agencies (28)			
Austria	Belgium	Czech Rep (H&V)	Cyprus (H)
Denmark	Estonia	Finland	France (H&V)
Germany	Greece	Hungary (H)	Ireland
Italy	Latvia	Lithuania	Malta
Netherlands	Poland	Portugal	Romania
Slovak Rep.	Slovenia	Spain	Sweden
UK (H&V)			



**4 Partners**  
EDQM  
EMA  
UNICEF  
WHO

# Current situation of candidates to PIC/S

## September 2014



### Applicants

Up to 6 years

1. **Brazil**
2. Philippines
3. Iran
4. Turkey
5. Hong Kong

### Pre – Applicants

Up to 2 years

1. Armenia
2. Belarus
3. Uganda
4. **Mexico**
5. Kazakhstan
6. **Chile**

### Interested

1. Thailand
2. **Nigeria**
3. China SFDA
4. Croatia
5. Bulgaria
6. Hungary (vet)
7. Saudi Arabia
8. Russia
9. Bhutan

Europe

Asia

Africa

America

## A citation about PIC/S at the 40th Anniversary Symposium Geneva, 31 May 2011



**Dr M. Hamburg, (US FDA Commissioner)  
with Mr. Tor Graberg, PIC/S Chair (2010-2011)**

- US FDA Commissioner, Dr. Margaret Hamburg, at her key-note address to the PIC/S 40<sup>th</sup> Anniversary Symposium, called upon all Regulatory Authorities to co-operate more closely and share information on GMP inspections, in particular in third countries. She said that ***"PIC/S' main advantage over a Mutual Recognition Agreement (MRA) is that it is not legally binding, thus allowing Participating Authorities to co-operate and share information informally (subject to confidentiality) while keeping complete control over imported medicinal products"***. What is perhaps most impressive is that you've ***created a high-functioning, cooperative arrangement among so many regulatory authorities from around the world***. By bringing us together, you (PIC/S) provide us with ***opportunities to share ideas and information*** and to exchange everything from inspection reports to recall alerts to visions of global drug quality."

# The Philosophy of PIC/S



**TRUST**

**+ COOPERATION**

**+ COLLABORATION**

**+ COMMUNICATION**



---

**HARMONISATION**

# Preparation of an Inspection



- The need for the inspection is determined in the cases:
  - **New site** (*usually scheduled to suit manufacturer after he submits an application*)
  - **Routine inspection** (*according to defined frequency or to risk based scheduling*)
  - **For-Cause Inspection** (*scheduled to investigate a quality problem*)
  - **Follow-up Inspection** (*after any other inspection, usually to verify CAPAs*)
- **Inspection frequency** based:
  - **Either according to existing legislation norms** (*every 2-3 years etc*)
  - **or according to risk factors**
  - **Here comes the Quality Risk Management Tool (QRM Tool)**

# Preparation of an Inspection

## Risk-Based Planning

The PIC/S Recommendation PI-037-1/01.01.2012 on

### *“A Recommended Model for Risk-Based Inspection Planning in the GMP Environment”*

Proposes the use of a simple QRM Tool defining:

- **Intrinsic risk:** *criticality and complexity of the site*
- **Compliance related risk:** *previously found deficiencies on site*
- ❖ **Risk Rating:** *deriving from the above two risks*
- ❖ **Frequency suggested:** *intervals according to the risk*
- ❖ **Scope of next routine Inspection:** *suggested based on above*





**PHARMACEUTICAL INSPECTION CONVENTION  
PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME**

PI 037-1  
2 Appendices  
1 January 2012

**RECOMMENDATION**

**A RECOMMENDED MODEL FOR  
RISK-BASED INSPECTION  
PLANNING IN THE GMP ENVIRONMENT**

# RECOMMENDED MODEL FOR RISK-BASED INSPECTION PLANNING

**Purpose** : to provide a simple and qualitative Quality Risk Management tool (QRM tool) in order to prioritize sites for inspection when planning.

**Methodology** : a simple two-page quality risk management tool.

Worksheet that is designed **to be completed by Inspectors immediately following an inspection** at the site. The worksheet is presented in Appendix 1 designed to not require more than several minutes to complete.

QRM tool should normally be applied to a site **AFTER a full inspection** has occurred. The **compliance status** of the site needs to be determined **BEFORE using this tool**.

