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Annex 3
WHO pharmaceutical starting materials certification scheme (SMACS): guidelines on implementation

Preamble

The quality of pharmaceuticals has been a concern of WHO since its inception. Owing to the nature of these products, this concern includes the quality of the starting materials, i.e. active pharmaceutical ingredients (APIs) and excipients, used for the production of pharmaceuticals.

This guidance text, in combination with other recommendations and guidelines issued by WHO, will be an important step towards ensuring the quality and traceability of pharmaceutical starting materials and in assigning the responsibility for specifications within the processes of manufacture, storage and distribution of pharmaceutical starting materials.

Member States are urged to establish and maintain a legal framework and regulatory approach to ensure that good practices for the trade and distribution of pharmaceutical starting materials are followed. Member States can establish appropriate regulatory control by implementing one or both of the following approaches:

— licensing of suppliers, including traders, brokers and distributors; and/or
— a registration or notification system of suppliers, including traders, brokers and distributors.

A variety of WHO guidelines ready for use and inclusion into national legislation are available. Their implementation will be crucial throughout the process towards ensuring the availability and use of quality pharmaceutical starting materials in the manufacture of medicines.

Where a licensing system already exists, inspections should be performed by persons from the competent national or regional statutory authority to assess compliance with good trade and distribution practices (GTDP). Where a notification or registration system is to be implemented, voluntary inspections may be performed before certification for compliance with GTDP.

The use of the new certification scheme is based on the existence of a quality assurance system for the production of starting materials.

All parties involved in the trade and distribution of pharmaceutical starting materials are strongly encouraged to comply with the GTDP. Manufacturers of pharmaceutical products should encourage and assist their suppliers to use good storage practice (GSP), GTDP and the relevant parts of good manufacturing practice (GMP).

Trade associations are also encouraged to incorporate these principles into their own codes of practice to be followed by their members.

Another recommendation is the development of a global database listing information on suppliers (e.g. names and addresses) to enable customers to verify supplier information. A global database could later be established to assist in the attempt to address the problem of counterfeiting of pharmaceutical materials.

Training workshops and conferences on GTDP should be planned to promote these principles.

The establishment of model certificates for GSP and GTDP should be envisaged.

National legislation should ensure that penalties can be enforced when persons or suppliers are found to be in violation of legislation.

An alert system should be established by the competent authority to prevent trade in non-conforming materials that could put patients at risk. WHO should be informed of such instances so that this information can be made available to other national or regional authorities for action as necessary.

Ultimate goal

Close collaboration of all partners throughout the distribution and trade chain should be established and maintained to protect patients' health.

Introduction

Further to the discussion during the Thirty-sixth meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations in 1999, which was triggered by the reported incidents of contamination with diethylene glycol, several activities to control and ensure safe trade of starting materials for pharmaceutical products have been

identified. The Expert Committee was informed of the recommendations of a consultation on "Starting materials for pharmaceutical products: control and safe trade", held in Geneva in May 1998, as well as of the report from this consultation which is available in Arabic, Chinese, English, French, Spanish and Russian. The report is also available on the Internet at http://www.who.int/medicines/docs/startmats.html.

The Committee also noted that the World Health Assembly had adopted the proposed resolution on the Revised Drug Strategy (WHA52.19) in May 1999, and was informed of a press release dated 22 May 1999 regarding the above-mentioned World Health Assembly resolution. The resolution requested WHO to prepare a new scheme for the certification of starting materials moving in international commerce. It was agreed at the thirty-eighth meeting of the Expert Committee that an increased awareness of existing guidelines should be promoted. The Committee noted that several recommendations had been made in the report of the consultation of May 1998 for action by governments, manufacturers, traders and brokers as well as by WHO. The Organization would need to collaborate with all the parties involved. It was suggested that the above-mentioned recommendations should be consolidated and priorities assigned, and the resulting document distributed widely to relevant associations and representative bodies.

On the basis of the above considerations, a new WHO Scheme for the Certification of Pharmaceutical Starting Materials Moving in International Commerce is being proposed. The document outlining the new scheme was drafted at an informal consultation before being circulated for comments and rediscussed during a consultation held in August 2001. Further rounds of consultation took place in 2002, including a meeting held in July of that year. The text was revised in accordance with the comments received.

