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A model for risk based planning for inspections of pharmaceutical manufacturers

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A model for risk based planning for inspections of pharmaceutical manufacturers

1. Introduction

1.1. According to Directive 2001/83/EC and Regulations 536/2014 and 2019/6, respectively, the Competent Authority shall ensure, by means of inspections, that the legal requirements governing medicinal products are complied with. The Competent Authority may also carry out unannounced inspections at the premises of manufacturers of active substances used as starting materials, or at the premises of marketing authorisation holders whenever it considers that there are grounds for suspecting non-compliance with the principles and guidelines of good manufacturing practice.

1.2. A risk based approach to inspection planning will enable the frequency, depth and breadth of inspections to be determined accordingly. This will allow flexible and effective administration and supervision whilst maintaining a high level of patient safety.

1.3. Competent Authorities of the Member States need to develop a systematic and risk-based approach to make the best use of their surveillance and enforcement resources while maximizing the impact of those resources on the public health

1.4. Each Competent Authority should have a written procedure that covers the preparation, realization and supervision of an annual inspection programme. This programme should ensure that the extent and frequency of inspections can be adhered to as planned. Sufficient resources must be determined and made available to ensure that the designated programme of inspections can be carried out in an appropriate manner.

1.5. This document sets out a simple and flexible Quality Risk Management tool that may be used by GMP Pharmaceutical Inspectorates when planning the frequency and scope of GMP inspections. It is a methodology that is based upon the concept of rating manufacturing sites on the basis of an estimated risk that they may pose to patients, consumers, animals and users of medicines. The methodology also takes into account the risk to product quality.

1.6. The methodology provides a simple two-page quality risk management worksheet that is designed to be completed by Inspectors immediately following an inspection at the site. The worksheet is presented in Appendix 1 to this document and is designed to not require more than several minutes to complete.

1.7. This Quality Risk Management tool was designed in line with the principles, concepts and guidance set out in the following official documents:

Figure: 1. PI-37-1- A Recommended Model for Risk-based Inspection Planning in the GMP Environment;

Figure: 2. ICH Q9 - Quality Risk Management;

Figure: 3. Annex 20 to the PIC/S GMP Guide;

Figure: 4. ICH Q10 – Pharmaceutical Quality Systems.

2. Purpose

2.1. This document outlines recommendations for a risk based planning system according to which sites that fall under regulatory supervision are subject to inspection.

2.2. It is intended that each GMP Pharmaceutical Inspectorate uses the document as the basis for developing and implementing its own annual inspection programme.

2.3. The purpose of this document is to provide a simple and qualitative Quality Risk Management tool that may be of use to GMP Pharmaceutical Inspectorates to prioritise sites for inspections when planning the frequency and scope of GMP inspections.

3. Scope

3.1. The scope of this document covers the following:

Figure: 1. The planning of routine GMP inspections of active substance and medicinal product manufacturers by the Competent Authorities of the Member States;

Figure: 2. Domestic and third country manufacturers;

Figure: 3. The planning of routine GMP inspections of Investigational Medicinal Product (IMP) manufacturers by the Competent Authorities of the Member States;

Figure: 4. 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. (Note: this normally occurs between inspections and the types of new information might include information on quality defects, product recalls, market surveillance test results, etc.);

Figure: 5. Note: While this methodology has not been designed for the planning of GDP inspection programmes or for the planning of inspections at pharmacies, some countries may choose to use it as a basis for those purposes and it may be of help in those areas.

3.2. The scope of this document does not extend to the following:

Figure: 6. The actual conduct of an inspection;

Figure: 7. The planning of inspections at new manufacturers before any inspection has taken place;

Figure: 8. This methodology requires knowledge of the GMP compliance status of the site. It is considered that new sites should not be rated for their initial inspection in accordance with this Quality Risk Management tool, because the GMP Pharmaceutical Inspectorate in question will not likely have sufficient knowledge about the site to assign a risk rating to that site. (However, certain aspects of this methodology, such as the intrinsic risk evaluation, may be useful to apply to new sites when planning inspections at new sites.);

Figure: 9. The planning of non-routine and emergency inspections at manufacturers, such as when a Critical deficiency or many Major deficiencies have been identified during a recent inspection;

Figure: 10.

