	TITLE	SOP No.	EP-INS-001
	Procedure forissue of "Written Confirmation" for active substances exported to the EU for medicinal products for human use, in accordance with Article 46(2)(b) of Directives No. 2001/83/EC	Effective Date	10/04/2013
		Review Date	09/04/2015
		Supersedes	NA
Division Name		Revision No.	00
Export Division		Page No.	1 of 5

Prepared By		Checked By		Approved By		Authorized By	
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Designation	Drugs Inspector	Designation	DDC(I)	Designation	DDC(I)	Designation	DCG(I)
Sign		Sign		Sign		Sign	
Date	03/04/2013	Date	05/04/2013	Date	09 /04/2013	Date	10 /04/2013

Control Status

1.0 Purpose

To lay down a procedure for issue of "Written Confirmation" for active substances exported to EU for medicinal products for human use, in accordance with Article 46b(2)(b) of Directive 2001/83/EC.

2.0 Scope

This document is applicable to all applications made for issue of "Written Confirmation" for active substances exported to the EU for medicinal products for human use, in accordance with Article 46(2)(b) of Directives No. 2001/83/EC.

3.0 Responsibility:

3.1 The personnel at a level of DI/ADC(I)/DDC(I) Zonal office of CDSCOshall review the application and conduct inspection for issue of "Written Confirmation" for active substances exported to the EU for medicinal products for human use, in accordance with Article 46(2)(b) of Directives No. 2001/83/EC.

3.2 The concerned ADC(I) shall be responsible for implementation of the SOP.

3.3 Concerned DDC(I) shall be responsible for the regular monitoring of compliance of this SOP.

3.4 DCG(I) shall be the "Competent Authority" to issue "Written Confirmation" for active substances exported to the EU for medicinal products for human use, in accordance with Article 46(2)(b) of Directives No. 2001/83/EC.

4.0 Accountability

DCG(I) & Concerned DDC(I) of Zonal office of CDSCO

5.0 Procedure

	TITLE	SOP No.	EP-INS-001
	Procedure forissue of "Written Confirmation" for active substances exported to the EU for medicinal products for human use, in accordance with Article 46(2)(b) of Directives No. 2001/83/EC	Effective Date	10/04/2013
		Review Date	09/04/2015
		Supersedes	NA
Division Name		Revision No.	00
Export Division		Page No.	2 of 5

Prepared By		Checked By		Approved By		Authorized By	
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Designation	Drugs Inspector	Designation	DDC(I)	Designation	DDC(I)	Designation	DCG(I)
Sign		Sign		Sign		Sign	
Date	05/04/2013	Date	05/04/2013	Date	09/04/2013	Date	10/04/2013

5.1 Application for issue of "Written Confirmation" for active substances exported to EU for medicinal products for human use, in accordance with Article 46b(2)(b) of Directive 2001/83/EC shall be made as per SOP No. EP-INS-002 "Requirement for submission of application for issue of "Written Confirmation" for active substances exported to the EU for medicinal products for human use, in accordance with Article 46(2)(b) of Directives No. 2001/83/EC".

5.2 The application shall be prescreened at the time of receipt of application for its completeness of documents as per checklist placed at Annexure-3. The application shall be accepted if all the documents are in place as per checklist.

5.3 The application received shall be scrutinized as per Annexure-3 for the details as submitted by the firm and clarification, in any, shall be asked from the firm.

5.4 Zonaloffice shall plan to conduct the inspection as per SOP No. EP-INS-003 "Procedure for Planning and Preparation of GMP Inspection for issue of "Written Confirmation" for active substances exported to the EU for medicinal products for human use, in accordance with Article 46(2)(b) of Directives No. 2001/83/EC".

5.5 Inspection shall be conducted, report shall be written as per SOP No. EP-INS-004 "Procedure for Conducting GMP Inspection and Report Writing for issue of "Written Confirmation" for active substances exported to the EU for medicinal products for human use, in accordance with Article 46(2)(b) of Directives No. 2001/83/EC".