There is currently insufficient legislative control over the manufacture and distribution of pharmaceutical starting materials in many WHO Member States. It is, however, recognized that in some Member States, efforts have been made to ensure implementation and monitoring of good manufacturing practices for starting materials. Alternative quality systems (e.g. International Standards Organization (ISO)) have been adopted by some manufacturers. These developments have formed the basis of the newly suggested certification scheme for pharmaceutical starting materials.

The proposed scheme is based on the "WHO certification scheme on the quality of pharmaceutical products moving in international

commerce". It should be noted, however, that the concept of this proposed scheme and its application differ in certain aspects from the scheme for pharmaceutical products, namely, in the provision made for alternative quality assurance systems and self-assessment by the manufacturers of pharmaceutical starting materials. The latter may also be linked to an inspection by a national authority other than the one in the country of manufacture.

It is further suggested to consider the use of the "Model certificate of analysis for active pharmaceutical ingredients, excipients and medicinal products (COA)" that would serve in the trade of starting materials and for manufacturers of pharmaceutical substances, excipients and medicinal products, as recommended by resolution WHA52.19 (Annex 2 of reference (*1*)) together with the "Considerations for requesting analysis of drug samples" (Annex 3 of reference (*1*)) to complement this scheme.

The newly proposed scheme consists of:

1. A Model Certificate for Manufacture of Pharmaceutical Starting Materials issued by the competent national authority,

or, alternatively:

2. A Model Certificate for Manufacture of Pharmaceutical Starting Materials issued by the manufacturer.

Scope

The scheme described in this document is intended for pharmaceutical starting materials, obtained through chemical synthesis. Blood and blood derivatives are beyond the scope of this scheme.

It is envisaged to evaluate this scheme describing a new global mechanism for its applicability and use after a certain length of time.

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1. Provisions and objectives

1.1 A comprehensive system of quality assurance should normally be founded on a reliable system of licensing and analysis of starting materials, as well as upon assurance, obtained through independent inspection, that all manufacturing operations are carried out in conformity with accepted norms referred to as good manufacturing practices (GMP). Production and quality control should be independent of one another.

1.2 The World Health Assembly endorsed the requirements for good practices in the manufacture and quality control of drugs (*2*) (referred to henceforth as "GMP as recommended by WHO"). The GMP text includes good manufacturing practices for pharmaceutical starting materials (active pharmaceutical ingredients and pharmaceutical excipients).

1.3 The Scheme is an administrative instrument that can be used by:

1.3.1 A Member State to attest that:

— a specific starting material is used in a pharmaceutical product authorized to be placed on the market within its jurisdiction or within another national jurisdiction; and
— the manufacturing site in which a specific starting material is produced is subject to inspections at suitable intervals to establish that the manufacturer conforms to GMP as recommended by WHO.

1.3.2 The Scheme can also be used by the manufacturer to attest compliance with a quality assurance system (subject to conditions for issuing a certificate as described in section 5 below).

1.4 The Scheme makes provision for a statement to indicate that the manufacturing site(s) in which the pharmaceutical starting material is produced has (have) implemented a suitable quality system.

2. Participating Member States

2.1 Any Member State intending to participate in the Scheme may do so by notifying the Director-General of WHO in writing, of:

— its willingness to participate in the scheme;
— any significant reservations it intends to observe relating to this participation (i.e. whether it intends to participate actively in the Scheme or to use it as a tool); and
— the name and address of its national regulatory authority or other competent authority.

Documentation on the national system should be provided, depending on the type of participation.

2.2 A Member State may opt to participate solely to control the importation of pharmaceutical starting materials. This intention should be stated explicitly in its notification to the World Health Organization.

2.3 A Member State intending to participate in the Scheme through issuing certificates should first satisfy itself that it can meet the following criteria.

- An effective national system is in place to identify the responsible manufacturers and distributors.
- It can perform inspections according to GMP requirements, consonant with those recommended by WHO, to which all manufacturers of pharmaceutical starting materials are required to conform.
- It is capable of establishing effective controls to monitor the quality of pharmaceutical starting materials manufactured within its country, and has access to an independent quality control laboratory.
- It has a national pharmaceuticals inspectorate, operating as an arm of the national drug regulatory authority, and having the technical competence, experience and resources to assess whether GMP and other controls are being effectively implemented, and has the legal power to conduct appropriate investigations to ensure that manufacturers conform to these requirements by, for example, examining premises and records and taking samples.
- It has the necessary administrative capacity to issue the required certificates, to institute enquiries in case of complaint, and to notify expeditiously both WHO and the competent authority in any Member State known to have imported a specific starting material that is subsequently associated with a potentially serious quality defect or other hazard.