Figure: 11. It is usually not necessary or indeed helpful to use a formal Quality Risk management methodology such as this one to determine whether a non-routine or emergency inspection should be performed;

Figure: 12. The planning of for-cause inspections that must be carried in order to approve or reject a variation application to a Marketing or Manufacturing Authorisation;

Figure: 13. The methodology presented in this document was not designed to apply to the inspection of blood and tissue establishments, but it may be modified for application in this area;

Figure: 14. This Quality Risk Management tool should not normally be applied to a site until a full inspection at the site has occurred. This is because the compliance status of the site needs to be determined in order to use this tool;

Figure: 15. If a site has had one initial inspection but if the GMP Pharmaceutical Inspectorate in question considers that this initial inspection was not a 'full' inspection of the site and that one or more additional inspections are required before the site can be considered to have had a 'full' inspection, such sites should not be rated using this Quality Risk Management tool until they have been subjected to a 'full' inspection;

Figure: 16. A useful rule of thumb to use is that the tool should not be applied to a site until the site 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;

Figure: 17. This procedure covers both human and veterinary medicinal products.

4. Procedure

4.1. Principle

Planning and scheduling of inspections is realised as follows:

Figure: 18. Complete the worksheet presented in Appendix 1 to this document immediately following an inspection at the site.

- Assign risk ranking (based on an intrinsic risk and a compliance-related risk) for each site;

- Establish the recommended inspection frequency;

- Establish the recommended scope of the next routine inspection.

Figure: 19. Establish the necessary expenditure of inspection time for each site (see Appendix 3);

Figure: 20. Update the frequency and/or scope of the next routine inspection as new information on the compliance status of the site or on its activities and products is received;

Figure: 21. In the case of manufacturing sites in third countries, this information should be put in EudraGMDP planning module.

4.2. This Quality Risk Management methodology is a simple tool that allows GMP Pharmaceutical Inspectorates to assign a relative risk rating to manufacturers when planning the routine inspection programme for those sites.

4.3. The risk ratings that are generated using this methodology may be used by the GMP Pharmaceutical Inspectorate to assign a frequency to the routine inspections that will be performed at the various manufacturers under its supervision.

4.4. The scope of an inspection may be general and cover the full range of activities at the site, or may be limited to specific activities. Where the latter approach is used, the Competent Authority should ensure that all relevant critical activities are covered within a 5 year period.

4.5. Generally the interval between inspections by trusted authorities[1] should not exceed 3 years as lack of continuity may give rise to lower awareness of current GMP or allow significant deficiencies to develop. The necessity to carry out immediate (non-routine) inspections e.g. due to product quality defects or significant changes of building, equipment or processes is not affected. This methodology is not designed to be used to determine when such non-routine inspection should occur, as there is usually no need to use a formal tool such as this one to decide when such an inspection should occur.

4.6. The risk ratings that are assigned to sites are based on an assessment of two different kinds of risk - an intrinsic risk and a compliance-related risk.

4.7. 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. These items (complexity and criticality) usually remain fairly constant regardless of the compliance status of the site. Therefore, one usually cannot estimate this risk on the basis of inspection deficiencies or compliance history.

4.8. 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.

4.9. Note: Guidance on how to assess the intrinsic risk is provided in Appendix 2. This is important to read before using the tool. A table is provided in the worksheet (Appendix 1) showing how to assess the compliance-related risk.

4.10. 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. It is this risk rating that is considered when deciding the frequency of the next routine inspection at the site.

4.11. To define the scope and date of the next inspection of the manufacturing site, the Competent Authority should also take into account the following factors:

4.11.1 Agency's knowledge of the company (overall compliance status and history of the company and facility).

4.11.2 Results of product testing by OMCL's.

4.11.3 Number and significance of quality defects (e.g. recall).

4.11.4 Marketing Authorisation variations affecting the site.

4.11.5 A failure to implement a Marketing Authorisation variation on time.

4.11.6 Compliance information from trusted authorities outside the EU.

The main pre-requisites for consideration of compliance information from international partners are:

[1] Please see 4.11.6. for a definition of 'trusted authorities'.

Figure: 1. The manufacturer has already undergone a full inspection by an EU/EEA Competent Authority in the past;

Figure: 2. The received compliance information is sufficient to enable the assessment of the GMP compliance of the site;

Figure: 3. 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).

Guidance on the delay of a re-inspection of a manufacturer based on the inspectorate's assessment of the intrinsic and compliance-related risks and compliance information from a trusted authority is provided in Appendix 4.