# PRINCIPLES

Concepts and guidance set out in the following official documents:

- **ICH Q9** - Quality Risk Management
- **ICH Q10** – Pharmaceutical Quality Systems
- The **EMA Compilations of Community Procedures** Document No. EMA/INS/GMP/499073/2006 – A Model for risk-based planning for inspections of Pharmaceutical Manufacturers

Recommendation pre-supposes that every manufacturer will be inspected **at least once every three years** in order to meet the validity period of GMP certificate

# SCOPE

The scope is **limited to Planning Routine GMP Inspections** of manufacturers of:

- **active substances (APIs)**
- **medicinal products (MPs)**
- **Investigational Medicinal Products (IMPs)**
- **Follow-up activities**, such as assigning a new risk rating to the site following the receipt of new information about the site or its products. (new information might include quality defects, product recalls, market surveillance test results, etc.)

While this methodology has not been designed for the planning of GDP inspection programs or for the planning of inspections at pharmacies, it may be used as a basis for those purposes and it may be of help.

# SCOPE

## The Scope **DOES NOT** cover:

- The actual conduct of the Inspection
- The inspection at NEW sites as compliance has to be known for the initial rating
- Non-routine and emergency inspections related to quality defects
- For cause inspections, for example in order to assess a variation in a Marketing Authorization
- The Inspection to Blood and Tissue establishments

**Rule of thumb:** the tool should not be applied to a site until it has been granted a Manufacturing Authorisation and/or a GMP Certificate, as these actions indicate that the site will have been assessed from a compliance perspective.

# DESCRIPTION of the QRM tool

- The QRM tool allows Inspectorates **to assign a Relative Risk Rating to manufacturers** when planning the routine inspection program.
- The Inspectorates use the risk ratings generated **to assign a frequency** to the routine inspections to be performed.
- The risk ratings that are assigned to sites **are based on an assessment of two different kinds of risk:**
  - ❖ **Intrinsic risk:** *criticality and complexity of the site*
  - ❖ **Compliance related risk:** *previously found deficiencies on site*

# PART A – Information about the site

## PART B - INTRINSIC Risk

**Intrinsic risk:** *criticality and complexity of the site*

The intrinsic risk estimated for a site reflects the **complexity** of the site, its **processes and products** as well as the **criticality** of the products or services provided by the site including from a supply perspective.

Complexity	Criticality		
	1	2	3
1	<b>1</b> (low)	<b>2</b> (low)	<b>3</b> (medium)
2	<b>2</b> (low)	<b>4</b> (medium)	<b>6</b> (high)
3	<b>3</b> (medium)	<b>6</b> (high)	<b>9</b> (high)

# PART C - COMPLIANCE Related Risk

**Compliance related risk:** *previously found deficiencies on site*

The **compliance-related risk** that is estimated for the site reflects the GMP compliance status of the site immediately following the most recent routine inspection at the site. When this risk is being estimated, the classification and number of deficiencies identified at the last inspection are taken into account.

Deficiency profile	Compliance related risk score
≥ 1 Critical or ≥ 5 Majors	High
1 – 5 Majors	Medium
No majors or Criticals	Low

# PART D - RISK Rating

Once the **intrinsic risk** and the **compliance-related risk** associated with the site have been estimated, those two risks are then combined using a **simple matrix** to generate a relative risk rating for the site.

Compliance Risk	Intrinsic Risk		
	Low	Medium	High
Low	A	A	B
Medium	A	B	C
High	B	C	C

# PART E - Recommended FREQUENCY

A possible way of assigning Inspection frequencies according to the **RISK RATING**. Other approaches are also possible and every inspectorate may apply differently. The times shown are intervals and not fixed times.

RISK RATING	Suggested FREQUENCY
A	Reduced, 2 to 3 years
B	Moderate, 1 to 2 years
C	Increased, < 1 year

**No site with a High Risk rating should be inspected with low frequency.**

The inspection frequency should reflect the number and severity of deficiencies found in the last inspection: eg. If two sites have same Risk rating B, but one has poorer inspection outcome, then this should be inspected towards the short interval, towards 1 year.

Other factors that may be used are: the **robustness of the QS**, the **good response to CAPAs** and the **overall compliance history** etc.

# PART F - SCOPE of next Inspection

## PART G - Persons Signatures

- In PART F the **Recommended Scope of the next Routine Inspection** is documented, in particular the **depth**, the **focus**, the **duration**, the **number of inspectors** at the team, the possible use of any **specific experts**.
  - *This PART F should be **periodically updated** if new information is received about the site before the next routine inspection that may warrant a change in the scope of that inspection.*
  - *For example, information relating to Quality Defects, Recalls, Market Surveillance Test Results, Enforcement Investigations, and other indicators of non-compliance (eg the failure to implement a variation to an MA), might require a change to the scope of the next inspection. Information of major changes at the site may warrant a change in scope.*
- The PART G, the final part with the **Names, Dates and Signatures** of the competent persons who compiled the QRM form.