2.4 Each Member State assumes the responsibility to determine, through a process of self-evaluation, whether it satisfies these prerequisites. The Scheme contains no provision for external inspection or assessment, either of a competent national authority or of a manu-

facturing facility. However, should a Member State so wish, it may approach WHO, or another drug regulatory authority, to occasionally delegate consultants to act as advisers in the course of national inspections and training activities for inspectors.

3. Requesting a certificate

3.1 A Certificate for Pharmaceutical Starting Materials can be requested within the scope of the Scheme by the exporter, importer or the competent authority of the importing country.

4. Certificates issued by competent regulatory authorities

4.1 The proposed formats for these documents are provided in Appendices 1 and 2 of these guidelines. For ease of use, these documents are presented in forms suitable for generation by a computer. All participating countries are henceforth urged to adopt these formats to facilitate the interpretation of certified information. The explanatory notes that accompany the two documents referred to above are very important. Although they are not part of the document to be certified, they should always be attached to the certificate.

4.2 The certificate should be issued by the competent authority in the format proposed in Appendix 1.

The following information should be listed as a minimum: for details see explanatory notes (Appendix 1).

4.2.1 Number of certificate given by the issuing authority.

4.2.2 Exporting (certifying) country.

4.2.3 Importing (requesting) country/countries.

4.2.4 Name of pharmaceutical starting material (International Nonproprietary Names (INNs) should be used whenever possible; alternatively, national nonproprietary names and/or grades, trademarks and other identifiers, such as official codes, CAS numbers etc. may be used).

4.2.5 Complete reference to, and compliance with, pharmacopoeial monograph(s), where applicable and/or attached specifications.

4.2.6 Information on whether the pharmaceutical starting material subject to this certificate is used in pharmaceutical products registered for marketing in the exporting country.

4.2.7 Indicate category of product, if applicable.

4.2.8. Marketing authorization, licence, Drug Master File or other reference(s), such as a certificate of suitability of pharmacopoeial monographs with which the starting material complies, as applicable.

4.2.9 Name and address of applicant for certificate.

4.2.10 Activities of the applicant (e.g. manufacturing, repacking or relabelling) and, if the applicant is not the original manufacturer, provide the name and address of the original manufacturer.

4.2.11 Compliance of facilities and operations with WHO GMP, if applicable.

4.2.12 Date of last inspection, if applicable.

4.2.13 Information regarding the certifying authority.

4.2.14 Stamp and date.

4.3 The certificate is a confidential document. As such, it can be issued by the competent authority in the exporting country ("the certifying authority") only with the permission of the applicant.

4.4 Once prepared, the certificate is transmitted to the requesting authority through the applicant and, when applicable, the agent in the importing country.

4.5 When any doubt arises about the status or validity of a certificate, the competent authority in the importing country should request a copy directly from the certifying authority, as provided for in section 4.2.13 of these guidelines.

4.6 In the absence of any specific agreement to the contrary, each certificate will be prepared exclusively in the working language(s) of the certifying authority. The applicant will be responsible for providing any notarized translation that may be required by the requesting authority.

4.7 Since the preparation of certificates imposes a significant administrative load on the certifying authorities, the service may need to be financed by charges levied upon applicants.

4.8 The certificate remains valid until the specified date.

4.9 The certificate becomes invalid if the manufacturing process certified is changed or if the manufacturer is no longer considered to be in compliance with GMP.

4.10 The certifying authority is responsible for assuring the authenticity of the certified data. Certificates should not bear the WHO emblem, but a statement should always be included to indicate

whether or not the document has been issued in the format recommended by WHO.

4.11 When the applicant is the manufacturer of the pharmaceutical starting material, the certifying authority should satisfy itself, before attesting compliance with GMP, that the applicant:

(a) applies identical GMP standards to the pharmaceutical starting materials of all batches manufactured within the facility, including those destined exclusively for export; and
(b) consents, in the event of identification of a quality defect consonant with the criteria set out, to relevant inspection reports being released, in confidence, to the competent authority in the country of import, should the latter so require.

4.12 When the applicant is not the manufacturer of the pharmaceutical starting material, the certifying authority should similarly satisfy itself in so far as it has the authority to inspect the records and relevant activities of the applicant, that it has the applicant's consent to release relevant reports on the same basis as described in section 4.11 (b) above.