4.11.7 Major changes of building, equipment, processes, personnel.

4.11.8 Experience with manufacturing of a product (e.g. frequency, volume, number of batches).

4.12. With regard to the scope of the next routine inspection at the site, this is not determined using the risk rating that is assigned to the site. Instead, this Quality Risk Management methodology requires certain other items to be considered when the recommended scope of the next inspection is being documented.

These other items are:

4.12.1 The required focus and depth of the next routine inspection of the site.

4.12.1 The required duration of the next routine inspection of the site.

4.12.1 The required number of inspectors to be assigned to the next routine inspection of the site.

4.12.1 Whether any specific competence or expertise will be required on the inspection team when performing the next routine inspection of the site.

4.13. When determining the required focus and depth of the next routine inspection, the methodology requires the inspector to consider the following items before making his/her recommendation:

4.13.1 The areas in which deficiencies were identified during the most recent inspection at the site, particularly major and critical deficiencies.

4.13.1 The areas that were not inspected (or that were not inspected in detail) during the most recent inspection at the site.

4.13.1 The areas that were considered during the last inspection to have been inadequately resourced at the site.

4.13.1 Any other area that the inspector feels requires detailed review at the next inspection.

4.14. The recommended scope of the next routine inspection is documented on the worksheet after the last inspection has been performed at the site. The person who should do this will normally be the inspector who led the last inspection at the site in question. (This approach is advantageous because it utilises the existing knowledge of the inspector who most recently inspected the site.)

4.15. Expenditure of time

Appendix 3 gives guidance values for the required inspection time per type of site. The time spent on the site may be adjusted in accordance with the national re-inspection programmes of the Competent Authorities. The type of manufacturing site is classified by the relevant dosage form and the manufacturing process, respectively.

The required time may be adjusted accordingly, depending on these factors:

- The type of inspection (full vs. part inspection);
- The complexity of the site (size, variety of facilities);
- The complexity of the manufacturing process (type and sequence of operations, process controls applied);
- The complexity of the product and its therapeutic significance;
- The patient exposure;
- The compliance history of the site.

4.16. This methodology recognises that new information on the compliance status of the site or on its activities and products may be received by the Inspectorate after the site has been rated using this methodology to determine the frequency of the next routine inspection, and after the scope of the next routine inspection has been documented.

4.17. This methodology also recognises that changes made (or proposed to be made) at a site may trigger a non-routine inspection at the site. Again, as stated above, this methodology is not designed to be used to determine when such non-routine inspection should occur, as there is usually no need to use a formal tool such as this one to decide when such an inspection should occur.

4.18. Calculation of the next inspection date

The calculation of the next inspection date results from the last inspection date and the inspectorate's risk assessment process following this procedure and is documented in the worksheet (Annex 1).

4.19. Responsibilities and supervision

The responsibility for the compilation and supervision of an annual inspection programme should be defined within the GMP Pharmaceutical Inspectorate. A periodical review of the inspection programme should ensure that serious deviations from the time plan are noticed and corrective actions taken as necessary.

5. How to Use This Quality Risk Management Tool

5.1. When using this Quality Risk Management tool, a two-page worksheet document needs to be completed for each site that is being rated. The format of this worksheet is shown in Appendix This worksheet contains seven parts, A through G.

5.2. Part A of the Quality Risk Management tool worksheet – Preliminary Information

Part A is where preliminary information about the site is documented. This includes the site name and address, the authorisation numbers held by the site, etc.

5.3. Part B of the Quality Risk Management tool worksheet – Intrinsic Risk

Part B is where the intrinsic risk associated with the site is estimated. There are two risk-indicating factors that need to be considered here – the complexity of the site, its processes and products, and the criticality of the products manufactured by the site (or the criticality of the services provided by the site, such as contract analytical testing services).

Appendix 2 provides detailed guidance on the meaning of each of these items (Complexity and Criticality) and on how to score each.

A score of 1, 2 or 3 is assigned to the Complexity factor and this is documented on the worksheet in Part B. (A complexity of 3 represents a high complexity; a complexity of 1 represents a low complexity.)

A score of 1, 2 or 3 is assigned to the Criticality factor and this is documented on the worksheet in Part B. (A complexity of 3 represents a high Criticality; a complexity of 1 represents a low Criticality.)