# Appendix 1: The Worksheet used by this Quality Risk Management Tool

## PART A – Preliminary Information about the Site

Site Name	
Site Address	
Licence Number (if any)	
FP or API Manufacturer?	
Last Inspection Date	
Name of previous lead Inspector	

## PART B – The Intrinsic Risk Associated with the Site

Risk Factor	Risk Score	Matrix for Estimating the Intrinsic Risk			
The Complexity of the site, its processes and products, is regarded as:	<div style="border: 2px solid orange; border-radius: 50%; padding: 5px; display: inline-block;">1 2 3</div> Circle one				
The Criticality of the products manufactured by the site, or the criticality of the analytical testing or other service offered provided by the site, is regarded as:	<div style="border: 2px solid red; border-radius: 50%; padding: 5px; display: inline-block;">1 2 3</div> Circle one				

	Criticality		
Complexity	1	2	3
1	1 (Low)	2 (Low)	3 (Med)
2	2 (Low)	4 (Med)	6 (High)
3	3 (Med)	6 (High)	9 (High)

**Use the above matrix and record the Intrinsic Risk associated with the site below:**

Low 
Medium 
High

## PART C – The Compliance-related Risk based on the last Inspection

The **compliance risk** indicated by the most recent deficiency profile of the site is:

Low   
 Medium   
 High

- No Major or Critical Deficiencies
- 1 to 5 Major Deficiencies: *Number of Majors = \_\_\_\_\_*
- 1 or more Critical Deficiencies or more than 5 Majors  
*(Note: Customise as appropriate)*

## PART D – The Risk-Rating assigned to the Site

Complete the matrix below by combining the Intrinsic risk score and the Compliance-related risk score to determine the **Risk Rating** for the site.

Compliance Risk	Intrinsic Risk		
	Low	Medium	High
Low	Risk Rating = A	Risk Rating = A	Risk Rating = B
Medium	Risk Rating = A	Risk Rating = B	Risk Rating = C
High	Risk Rating = B	Risk Rating = C	Risk Rating = C

The Risk Rating associated with this site is: A     B     C

## PART E – The Recommended Frequency for Routine Inspections at the Site

A	Reduced Freq, 2 to 3 yrs
B	Moderate Freq, 1 to 2 Yrs
C	increased Freq, < 1 yrs

*Customise as appropriate*

Using the Risk Rating, the recommended frequency for routine inspections at the site is an inspection every:

\_\_\_\_\_ Years or \_\_\_\_\_ Months

## PART F – Recommended Scope of the next Routine Inspection

*Note: This Part should be periodically updated if new information is received about the site before the next routine inspection that may warrant a change in the scope of that inspection.*

*For example, information can be received relating to, Quality Defects, Recalls, Market Surveillance Test Results, Enforcement Investigations, and other indicators of non-compliance, such as the failure to implement a variation to an MA, that might require the scope of the next inspection to be changed. Information may also relate to major changes at the site (indicated perhaps via an MA variation or a manufacturing authorisation variation submission) and this may warrant a change in scope.*

Document on the right the **recommended focus & depth** of the next routine inspection.

**Note:** Take into account the following:

- The areas in which deficiencies were identified during the most recent inspection at the site, particularly major and critical deficiencies;
- The areas that were not inspected (or that were not inspected in detail) during the most recent inspection at the site;
- The areas that were considered inadequately resourced at last inspection;
- Planned changes at the site that may alter the complexity or criticality risk ratings associated with the site
- Any other area that the inspector feels warrants review at the next inspection.

Document on the right the **required duration** of the next routine inspection:

Document on the right the **required number of inspectors** that should be assigned to the next routine inspection:

Document on the right any **specific competence or expertise** that will be required on the inspection team when performing the next routine inspection of the site:

## PART G – Signatures & Dates

Record here the names of the persons who completed this quality Risk management exercise, and sign and date this form:

Name: \_\_\_\_\_ Name: \_\_\_\_\_

Name: \_\_\_\_\_ Name: \_\_\_\_\_

Signed: \_\_\_\_\_ Date: \_\_\_\_\_

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Pharmaceutical Inspection Co-operation Scheme

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**Welcome to the PIC/S Website!**

The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (jointly referred to as PIC/S) are two international instruments between countries and pharmaceutical inspection authorities, which provide together an active and constructive co-operation in the field of GMP.

PIC/S' mission is "to lead the international development, implementation and maintenance of harmonised Good Manufacturing Practice (GMP) standards and quality systems of inspectorates in the field of medicinal products."