4.13 Whenever a starting material is purchased through a broker or another intermediary, or when more than one set of premises has been used for the manufacture and packaging of a starting material, the certifying authority should consider whether it has received sufficient information to satisfy itself that those aspects of the manufacture of the starting material for which the applicant is not directly responsible have been undertaken in compliance with GMP and good trading and distribution practices (GTDP)[a] as recommended by WHO.

4.14 Each certificate should identify the importing country and be stamped on every page with the official seal of the certifying authority to avert potential abuse of the Scheme, to frustrate attempts at falsification, to render routine authentication of certificates by an independent authority superfluous and to enable the certifying authority to maintain comprehensive records of countries to which specific starting materials have been exported. If requested, an identical copy, clearly marked as "duplicate", should be forwarded on demand by the certifying authority directly to the requesting authority in the importing country.

[a] WHO Good Trading and Distribution Practices (GTDP), see guidance text in WHO Technical Report No. 917, Annex 2.

5. Certificates issued by manufacturers

5.1 A manufacturer may issue a certificate, for instance when there is no national authority in the exporting country that could issue a certificate and/or no legal framework, and provided that there is an independent certifying body or competent authority to assess the compliance with the quality assurance system.

5.2 The certificate of the manufacturer should be accompanied by a copy of the certificate or document issued by the independent certifying body or competent authority.

5.3 The format of the certificate should be as in Appendix 2.

The following information should be listed.

5.3.1 Number of certificate given by the manufacturer.

5.3.2 Exporting country.

5.3.3 Importing (requesting) country/countries.

5.3.4 Name of pharmaceutical starting material (use International Nonproprietary Names (INNs) whenever possible; alternatively national nonproprietary names and/or grades, trademarks and other identifiers, such as official codes, CAS numbers, etc. may be used).

5.3.5 Complete reference to, and compliance with, pharmacopoeial monograph(s), where applicable and/or attached specifications.

5.3.6 Whether the pharmaceutical starting material is used for pharmaceutical purposes in the exporting country.

5.3.7. Whether the pharmaceutical starting material subject to this certificate is used in pharmaceutical products registered for marketing in the exporting country.

5.3.8 Type of product, if applicable.

5.3.9 Name and address of manufacturer (issuer of certificate), including e-mail address, telephone number and fax number.

5.3.10 (a) Activities of issuer of certificate, e.g. manufacturing or repacking, etc., and, if the issuer of the certificate is not the manufacturer, provide
(b) the name and address of the original manufacturer/manufacturing site(s).

5.3.11 Indication of the main categories of materials produced at the manufacturing site.

5.3.12 Additional regulatory information, such as reference to licence, Drug Master File or other reference as applicable.

5.3.13 The certificate is based on the information obtained from:

5.3.13.1 Inspection by competent authority:

— name of competent authority, including e-mail address, telephone number, fax number and name and function of contact person;
— date of inspection;
— quality assurance system inspected;
— standard used for inspection;
— result of inspection; and
— certificate and supplementary documents to be attached, if available.

5.3.13.2 Audit by an independent certifying body:

— name of independent certifying body, including e-mail, telephone number, fax number and name and function of contact person;
— date of audit;
— quality assurance system audited;
— standard used for audit;
— result of audit; and
— certificate and supplementary documents to be attached, if available.

5.3.14 Name and function of responsible person issuing the statement on behalf of the manufacturer.

5.3.15 Date of issue.

5.3.16 Stamp and signature.

The period of validity of the certificate is suggested to be 2 years.

6. Notifying and investigating a quality defect

6.1 Recognizing that the notification of a defect is an important aspect of the quality assurance of starting materials, the manufacturer should have a system in place to notify its customers and the regulatory authorities of defects that have a potential impact on the quality and safety of the starting material and to ensure that a thorough investigation is conducted. Specifically the manufacturer should notify the recipient(s) of the certificate, as well as the competent authority, of any serious quality defect related to the starting material that was exported in accordance with the provisions of the Scheme, by communicating the relevant facts, through the competent authorities in the importing countries.

6.2 The competent authority should follow up on the investigation undertaken by the manufacturer and take action as necessary.

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6.3 It is the responsibility of the Member State adhering to the Scheme to ensure that provisions for carrying out the tasks described in 6.1 and 6.2 above are in place.