5.6 The inspection report or investigation report shall be reviewed as per SOP No. EP-INS-005 "Procedure for review of Inspection Report and issue of "Written Confirmation' for active substances exported to the EU for medicinal products for human use, in accordance with Article 46(2)(b) of Directives No. 2001/83/EC".

5.7 On the basis of recommendations of inspection report or investigation report submitted by Concerned DDC(I)Zonal office of CDSCO, necessary action shall be initiated for issue of

	TITLE	SOP No.	EP-INS-001
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Export Division		Review Date	09/04/2015
		Supersedes	NA
		Revision No.	00
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Prepared By		Checked By		Approved By		Authorized By	
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Designation	Drugs Inspector	Designation	DDC(I)	Designation	DDC(I)	Designation	DCG(I)
Sign		Sign		Sign		Sign	
Date	03/04/2013	Date	05/04/2013	Date	09/04/2013	Date	10/04/2013

"Written Confirmation" for active substances exported to the EU for medicinal products for human use, in accordance with Article 46(2)(b) of Directives No. 2001/83/EC as per format attached.

5.7.1 Non Compliances, if any, shall be communicated to the firm and/or EU as per SOP No. EP-INS-006 "Procedure forforwarding of Non Compliances to EU".

5.8 The complied inspection report shall be immediately forwarded in soft as well as hard copy to the DCG(I)with clear recommendations of the inspection.

5.9 DCG(I) is the "Competent Authority" to issue "Written Confirmation" for active substances exported to the EU for medicinal products for human use, in accordance with Article 46(2)(b) of Directives No. 2001/83/EC.

5.10 The following standards shall be applicable for issue of "Written Confirmation" for active substances exported to the EU for medicinal products for human use, in accordance with Article 46(2)(b) of Directives No. 2001/83/EC:

5.10.1 GMP requirements as per Directives No. 2001/83/EC latest amended vide Directive 2011/62/EU, or

5.10.2 WHO Good Manufacturing Practices (GMP) for active pharmaceutical ingredients stated as per Annex 2- WHO Technical report Series(TRS), No. 957, 2010, or

5.10.3 Good Manufacturing Practice guide for Active Pharmaceutical Ingredients ICH Harmonised Triplicate Guideline stated as per ICH Q7.

5.11 Following timelines shall be undertaken for the issue of "Written Confirmation":

Review of application and planning for inspection:	15 days
Conduct of Inspection after review of application:	15 days
Issue of "Written Confirmation" after conduct of inspection: (if report found satisfactory)	15 days

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Prepared By		Checked By		Approved By		Authorized By	
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Designation	Drugs Inspector	Designation	DDC(I)	Designation	DDC(I)	Designation	DCG(I)
Sign		Sign		Sign		Sign	
Date	03/04/2013	Date	05/04/2013	Date	09/04/2013	Date	10/04/2013

5.12 The "Written Confirmation" issued shall be valid for a period of 3 years from the date of issue. Surveillance inspections/ Inspection for Cause/ Sudden Inspection/ Inspection after major changes may be conducted as directed by the "Competent Authority"

5.13 Renewal application should be made at least 6 months prior to expiry of the "Written Confirmation".

5.14 Upon conduct of renewal application if grant of "Written Confirmation" is recommended before the expiry of valid "Written Confirmation" the renewed "Written Confirmation" shall be issued from the date of expiry of previous "Written Confirmation".

6.0 Annexure

Annexure/Format No.	Title
Annexure 1	"Written Confirmation" for active substances exported to the EU for medicinal products for human use, In accordance with Article 46(2)(b) of Directives No. 2001/83/EC
Annexure 2	GMP requirements as per Directives No. 2001/83/EC latest amended vide Directive 2011/62/EU
Annexure 3	Checklist for documents to be submitted for application of "Written Confirmation" for active substances exported to the EU for medicinal products for human use, In accordance with Article 46(2)(b) of Directives No. 2001/83/EC
Annexure 4	WHO Good Manufacturing Practices (GMP) for active pharmaceutical ingredients stated as per Annex 2- WHO Technical report Series(TRS), No. 957, 2010
Annexure 5	Good Manufacturing Practice guide for Active Pharmaceutical Ingredients ICH Harmonised Triplicate Guideline stated as per ICH Q7