This is to be achieved by developing and promoting harmonised GMP standards and guidance documents; training competent authorities, in particular inspectors; assessing (and reassessing)

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# How EU / EMA adopted the PIC/S Recommendation



- European Medicines Agency (EMA) first adopted a Risk based approach document in Nov 2007, as already mentioned.
- EMA revised it as Document No. EMA/INS/GMP/321252/2012, in order to incorporate the PIC/S document.
- It is included in the **COMPILATION OF COMMUNITY PROCEDURES** that can be found in the EMA website (<http://www.ema.europa.eu>) and are used by all EU authorities.
- The 3<sup>rd</sup> country manufacturers are included in the SCOPE
- The EudraGMDP Database has to be updated. See Part E of the form:

PART E – The Recommended Frequency for Routine Inspections at the Site							
<table border="1"> <tr> <td style="width: 5%;">A</td> <td>Reduced Freq, 2 to 3 yrs</td> </tr> <tr> <td>B</td> <td>Moderate Freq, 1 to 2 Yrs</td> </tr> <tr> <td>C</td> <td>increased Freq, &lt; 1 yrs</td> </tr> </table>	A	Reduced Freq, 2 to 3 yrs	B	Moderate Freq, 1 to 2 Yrs	C	increased Freq, < 1 yrs	<p>Using the Risk Rating,</p> <p>1) the estimated re-inspection date is (Please update in EudraGMDP): .....</p> <p>2) the delay of re-inspection based on Appendix 4 is: max.....(months/years)</p> <p>3) the date of the next inspection by the Supervisory Authority is (Please update in EudraGMDP): .....</p>
A	Reduced Freq, 2 to 3 yrs						
B	Moderate Freq, 1 to 2 Yrs						
C	increased Freq, < 1 yrs						

# How EU / EMA adopted the Recommendation



More **FACTORS** are added to consider the **FREQUENCY** on top of the PIC/S document, mostly based on EU's legislation:

- The agency's knowledge of the company (overall compliance status and history of the company and facility).
- Results of product testing by OMCL's.
- Number and significance of quality defects (e.g. recalls).
- Marketing Authorisation variations affecting the site.
- A failure to implement a Marketing Authorisation variation on time.
- Compliance information from **trusted** authorities outside the EU.
  - The received compliance information is sufficient to enable the assessment of the GMP compliance of the site;
  - An authority can be considered as '**trusted**' when there is a high degree of similarity between the EEA's and the authority's inspection procedures and GMP standards (currently equivalent inspections can be considered in connection with an MRA, AACA and PIC/S).
- Major changes of building, equipment, processes, personnel.
- Experience with manufacturing of a product (e.g. frequency, volume, number of batches).

# How EU / EMA adopted the Recommendation



The EMA document has included **3 more Appendices** that deal in more detail with:

➤ **Guidance how to score the Intrinsic Risk Factors**

- *It includes a detailed description of how to assess the Site Complexity, the Process Complexity, the Product Complexity, and the Criticality*

➤ **Expenditure of time for Inspection**

- *According to the products produced*

➤ **Guidance on the delay of a re-inspection based on compliance information from a trusted authority**

- *Mainly used to decide on 3rd countries manufacturers and assess the «trusted» authorities information*

# EU GMP inspections organization:

## The Compilation of Procedures (<http://www.ema.europa.eu>)



Legal basis

Art. 3(1) Directive 2003/94

- Handling suspected defects and rapid alerts
- Dealing with GMP non-compliance
- Inspection procedures (GMP and GDP)
- Formats for manufacturing authorisation, GMP certificates and inspection reports
- Exchange of information procedures
- Training & Qualifications of GMDP Inspectors
- Triggers for API inspections
- Procedures for centralised inspections
- Verification of GMP in 3<sup>rd</sup> countries
- **Risk-based inspection planning**
- Quality System for GMP inspectorates

# Actual situation within PIC/S

## CONCLUSION



In conclusion, the PIC/S Recommendation is gradually applied by plenty of the PIC/S participating authorities, but in a variety of ways, while the main concept and principles are maintained:

- **Some authorities have elaborated sophisticated IT systems that support the Risk Rating, like MHRA/UK, TGA/Australia etc**
  - *Those systems are described in their respective websites*
- **Other authorities have started to use risk based approach planning in a step-by-step approach, often as a pilot project**

The **Risk-based approach of scheduling Inspections** is one of the recommendations promoting the **global cooperation of authorities and the reasonable use of resources.**

*Doing now what patients need next*