A Matrix, table, shown in Table 1 below, is provided on the worksheet for combining these two scores to generate an estimate of the Intrinsic risk associated with the site, and this is also documented in Part B.

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

Table 1: Intrinsic Risk Matrix

A total score of 1 or 2 represents a Low Intrinsic Risk

A total score of 3 or 4 represents a Medium Intrinsic Risk

A total score of 6 or 9 represents a High Intrinsic Risk

5.4. Part C of the Quality Risk Management tool worksheet – Compliance Risk

Part C is where the *compliance-related risk* associated with the site is estimated and documented. This is solely based on the deficiencies identified at the last inspection of the site. (Note: If the last inspection was not a routine or a full inspection, the deficiencies identified at the last routine (or full)

inspection as well as those identified at the last non-routine inspection should be taken into account when scoring this risk).

The following table is provided as guidance when scoring the *compliance- related risk* associated with the site. The contents of this table may be customised to reflect the policy of the Inspectorate using this methodology.

2. Deficiency Profile	3. Compliance-related Risk Score
a. or more Critical	5. High
6. From 1 to 5 Major Deficiencies	7. Medium
8. No Major or Critical Deficiencies	9. Low

Table 2: Compliance Risk Table

A score of High, Medium or Low is assigned to the *compliance-related risk* associated with the site, and this is documented on the worksheet in Part C.

It is recognised that sites with a High Compliance-related Risk Score may need to be inspected again very soon after the inspection that identified the poor state of compliance. Such sites may also be directed to cease production and they may have their manufacturing licence revoked or varied until they demonstrate a satisfactory level of compliance during a follow-up inspection.

In this regard, it is important to note the following:

- Such follow-up inspections are by definition non-routine. They are also sometimes referred to as 'for-cause' or 'emergency' inspections and they may occur when a site has had a Critical or many Major deficiencies (e.g. 6 or more Majors) identified;
- When a site warrants such a follow-up inspection, (e.g. within 3 months of the previous inspection), the use of this Quality Risk Management tool should be suspended until after the for-cause inspection, at which time the routine inspection programme will likely restart for the site. In practice, this can mean that, when a site has been given a Critical or a large number of Major deficiencies, (e.g. 6 or more), and if a follow-up for-cause inspection is planned in response to those deficiencies, the GMP Pharmaceutical Inspectorate should only apply this tool to the site again after the for-cause follow-up inspection has been completed and the routine inspection programme restarted;
- When resuming use of this tool in relation to the site in question, the Compliance Risk Score assigned to the site should be based on the deficiencies identified during the initial problematic inspection (i.e. the one with the Critical or the many Major deficiencies) as well as any deficiencies identified during the follow-up inspection;

5.5. Part D of the Quality Risk Management tool worksheet – Overall Risk Rating

Part D is where the intrinsic risk and the compliance-related risk associated with the site are combined to generate the overall risk rating for the site.

A simple matrix, as shown in Table 3 below, is provided on the worksheet for generating this risk rating, and the resulting risk rating is documented in Part D of the Worksheet.

10.	11. Intrinsic Risk		
12. Compliance Risk	13. Low	14. Medium	15. High

16. Low	17. Risk Rating = A	18. Risk Rating = A	19. Risk Rating = B
20. Medium	21. Risk Rating = A	22. Risk Rating = B	23. Risk Rating = C
24. High	25. Risk Rating = B	26. Risk Rating = C	27. Risk Rating = C

Table 3: Risk Rating Matrix

There are three possible risk ratings, A, B & C. ('A' represents a relatively low risk site and 'C' represents a relatively high risk site).

5.6. Part E of the Quality Risk Management tool worksheet – Inspection Frequency

Part E is where the risk rating from Part D is used to generate and document the recommended frequency for routine inspections at the site.

Sites with an 'A' Risk Rating have at least one Low risk score for Intrinsic risk or for Compliance risk. During routine inspection programmes, these sites may be inspected at a reduced frequency, for example, at a frequency less than every two years (e.g. one inspection every 2.5 years);

Sites with a 'C' Risk Rating have at least one High risk score for Intrinsic or for Compliance risk. During routine inspection programmes, these sites may be inspected at an increased frequency, for example, at least annually or even more frequently;

Sites with a 'B' Risk Rating lie in-between and during routine inspection programmes, these sites may be inspected at an intermediate frequency, for example, between 12 and 24 months.

