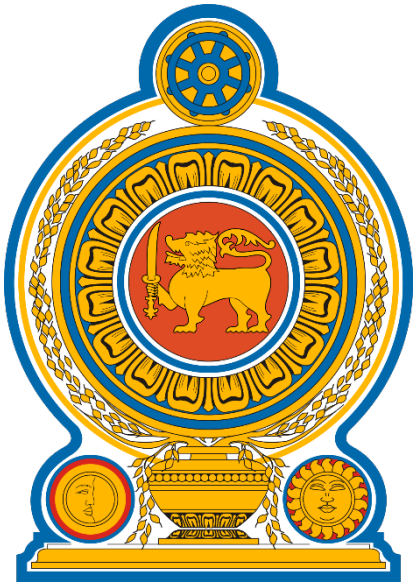

Guideline on Approval of an Overseas Manufacturing Plant of Medicine

JUNE 1, 2021

NATIONAL MEDICINE REGULATORY AUTHORITY
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GUIDELINE ON APPROVAL OF AN OVERSEAS MANUFACTURING PLANT OF MEDICINE

CONTENTS

1. INTRODUCTION

Section 47 (3) of the NMRA Act specifies quality and safety amongst the criteria for registration of a medicine. Section 51 of the Act further elaborate necessity for approval of premises, process, and condition of manufacture, and section 49 (2) implicates manufacture of medicines without adhering to Good Manufacturing Practices as an offence.

Local manufacturers are subjected to periodical GMP inspections and subsequent licensing of their premises. However, it is not practically possible to NMRA to inspect each and every manufacturing site located outside Sri Lanka. Therefore, when an application is submitted for a foreign manufacturing site, NMRA first carries out a desktop review. NMRA may proceed for an onsite GMP inspection of the site or may reject the application, based on the outcome of the desktop review. NMRA may exempt onsite inspection based on reliance, if the site had been inspected by a reference NRA or WHO.

The application for a manufacturing site approval has to be submitted online via NMRA's web portal eNMRA, which requires uploading of essential information and documents to enable a desk review. The NMRA website also comprises a user manual to guide the applicants on the online application process.

2. PURPOSE

The guideline is intended to provide information on how to apply for a site approval of a medicines manufacturing plant located outside Sri Lanka, which is a pre-requisite to apply for marketing authorization of products manufactured at such site.

The regulations 2 to 10 of part I of medicines regulations no. 2145/1 of 14th October 2020 articulate the legal requirements for approving an overseas manufacturing site. NMRA may exempt onsite GMP inspection based on reliance (refer to annex 1), in terms of regulation 24 of medicines regulations no. 2145/1 dated 14th October 2020.

3. SCOPE

This guideline applies to all manufacturers of medicines located outside Sri Lanka, who intend to obtain marketing authorization(s) in Sri Lanka.

Details on preparation and conduct of GMP inspection is specified in a separate guideline (GL-024)

4. ACRONYMS

CAPA	-	Corrective and preventive actions
COPP	-	Certificate of a Pharmaceutical Product
GMP	-	Good Manufacturing Practices
NMRA	-	National Medicines Regulatory Authority
NRA	-	National Regulatory Authority
PQR	-	Product Quality review
PIC/s	-	Pharmaceutical Inspection Co-operation Scheme
WHO	-	World Health Organization

5. DEFINITIONS

Applicant -
The person who furnishes the application to the NMRA in order to get an approval for a product, process, or premises. In case of applications relevant to overseas manufacturers, the authorized importer is the applicant who takes the responsibility for the documents submitted with the application. After registration of a medicine, the applicant would become the marketing authorization holder for the particular medicine.

Authorized importer -
The local business entity appointed by a foreign manufacturer to be its legal and technical representative in Sri Lanka. Being a licenced importer of medicine in terms of part III of medicines regulations is a pre-requisite to become an authorized importer. He would become the applicant for overseas sites, processes and products on behalf of the foreign manufacturer and would take responsibility for import, wholesale and post marketing monitoring once becoming the marketing authorization holder.

Competent Regulatory Authority-
The organization in a particular country that is legally empowered to perform designated regulatory functions relevant to medical products

Desk review/Desktop review -
Abridged regulatory pathway used to carry out an audit of a site's compliance to Good Practices (e.g. GMP, GCP) without visiting the particular site but reviewing a set of documents, which includes inspection report by a reference regulatory authority.

Finished product -
A product that has undergone all stages of production including packaging in its final container and labelling.

GMP Inspection -
An audit carried out particularly by a competent regulatory authority in order to ensure compliance by a manufacturer with Good Manufacturing Practices as prescribed in relevant GMP guidelines.