6.4 In the case of obvious doubt, a participating national authority may request WHO to assist in providing a list of quality control laboratories to carry out tests for the purposes of quality control.

6.5 Each certifying authority undertakes to inform WHO and, as far as possible, all competent national authorities, of any serious hazard newly associated with a starting material exported under the provisions of the Scheme, or of any criminal abuse of the Scheme, in particular, the export of falsely labelled, spurious, counterfeited or substandard pharmaceutical starting materials. On receipt of such notification, WHO will immediately inform the competent national authority in each Member State.

6.6 WHO stands prepared to offer advice should any difficulty arise in implementing any aspect of the Scheme or in resolving a complaint, but it cannot be a party to any resulting litigation or arbitration.

References

1. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report.* Geneva, World Health Organization, 2002 (WHO Technical Report Series, No. 902).
2. Quality control of drugs. In: *Twenty-second World Health Assembly, Boston, Massachusetts, 8–25 July 1969. Part 1. Resolutions and decisions, annexes*. Geneva, World Health Organization, 1969 (Official Records of the World Health Organization, No. 176): 99–105.

Further reading

Certification scheme on the quality of pharmaceutical starting materials moving in international commerce. *In: Twenty-eighth World Health Assembly, Geneva, 13–30 May 1975. Part 1. Resolutions and decisions, annexes*. Geneva, World Health Organization, 1975 (Official Records of the World Health Organization, No. 226): 94–95.

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WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report. Geneva, World Health Organization, 2002 (WHO Technical Report Series, No. 902).

WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-seventh report. Geneva, World Health Organization, 2003 (WHO Technical Report Series, No. 908).

WHO certification scheme on the quality of pharmaceutical starting materials moving in international commerce. In: *Forty-first World Health Assembly, Geneva, 2–13 May 1988. Resolutions and decisions, annexes*. Geneva, World Health Organization, 1988 (Document WHA41/1988/REC/1): 53–55.

Revised drug strategy. In: *Fifty-second World Health Assembly, Geneva, 17–25 May 1999*. Geneva, World Health Organization, 1999 (Resolution WHA52.19).

Appendix 1

Model Certificate for Pharmaceutical Starting Materials issued by the competent national authority

(Letterhead of issuing authority)

Certificate of a Pharmaceutical Starting Material[1]

This certificate conforms to the format recommended by the World Health Organization (general instructions and explanatory notes attached).

1. Certificate number:

_____

2. Exporting (certifying) country:

_____

3. Importing (requesting) countries:

_____

4. Name of Pharmaceutical Starting Material:[2]

_____

5. Indicate complete reference and compliance with pharmacopoeial monograph(s), where applicable and/or attached specifications:

_____

6. Is the Pharmaceutical Starting Material subject to this certificate used in pharmaceutical products registered for marketing in the exporting country? yes / no / unknown *(key in as appropriate)*

7. If yes, which types of product?[3]

_____

8. Indicate marketing authorization, licence, Drug Master File or other reference as applicable:

_____

9. Applicant for certificate (name and address):

_____

10. Activities and site(s):

10.1 Activities of applicant: specify whether the manufacturer responsible for placing the Pharmaceutical Starting Material on the market:

(a) manufactures the Pharmaceutical Starting Material;
(b) repackages and/or relabels the Pharmaceutical Starting Material manufactured by an independent company, or;
(c) is involved in none of the above (e.g. distributes, trades);
(d) manufactures the Pharmaceutical Starting Material and further manufacturing sites may be involved.[4]

10.2 If answers b, c or d apply, provide name and address of the manufacturing site(s):

_____

11. Does the manufacturer comply with WHO GMP?[5]
yes / no / not applicable[6] *(for* "no" *and* "not applicable"*: please explain and specify)*:

_____

12. Date of last inspection, if applicable: _____

I herewith confirm that the data above are valid. Any changes that could affect the validity of this certificate shall be notified by the applicant. Under normal circumstances the certificate is valid for 2 years.

13. ***Information regarding the regulatory certifying authority***

Name and address of certifying competent authority: _____ _____ E-mail: _____ Telephone no.: _____ Fax no.: _____ Name and function of responsible person: _____ Signature of responsible person: _____

14. Stamp and date:

_____

Attachments:[7]

List of documents attached:

_____

_____

General instructions

Please refer to the guidelines for full instructions on how to complete this form and for information on the implementation of the Scheme. Only originals or certified copies will be accepted.