Table 4 below shows one possible way of assigning inspection frequencies based on the Risk Rating. Other approaches may also be used.

28. Risk Rating	29. Suggested Inspection Frequency
30. A	31. Reduced Frequency, 2 to 3 yrs
32. B	33. Moderate Frequency, 1 to 2 yrs
34. C	35. Increased Frequency, < 1 yr

Table 4: Suggested Inspection Frequency for Each Risk Rating

Note 1: The above Risk Rating matrix is designed so that no site with a High Intrinsic Risk score or a High Compliance Risk score is assigned a reduced inspection frequency. This is because it is considered wise to adopt a policy of inspecting all sites with a high intrinsic or compliance risk rating at least once every two years during routine inspection programmes. However, when a site has been given a High Compliance Risk score, as noted above in Section 7.1.3, a non-routine, for-cause inspection may be required at the site, and this has implications for the use of this tool during that time. See Section 5.1.3 for further details.

Note 2: It is important to note that the inspection frequencies shown in Table 4 above are presented in terms of time range intervals, not absolute time intervals.

For example, for sites assigned a 'B' Risk Rating, the time range for the inspection frequency is set out at 1-2 years; it is not an absolute 2 years;

The actual inspection frequency assigned to a site within any one Risk Rating (A, B or C) should reflect the number and type of deficiencies that were identified during the last inspection;

For example, if two sites are assigned a Risk Rating of B, but if one of the sites had a poorer last inspection outcome than the other (e.g. five Major deficiencies versus one Major) the exact inspection

frequency assigned to the former site should generally be towards the more restrictive end of the time range (i.e. an inspection frequency closer to one year than to two years);

In addition, the inspection frequencies assigned to sites that have the same Risk Ratings may take into account the individual scores for the intrinsic and compliance risks. For example, when a site has both a High Intrinsic Risk and a High Compliance Risk, resulting in an overall Risk Rating of C, the assigned inspection frequency (e.g. 9 months) may be higher than that assigned to a site which has a High Intrinsic Risk but a Medium Compliance Risk, which also results in an overall Risk Rating of C;

Note 3: In some cases, the Inspector(s) who last inspected a site may disagree with the inspection frequency that is assigned to that site using this methodology.

If this occurs and if the Inspector(s) believe that a different Inspection frequency should be assigned to the site, the reasons for this should be formally documented. Factors which may be useful to consider here are:

- The robustness of the Quality Management System, including its approach to Quality Risk Management;
- The general GMP compliance history of the site, taking into account recurring non-compliance issues and failures to address deficiencies following inspections in a satisfactory manner;
- Significant failures to address previous GMP deficiencies.

Recognising that the outcomes of Quality Risk Management work can be subjective and uncertain, the Inspector's views may modify the inspection frequency assigned by this methodology;

However, each Inspectorate may wish to adopt its own approach when such situations arise, and those approaches may differ from that presented above.

5.7. Part F of the Quality Risk Management tool worksheet – Inspection Scope

Part F is where the recommended scope of the next routine inspection is documented. This Part should be completed either immediately after the inspection, or once the inspection report has been issued, and ideally at the same time as the previous sections.

There are four sections to complete in Part F, as follows:

- The required focus and depth of the next routine inspection of the site;
- The required duration of the next routine inspection of the site;
- The required number of inspectors to be assigned to the next routine inspection of the site;
- Whether any specific competence or expertise will be required on the inspection team when performing the next routine inspection of the site.

Once Parts E and F have been completed, the recommended frequency and scope of the next routine inspection will have been documented on the worksheet. It is anticipated that the inspection planning staff at the GMP Pharmaceutical Inspectorate in question may then use this information when planning the routine inspection programme for the manufacturing sites under their supervision.

5.8. Part G of the Quality Risk Management tool worksheet – Who & When

Part G is where the names of the persons that have completed the Quality Risk Management exercise are documented, and the signature (and date) of the person who completed the worksheet form is also recorded here.

Reviewing and Updating the Quality Risk Management exercises as required

The outputs of Quality Risk Management exercises performed using this methodology should be reviewed when new information becomes available to the Inspectorate that may change the risk profile of a site.