Manufacture –
All operations of purchase of material, production, quality control, batch release, storage and dispatch of finished products, and the related controls.

Manufacturer –
A company that carries out at least one step of manufacture

Marketing authorization -
A legal document (E. g. Certificate of registration) issued by the competent regulatory authority allowing marketing of the particular product within the country, while establishing the detailed composition and formulation of the product, pharmacopoeial or other recognized specifications, and includes details of packaging, pack size, and shelf life.

Reference Regulatory Authority -
A national or a regional authority being relied upon by another regulatory authority.

Reliance -
For the purpose of this document, consideration of assessments performed by other NRAs or trusted organizations as part of routine regulatory oversight and/or during special circumstances such as public health emergencies in reaching own decisions, while remaining independent, responsible and accountable regarding the decisions taken.

Site master file

A document prepared by the manufacturer containing specific and factual GMP information about the production and/or control of pharmaceutical manufacturing operations carried out at the named site and any closely integrated operations at adjacent and nearby buildings.

6. SUBMISSION AND ASSESSMENT OF THE APPLICATION

6.1 General

1. A foreign manufacturer who wishes to market a medicine in Sri Lanka should appoint a local pharmaceutical company which has been licensed as a 'licensed importer of medicine', to act as its authorized importer in Sri Lanka.
2. It is the responsibility of the authorized importer to submit an application through NMRA's web portal eNMRA, in order to get the manufacturing site where the product(s) intended to be marketed in Sri Lanka would be manufactured, approved.
3. NMRA has published a web-based user manual for applicants, which can be accessed from body content titled 'eNMRA guidance'. The direct link to the manual on 'foreign manufacturer site' is from www.nmra.gov.lk/images/PDF/usermanuals/foreignManufacturerSite.pdf
4. Information to be filled or selected from dropdown menus in the online application include contact details of the applicant, contact details of the manufacturer, product types and product categories manufactured at the site.
5. Once the application is submitted, NMRA will communicate all correspondence relevant to the application via email address provided by the applicant.
6. A reference number will be generated to each of the applications and application will be processed on a first cum first basis.
7. The application will be screened for availability and completeness of mandatory documents within a timeline of 10 working days. Any deficient documents will be informed. The time taken to submit the deficient documents will be considered as stop clocks.
8. In general, manufacturer should be able to prove marketing authorization for its products in the country of origin and three other counties.
9. Requirement for foreign sales may be exempted if the product range manufactured at the site includes products identified as in need of (more) sources of supply in Sri Lanka or when manufacturing of an existing product is transferred to a new site.
10. A payment notice will be generated for applications that fulfil minimum requirements at the end of screening process and, a fee specified in Gazette Extraordinary no.2052/ 33 of 05th January 2018 should be paid as the fee for processing the application.
11. NMRA may request for clarifications and/or additional documents during the course of evaluation.
12. Timeline for processing the application is 80 working days from the date of uploading the payment and will include stop clocks.
13. Once the applicant fulfils all documentary requirements, the next step would be to carry out an onsite GMP inspection of the facility.
14. NMRA may reject the application at the end of the documentary review without undertaking a site inspection, or after the GMP inspection, with reasons for rejection.

15. NMRA may exempt onsite GMP inspection based on reliance, if a recent (within last five years) GMP inspection report to the site by a reference regulatory authority (see annex I) or by WHO has been submitted.
16. After successful completion of these procedures, the approved foreign manufacturer can proceed to submit applications for marketing authorization of individual products through his authorized importer.
17. NMRA reserves the right to carry out onsite inspections of the facility prior to approval, periodically on a risk based criteria, or in a situation of concern such as a serious quality issue or suspected forgery.

6.3 Documents to be submitted along with the application:

- Site master file
- Letter of authorization and copy of the agreement between the manufacturer and the authorized importer
- Letter by responsible person of the manufacturer, certifying that the content submitted are true and accurate
- Copy of business registration of the authorized importer by registrar of companies.
- Copy of the wholesale license of the authorized importer by NMRA.
- Minimum of three COPPs issued to three different countries.
- Certificates of registration issued by three different authorities other than the country of origin.
- Copy of the last inspection report by the competent authority of the country of origin.
- Full inspection report(s) for inspections performed by competent NRAs within last five years.
- An undertaking by the manufacturer that it is agreeable to an onsite GMP inspection if and when required.
- CAPA and proof of CAPA implementation related to the last inspection report observations/deficiencies or any warning letters or equivalent regulatory actions (production line specific).
- The most recent product quality review(s) (PQRs) of the concerned products (WHO Technical Report Series No. 986 Annex 2) or equivalent documentation covering all required subsections and trend results.
- A list of any recalls in the last three years related to quality defective products.
- A copy of any warning letter or equivalent regulatory action issued by any competent authority to which the site provides or has applied to provide the product.