The forms are suitable for generation by computer. They should always be submitted as hard copy, with responses printed in type rather than handwritten.

Additional sheets should be appended, as necessary, to accommodate remarks and explanations.

Certifying authorities shall indicate the total number of pages included in the certificate and shall number them, e.g. page *x* of *y*, and initial every page.

Explanatory notes

(1) This certificate, which is in the format recommended by WHO, establishes the status of the Pharmaceutical Starting Material and of the applicant for the certificate in the exporting country. It is for a single Pharmaceutical Starting Material only.

(2) Whenever available, use International Nonproprietary Names (INNs); alternatively, national nonproprietary names and/or grades, trademarks and other identifiers, such as official codes, CAS numbers etc. may be used.

(3) List the dosage forms and categories. Example given below.

Pharmaceutical Product(s)[a]	Category(ies)
Dosage form(s):	
Tablets	Cytotoxic
	Hormone
	Penicillin
Injectables	Cefalosporin

(4) Specify whether the manufacturer responsible for placing the Pharmaceutical Starting Material on the market:

(a) manufactures the Pharmaceutical Starting Material;
(b) repackages and/or relabels the Pharmaceutical Starting Material manufactured by an independent company, or;

[a] Pharmaceutical products: Any medicine intended for human use or veterinary product administered to food-producing animals, presented in its finished dosage for or as a starting material for use in such a dosage form, that is subject to control by pharmaceutical legislation in both the exporting state and the importing state.

(c) is involved in none of the above (e.g. distributes, trades);
(d) manufactures the pharmaceutical starting material and further manufacturing sites may be involved.

If the manufacturer is not the original manufacturer, the site should be given.

(5) The requirements for good practices in the manufacture and quality control of drugs referred to in the certificate are those included in *Quality assurance of pharmaceuticals: a compendium of guidelines and related materials. Good manufacturing practices and inspection, Volume 2, Updated edition.* Geneva, World Health Organization, 2004.
(6) "Not applicable" means that no legal requirements may be in place or implemented for GMP inspection of the Pharmaceutical Starting Materials for which the certificate is issued.
(7) Including specifications referred to under point 5.

Appendix 2

Model Certificate for Manufacture of Pharmaceutical Starting Materials issued by the manufacturer[1]

(*Letterhead of the manufacturer*)

Certificate of a Pharmaceutical Starting Material[1]

This certificate conforms to the format recommended by the World Health Organization (general instructions and explanatory notes attached).

1. Certificate number:

_____

2. Exporting country:

_____

3. Importing country:

_____

4. Name of Pharmaceutical Starting Material:[2]

_____

5. Indicate complete reference and compliance with pharmacopoeial monograph(s) where applicable and/or attached specifications:

_____

6. Is this Pharmaceutical Starting Material used for pharmaceutical purposes in the exporting country? yes / no / unknown *(key in as appropriate)*

_____

7. Is the Pharmaceutical Starting Material subject to this certificate used in pharmaceutical products registered for marketing in the exporting country? yes / no / unknown *(key in as appropriate)*

8. If yes, which types of product:[3]

9. Name and address of manufacturer (issuer of certificate):

_____

E-mail: _____ Telephone no.: _____ Fax no.: _____

10. Activities and site(s):

10.1 Activities of issuer of the certificate[4]:

State whether the issuer:

(a) manufactures the Pharmaceutical Starting Material;
(b) repackages and/or relabels the Pharmaceutical Starting Material manufactured by an independent company, or;
(c) is involved in none of the above (e.g. distributes, trades);
(d) manufactures the Pharmaceutical Starting Material and further manufacturing sites may be involved.

10.2 If answers a, b, c or d apply, provide name and address of the manufacturing site(s):

_____

11. Main categories of materials produced on site:[5]

— Pharmaceutical starting materials: _____

— Active pharmaceutical ingredients: _____

— Excipients: _____

— Cosmetics: _____

— Foodstuffs: _____

— Agrochemicals: _____

— Others (please specify): _____

12. Indicate additional regulatory information, such as reference to licence, Drug Master File, or other reference as applicable:

_____

13. Information based on:

_____

13.1 Inspection by competent authority:
Country: _____

Name of competent authority: _____

E-mail: _____ Telephone no.: _____ Fax no.: _____

Name and function of contact person: _____

— date of inspection: _____

— quality assurance system inspected: _____

— standard used for inspection:[6] _____

— result of inspection: _____

— attach certificate or supporting document, if available.