Such new information may arise from quality defect issues, recalls, market surveillance test results, assessment findings, enforcement investigations, site changes, etc;

In addition, variations to Marketing or Manufacturing Authorisations may mean that the activities of a site are to expand or change substantially. For example, an MA variation to switch from glass to plastic ampoules as the primary packaging component for a product may require the introduction of blow-fill-seal technology at the manufacturing site. Such MA variations may change the complexity or criticality associated with the site and, for the purposes of this methodology, such variations may be regarded as new information about the site;

Significant changes in the number of personnel at a site are also useful to consider from a risk perspective during the review phases, because such changes may indicate a change in the complexity of the site, thus possibly affecting the intrinsic risk, or, they may mean that there are fewer QA resources available at the site, which could lead to compliance problems later on;

Also, the company's response report following the most recent inspection report should be considered as new information and is useful to review during this stage of applying this methodology. This is because the Inspector who reviews the company's response report may decide that there are specific aspects relating to the responses that need to be closely followed up on during the next inspection; this may thus warrant an expansion in the scope of the next routine inspection.

The above types of new information may warrant not only a change in the recommended scope of the next routine inspection, they may also require a change in the recommended frequency of the next routine inspection. It is left up to each individual Inspectorate to manage how the Quality Risk Management exercise pertaining to an individual site should be updated upon receipt of new information about the site.

It is recommended that these Quality Risk Management exercises be subjected to formal periodic review.

6. Revision History

Date	Version Number	Reasons for revision

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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:	**1 2 3** **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:	**1 2 3** **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.

	Intrinsic Risk		
Compliance 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

Using the Risk Rating,
1) the estimated re-inspection date is (Please update in EudraGMDP): ……
2) the delay of re-inspection based on Appendix 4 is: max..... (months/years)
3) the date of the next inspection by the Supervisory Authority is (Please update in EudraGMDP): …….

Appendix 1 cont'd

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 risk rating and 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:	
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: _____	

Appendix 2: Guidance on How to Score the Intrinsic Risk Factors

No.	Intrinsic Risk Factor & Scoring Mechanism
1	**Complexity** **This concerns the complexity of the site, its processes and its products.** (Note: The Site Master File (if available) and the last GMP inspection report can be useful sources of information on which to assign the Complexity score.) There are three possible scores here, 1, 2 and3. Sites with a low risk factor score in this area are known to have a low level of complexity in the design of the site, in its products and processes. When scoring this Risk Factor, it is useful to consider the following: General but useful indicators of **site complexity** are: • The size of the site – large sites are rated more complex than smaller sites • The number of different manufacturing or distribution processes that are in use at the site – larger numbers generally give rise to more complexity • The level of dedication of equipment and facilities (e.g. Air Handling Units) that is in place at the site – sites with a low level of dedication are considered more complex than other sites • The number of staff at the site – larger numbers generally give rise to more complexity • The number of commercial markets/countries supplied by the site - larger numbers generally give rise to more complexity • The number of customers supplied by the site - larger numbers generally give rise to more complexity • If the site is a contract manufacturer or contract laboratory, the site can be regarded as being relatively complex General but useful indicators of **process complexity** are: • Sterile and aseptic manufacturing processes – these are always considered highly complex processes. • Parametric release activities – these are usually considered highly complex processes. • The number of critical steps that must be controlled within a process – generally, processes with a high number of critical steps can be considered to be more complex processes. • The type of products manufactured – some product types such as low-concentration/high potency dosage forms and sustained released dosage forms can be more complex to manufacture than other types of products (such as immediate release tablets) and the complexity of their manufacturing process should be rated more highly here. • The number of unit operations in a non-sterile manufacturing process - larger numbers generally gives rise to more complexity. • Repackaging activities - repackaging an already packaged batch can be considered a moderately to highly complex process. • The extent of reprocessing or reworking taking place at the site: these activities can add complexity to the process • Biological processes