6.4 General requirements for documents

- All certificates, reports and other supporting documents should be in English.
- If a document is not in English, it should be submitted with a certified English translation.
- Documents must be the most recent and should reflect the current status of the manufacturer
- Copies of certificates, licenses, and diagrams relevant to the manufacturing plant should be legible.

- Content in Site Master File should clearly demonstration segregation of specific zones. Plans of relevant buildings or floors should be clearly labelled.

7. REFERENCES

- NMRA Act No. 05 of 2015
- Guidance on good practices for desk assessment of compliance with good manufacturing practices, good laboratory practices and good clinical practices for medical products regulatory decisions, Annex 9, WHO TRS No. 1010, 2018
- GMP inspection reliance, PI 048-1, 1 June 2018, PIC/S
- Regulatory guidance; GMP conformity assessment of an overseas manufacturer, Dec 2018; HSA Singapore
- WHO guideline for drafting a site master file, Annex 14, WHO TRS No. 961, 2011

8. FEEDBACK

9.1 Staff and customers may provide feedback about this document by emailing to info@nmra.gov.lk.

Annex I

The list of reference regulatory authorities relevant to GMP inspection reliance

A. For facilities that manufacture multisource products

A GMP full report by WHO or any of the following current participating members of PIC scheme shall be accepted in order to exempt an onsite GMP inspection.

1. Argentina – **ANMAT** [Inspectorate Department, National Institute of Drugs (**INAME**)]
   Accession to PIC/s in January 2008
2. Australia – **TGA** (Therapeutic Goods Administration)
   Accession to PIC/s in November 1995
3. Austria – **AGES** (Austrian Agency for Health and Food Safety)
   Accession to PIC/s in November1999
4. Belgium – **FAMHP** (Federal Agency for Health and Health Products)
   Accession to PIC/s in February 1997
5. Brazil – **ANVISA** (National Health Surveillance Agency)
   Accession to PIC/s in January 2021
6. Canada – **Health Canada**
   Accession to PIC/s in January 1999
7. Chinese Taipei – **TFDA** (Taiwan Food and Drug Administration)
   Accession to PIC/s in January 2013
8. Croatia – **HALMED** (Agency for Medicinal and Products and Medical Devices of Croatia)
   Accession to PIC/s in January 2016
9. Cyprus – **CyPHS** (Pharmaceutical Services)
   Accession to PIC/s in July 2008
10. Czech Republic – **SÚKL** (State Institute of Drug Control)
    Accession to PIC/s in January 1997
11. Denmark – **DKMA** (Danish Medicines Agency)
    Accession to PIC/s in November 1995
12. Estonia – **SAM** (State Agency of Medicines)
    Accession to PIC/s in January 2007
13. Finland – **FIMEA** (Finnish Medicines Agency)
    Accession to PIC/s in January 1996
14. France – **ANSM** (French National Agency for Medicines and Health Products Safety)
    Accession to PIC/s in February 1997
15. Germany – **ZLG** (Central Authority of the Laender for Health Protection regarding Medicinal Products and Medical Devices)
    Accession to PIC/s in December 2000
16. Greece – **EOF** (Greek National Organization for Medicines)
    Accession to PIC/s in January 2002
17. Hong Kong SAR, China – **PPBHK** (Pharmacy and Poisons Board of Hong Kong)
    Accession to PIC/s in January 2016
18. Hungary – **NIPN** (National Institute of Pharmacy and Nutrition)
    Accession to PIC/s in December 1995