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13.2 Audit by an independent certifying body:

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Name of independent certifying body: _____

E-mail: _____ Telephone no.: _____ Fax no.: _____

Name and function of contact person: _____

— date of audit: _____

— quality assurance system audited: _____

— standard used for audit: _____

— result of audit: _____

— attach certificate or supporting document, if available.

14. Name and function of responsible person:

_____

I herewith confirm that the data above are valid. Any changes that could affect the quality of the pharmaceutical starting material and that will change the data on the certificate will be communicated. Under normal circumstances the certificate is valid for 2 years.

15. Date: _____

16. Stamp and signature: _____

Attachments:[7]

List of documents attached:

_____

_____

General instructions

Please refer to the guidelines for full instructions on how to complete this form and for information on the implementation of the Scheme. Only originals or certified copies of this document will be accepted.

The forms are suitable for generation by computer. They should always be submitted as hard copy, with responses printed in type rather than handwritten.

Additional sheets should be appended, as necessary, to accommodate remarks and explanations.

Certifying authorities shall indicate the total number of pages included in the certificate and shall number them, e.g. page *x* of *y*, and initial every page.

Explanatory notes

(1) This certificate, which is in the format recommended by WHO, establishes the status of the Pharmaceutical Starting Material and of the applicant for the certificate in the exporting country. It is for a single Pharmaceutical Starting Material only.

(2) Whenever available, use International Nonproprietary Names (INNs); alternatively, national nonproprietary names and/or grades, trademarks and other identifiers, such as official codes, CAS numbers etc. may be used.

(3) List the dosage forms and categories. Example given below.

Pharmaceutical Product(s)[a]	Category(ies)
Dosage form(s):	
Tablets	Cytotoxic
	Hormone
	Penicillin
Injectables	Cefalosporin

(4) Specify whether the manufacturer responsible for placing the Pharmaceutical Starting Material on the market:
  (a) manufactures the Pharmaceutical Starting Material;
  (b) repackages and/or relabels the Pharmaceutical Starting Material manufactured by an independent company, or;
  (c) is involved in none of the above (e.g. distributes, trades);
  (d) manufactures the pharmaceutical starting material and further manufacturing sites may be involved.

If the manufacturer is not the original manufacturer, the site should be given.

(5) The categories of materials produced on site will give information about the profile of the manufacturing site.

(6) The requirements for good practices in the manufacture and quality control of drugs referred to in the certificate are those included in *Quality assurance of pharmaceuticals: a compendium*

[a] Pharmaceutical products: Any medicine intended for human use or veterinary product administered to food-producing animals, presented in its finished dosage for or as a starting material for use in such a dosage form, that is subject to control by pharmaceutical legislation in both the exporting state and the importing state.

of guidelines and related materials. Good manufacturing practices and inspection, Volume 2, Updated edition. Geneva, World Health Organization, 2004.

(7) Including specifications referred to under point 5.

Appendix 3
Glossary and key words

This glossary explains terms used in these Guidelines and/or refers to relevant sections. It is intended as supplementary information and not as a formal part of the Scheme. Note that the definitions given below apply to the terms as used in these Guidelines. They may have different meanings in other contexts.

Applicant
The party applying for a certificate for a pharmaceutical starting material.

Competent authority
The national regulatory authority in the Member State. The competent authority can issue or receive certificates.

Good manufacturing practices (GMP)
That part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization. (In: *Quality assurance of pharmaceuticals: a compendium of guidelines and related materials. Good manufacturing practices and inspection. Volume 2, Updated edition*. Geneva, World Health Organization, 2004).

GTDP
Good Trade and Distribution Practices (Annex 2, WHO Technical Report Series, No. 917).

Manufacture
All operations of purchase of materials and starting materials, production, quality control, release, storage, shipment of finished starting materials, and the related controls.

Pharmaceutical starting material
Any substance of a defined quality used in the production of a pharmaceutical product, but excluding packaging materials. This includes active pharmaceutical ingredients (APIs) and pharmaceutical excipients.

Starting material (see pharmaceutical starting material)

Certificate of a pharmaceutical starting material
A document containing the information (as set out in Appendix 1 of these Guidelines) that is validated and issued for a specific starting

material by the competent authority of the exporting country and intended for use by the competent authority in the importing country or in the absence of such an authority by, for example, the manufacturer of the finished product when exporting.

WHO responsibility (see item 6.6 of guidelines above)