	• The extent of subcontracting in use by the site - a significant use of contract manufacturers, off-site distribution sites or contract laboratories generally gives rise to complexity. • In case of importers, the complexity of importation, batch release and product distribution processes – sometimes the arrangements in place for importation can be quite complex. General but useful indicators of **product complexity** are: • The number of components that make up any one product pack - larger numbers of components in a pack generally give rise to more product complexity. For example, a pack of an injectable product may have 4 components within it (a lyophilised vial, a diluent vial, a transfer needle and a technical leaflet, whereas a pack of a tablet product may have just a blister strip and a patient information leaflet within it.) • Products requiring special storage and distribution: (e.g. cold chain products and short-shelf-life products such as radiopharmaceuticals can be complex to manage.) **Tip: When considering product complexity, it is useful to imagine that you are holding a pack of the product in your hand and are asked: "What aspects of this product render it a complex product?"** Scoring Guideline: Assign a score of 1 to sites with a low overall level of Complexity Assign a score of 2 to sites with a moderate overall level of Complexity Assign a score of 3 to sites with a high overall level of Complexity Note: When assigning the overall complexity rating, the rating (1, 2 or 3) which most reflects the various individual complexity ratings that were assigned to site, process and product complexity should be chosen. This is similar to taking an average of all of the individual complexity ratings that were assigned. In cases where there is insufficient information or knowledge about the complexity associated with the site, its processes and products, a medium score of 2 should be assigned.
2	**Criticality:** **This concerns how critical the availability of the products manufactured by the site is from a supply perspective, or how critical the services provided by the site are. An example of a critical service provided by a site may be an analytical testing service performed for several other companies.** (Note: The Site Master File (if available) and the last GMP inspection report can be useful sources of information on which to assign the Criticality score.) There are three possible scores here, 1, 2 and3. Scoring Guideline: Assign a high score (of 3) to sites that are known to manufacture essential products or that are known to be sites that provide an essential service that is not readily available elsewhere.

	Figure: 1. These may be sites that are the major or sole supplier of an essential product (such as an important vaccine, a critical blood product, etc.). Note: it is recognised that being the major or the sole supplier of an essential product does not present any risk to product quality; rather, it presents a risk to product availability. Figure: 2. The test methods (and related equipment) used by these sites cannot easily or readily be performed or used by other laboratories. Figure: 3. These may be sites that provide a contract manufacturing or testing service to a number of other manufacturers and a disruption in such services would have a significant impact on product availability. Figure: 4. Assign a low score (of 1) to sites that are known to manufacture only non-essential products or that are known to be sites that do not provide an essential service. Figure: 5. These may be sites that are not the sole supplier of any important products (such as an important vaccine, a critical blood product, etc.). Figure: 6. The test methods (and related equipment) used by these sites are not such that they cannot be readily performed or used by other laboratories. Figure: 7. These are not sites that provide a contract manufacturing or testing service to many other manufacturers, where a disruption in such services would have a significant impact on product availability. Assign a medium score (of 2) to sites that are in between the above types of sites. Note: In cases where there is insufficient information or knowledge about the criticality associated with the site, a medium score of 2 should be assigned.

Appendix 3- Expenditure of Time

Classification of manufacturing or importation sites according to the type of product/process		Overall inspection days
1.1	**Sterile Products**	
	1.1.1 Aseptically prepared (list of dosage forms) 1.1.1.1 Large volume liquids 1.1.1.2 Lyophilisates 1.1.1.3 Semi-solids 1.1.1.4 Small volume liquids 1.1.1.5 Solids and implants	**≥ 10**
	1.1.2 Terminally sterilised (list of dosage forms) 1.1.2.1 Large volume liquids 1.1.2.2 Semi-solids 1.1.2.3 Small volume liquids 1.1.2.4 Solids and implants	**≥ 8**
	1.1.3 Batch certification only	**≥ 1**
1.2	**Non-sterile products**	
	1.2.1 Non-sterile products (list of dosage forms) 1.2.1.1 Capsules, hard shell 1.2.1.2 Capsules, soft shell 1.2.1.3 Chewing gums 1.2.1.4 Impregnated matrices 1.2.1.5 Liquids for external use 1.2.1.6 Liquids for internal use 1.2.1.7 Medicinal gases 1.2.1.8 Other solid dosage forms 1.2.1.9 Pressurised preparations 1.2.1.10 Radionuclide generators 1.2.1.11 Semi-solids 1.2.1.12 Suppositories 1.2.1.13 Tablets 1.2.1.14 Transdermal patches 1.2.1.15 Intraruminal devices 1.2.1.16 Veterinary premixes	**≥ 4**
	1.2.2 Batch certification only	**≥ 1**
1.3	**Biological medicinal products**	
	1.3.1 Biological medicinal products 1.3.1.1 Blood products 1.3.1.2 Immunological products 1.3.1.3 Cell therapy products 1.3.1.4 Gene therapy products 1.3.1.5 Biotechnology products 1.3.1.6 Human or animal extracted products	**≥ 7**
	1.3.2 Batch certification only (list of product types) 1.3.2.1 Blood products 1.3.2.2 Immunological products 1.3.2.3 Cell therapy products 1.3.2.4 Gene therapy products 1.3.2.5 Biotechnology products 1.3.2.6 Human or animal extracted products	**≥ 1**