19. Iceland – **IMA** (Icelandic Medicines Agency)
    Accession to PIC/s in November 1995
20. Indonesia – **NADFC** (National Agency for Drug and Food Control)
    Accession to PIC/s in July 2012
21. Iran – **IFDA** (Iran Food and Drug Administration)
    Accession to PIC/s in January 2018
22. Ireland – **HPRA** (Health Products Regulatory Authority)
    Accession to PIC/s in February 1996
23. Israel – **ISCP** (Institute of Standardization and Control of Pharmaceuticals)
    Accession to PIC/s in January 2009
24. Italy – **AIFA** (Italian Medicines Agency)
    Accession to PIC/s in February 2000
25. Japan – **PMDA** (Pharmaceuticals and Medical Devices Agency) & **MHLW** (Ministry of Health, Labour and Welfare)
    Accession to PIC/s in July 2014
26. Korea (Republic of) – **MFDS** (Ministry of Food and Drug Safety)
    Accession to PIC/s in July 2014
27. Latvia – **ZVA** (State Agency of Medicines)
    Accession to PIC/s in January 2004
28. Liechtenstein – **AG** (Office of Healthcare)
    Accession to PIC/s in November 1995
29. Lithuania – **SMCA** (State Medicines Control Agency
    Accession to PIC/s in July 2009
30. Malaysia – **NPRA** (National Pharmaceutical Regulatory Agency)
    Accession to PIC/s in January 2002
31. Malta – **MMA** (Malta Medicines Authority)
    Accession to PIC/s in January 2008
32. Mexico – **CFEPRIS** (Federal Commission for the Protection Against Sanitary Risks)
    Accession to PIC/s in January 2018
33. Netherlands – **IGJ** (Health and Youth Care Inspectorate)
    Accession to PIC/s in November 1995
34. New Zealand – **MEDSAFE** (Medicines and Medical Devices Safety Authority)
    Accession to PIC/s in January 2013
35. Norway – **NOMA** (Norwegian Medicines Agency)
    Accession to PIC/s in November 1995
36. Poland – **CPI** (Chief Pharmaceutical Inspectorate)
    Accession to PIC/s in January 2006
37. Portugal – **Infarmed** (National Authority of Medicines and Health Products, IP)
    Accession to PIC/s in January 1999
38. Romania – **NAMMDR** (National Agency for Medicines and Medical Devices of Romania)
    Accession to PIC/s in November 1995
39. Singapore – **HSA** (Health Science Authority)
    Accession to PIC/s in January 2000
40. Slovak Republic – **SIDC** (State Institute of Drug Control)PIC/s member
    Accession to PIC/s in January 1997

41. Slovenia – **JAZMP** (Agency for Medical Products and Medical Devices)
    Accession to PIC/s in January 2012
42. South Africa – **SAHPRA** (South African Health Products Regulatory Authority)
    Accession to PIC/s in July 2007
43. Spain – **AEMPS** (Spanish Agency of Medicines and Medical Devices)
    Accession to PIC/s in January 1998
44. Sweden – **MPA** (Swedish Medical Products Agency)
    Accession to PIC/s in February 1996
45. Switzerland – **Swissmedic** (Swiss Agency for Therapeutic Products)
    Accession to PIC/s in February 1996
46. Thailand – **Thai FDA** (Food and Drug Administration)
    Accession to PIC/s in August 2016
47. Turkey – **TMMDA** (Turkish Medicines and Medical Devices Agency)
    Accession to PIC/s in January 2018
48. Ukraine – **SMDC** (State Service of Ukraine Medicines and Drug Control)
    Accession to PIC/s in January 2011
49. United Kingdom – **MHRA** (Medicines and Healthcare Products Regulatory Agency)
    Accession to PIC/s in June 1999
50. U. S. A. - **US FDA** (U.S. Food and Drug Administration)
    Accession to PIC/s in January 2011

B. For facilities that manufacture vaccines, biotherapeutic products, plasma products

If the manufacturing facility is located in a PIC/s participating country, GMP report by the NRA of the country of origin shall be accepted.

For facilities situated outside PIC/s participating countries, a full GMP report by WHO or any of the following reference NRAs shall be considered.

- USFDA, USA (ICH founding regulatory member, WHO stringent NRA, PIC/s member)
- MHLW/PMDA, Japan (ICH founding regulatory member, WHO stringent NRA, PIC/s member)
- Health Canada, Canada (ICH standing regulatory member, WHO stringent NRA, PIC/s member)
- Swissmedics, Switzerland (ICH standing regulatory member, PIC/s member)
- TGA Australia (WHO stringent NRA, ICH observer, PIC/s member)
- AIFA Italy (WHO stringent NRA, PIC/s member)
- ANSM, France (WHO stringent NRA, PIC/s member)
- DKMA, Denmark (WHO stringent NRA, PIC/s member)
- FAMPH Belgium (WHO stringent NRA, PIC/s member)
- IGJ Netherland (WHO stringent NRA, PIC/s member)
- MHRA United Kingdom (WHO stringent NRA, PIC/s member)
- MPA Sweden (WHO stringent NRA, PIC/s member)
- FDA, Chinese Taipei (ICH regulatory member, PIC/s member)
- HSA, Singapore (ICH regulatory member, PIC/s member)
- MFDS, Republic of Korea (ICH regulatory member, PIC/s member)