1.4	**Other products or manufacturing activity**	
	1.4.1 Manufacture of: 1.4.1.1 Herbal products 1.4.1.2 Homoeopathic products 1.4.1.3 Biological active starting materials *1.4.2 Sterilisation of active substances/excipients/finished product:* 1.4.2.1 Filtration 1.4.2.2 Dry heat 1.4.2.3 Moist heat 1.4.2.4 Chemical 1.4.2.5 Gamma irradiation 1.4.2.6 Electron beam	**> 3** **>2**
1.5	**Packaging only**	
	1.5.1 Primary packing 1.5.1.1 Capsules, hard shell 1.5.1.2 Capsules, soft shell 1.5.1.3 Chewing gums 1.5.1.4 Impregnated matrices 1.5.1.5 Liquids for external use 1.5.1.6 Liquids for internal use 1.5.1.7 Medicinal gases 1.5.1.8 Other solid dosage forms 1.5.1.9 Pressurised preparations 1.5.1.10 Radionuclide generators 1.5.1.11 Semi-solids 1.5.1.12 Suppositories 1.5.1.13 Tablets 1.5.1.14 Transdermal patches 1.5.1.15 Intraruminal devices 1.5.1.16 Veterinary premixes	**> 2**
	1.5.2 Secondary packing	**> 1**
1.6	**Quality control testing**	
	1.6.1 Microbiological: sterility *1.6.2 Microbiological: non-sterility* *1.6.3 Chemical/Physical* *1.6.4 Biological*	**> 2**

The overall inspection days are guidance values and include the necessary time for preparation and report of the inspection and represent the total personnel expenditure (e.g. 10 overall inspection days equal 2 inspectors inspecting for 5 days or 4 inspectors inspecting for 2½ days; preparation and report time included).

Appendix 4: Guidance on the delay of a re-inspection based on compliance information from a trusted authority

Procedure Steps:

1a. Select sites based on the compliance risk resulting from the last inspection by the Supervisory Authority (in line with Appendix 1 Part C, and item 5.1.3. of the procedure).

1b. Determine the intrinsic risk of the site (in line with Appendix 1 Part B and item 5.1.2. of the procedure).

2. Request compliance information from a trusted authority that has inspected the site since the last inspection by the Supervisory Authority.

3. Evaluate the compliance information received from the trusted authority to establish the Current Compliance Risk (in analogy to Step 1a and Item 5.3.1 of the procedure whereby deficiencies reported by the trusted authority may have to be re-categorised in line with the EU definitions of "critical" and "major".)

4. Delay the routine re-inspection by the Supervisory Authority in line with the below table and document this in Appendix 1 Part E.

	Step 1a	**Step 1b**		**Step 2**	**Step 3**	**Step 4**
Scenario	**Compliance Risk post last inspection**	**Intrinsic Risk**	**Risk Rating**	**Request compliance information** from a trusted authority.	**Current Compliance Risk**	**Re-Inspection Delay (+ max. years)**
Trusted Authority's domestic site but product NOT in the operational scope of a legal agreement	Low	**High**	B		Low	**+1**
	Low/Medium	Medium	A/B		Medium	**+1**
	Low/Medium	Medium			Low	**+1.5**
	Low/Medium	Low	A		Medium	**+1.5**
	Low/Medium	Low			Low	**+2**
THIRD COUNTRY[1] site but product in the operational scope of a legal agreement	Low/Medium	Medium	A/B		Medium	**+1**
	Low/Medium	Medium			Low	**+1.5**
	Low/Medium	Low	A		Medium	**+1.5**
	Low/Medium	Low			Low	**+2**
THIRD COUNTRY site and product NOT in the operational scope of an agreement or no legal agreement in place	Low/Medium	Low	A		Medium	**+1**
	Low/Medium	Low			Low	**+1.5**

[1] Third Country = outside of the EU/EEA