7.0 References

Doc. No.	Title
1	GMP requirements as per Directives No. 2001/83/EC latest amended vide Directive 2011/62/EU
2	WHO Good Manufacturing Practices (GMP) for active

	TITLE	SOP No.	EP-INS-001
Division Name	**Procedure forissue of "Written Confirmation" for active substances exported to the EU for medicinal products for human use, in accordance with Article 46(2)(b) of Directives No. 2001/83/EC**	Effective Date	10/04/2013
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Prepared By		Checked By		Approved By		Authorized By	
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Designation	Drugs Inspector	Designation	DDC(I)	Designation	DDC(I)	Designation	DCG(I)
Sign		Sign		Sign		Sign	
Date	03/04/2013	Date	05/04/2013	Date	09/04/2013	Date	10/04/2013

	pharmaceutical ingredients stated as per Annex 2- WHO Technical report Series(TRS), No. 957, 2010
3	Good Manufacturing Practice guide for Active Pharmaceutical Ingredients ICH Harmonised Triplicate Guideline stated as per ICH Q7

8.0 Abbreviation

Acronym	Full Form
DCG (I)	Drugs Controller General, India
ADC (I)	Assistant Drug Controller, India
DI	Drug Inspector
DDC (I)	Deputy Drugs Controller, India
SOP	Standard Operating Procedure
INS	Inspection
EU	European Union
EC	European Council

9.0 Revision History

Revision No.	Reason(s) for Revision
00	Implementation of New Format

	TITLE	SOP No.	EP-INS-002
	Requirement for submission of application for issue of "Written Confirmation" for active substances exported to the EU for medicinal products for human use, in accordance with Article 46(2)(b) of Directives No. 2001/83/EC	Effective Date	10/04/2013
		Review Date	09/04/2015
		Supersedes	NA
Division Name		Revision No.	00
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Prepared By		Checked By		Approved By		Authorized By	
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Designation	Drugs Inspector	Designation	DDC(I)	Designation	DDC(I)	Designation	DCG(I)
Sign		Sign		Sign		Sign	
Date	03/04/2013	Date	05/04/2013	Date	09/04/2013	Date	10/04/2013

Control Status

1.0 Purpose

To lay down requirement for submission of application for issue of "Written Confirmation"for active substances exported to the EU for medicinal products for human use, in accordance with Article 46(2)(b) of Directives No. 2001/83/EC.

2.0 Scope

This document is applicable forrequirement for submission of application for issue of "Written Confirmation"for active substances exported to the EU for medicinal products for human use, in accordance with Article 46(2)(b) of Directives No. 2001/83/EC to theoffice of CDSCO.

3.0 Responsibility

3.1 The Drugs Inspectors, shall be responsible for checking the complete receipt of documents upon the receipt of application for issue of "Written Confirmation"for active substances exported to the EU for medicinal products for human use, in accordance with Article 46(2)(b) of Directives No. 2001/83/EC.

3.2 The Head of concerned Zoneshall be responsible for overall compliance of the SOP.

4.0 Accountability

Head of concerned Zone and DCG (I).

5.0 Procedure

5.1 Application shall be submitted to the Head of concerned Zonal office of CDSCO for issue of "Written Confirmation"for active substances exported to the EU for medicinal products for human use, in accordance with Article 46(2)(b) of Directives No. 2001/83/EC .

	TITLE	SOP No.	EP-INS-002
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		Review Date	09/04/2015
		Supersedes	NA
Division Name		Revision No.	00
Export Division		Page No.	2 of 5

Prepared By		Checked By		Approved By		Authorized By	
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Designation	Drugs Inspector	Designation	DDC(I)	Designation	DDC(I)	Designation	DCG(I)
Sign		Sign		Sign		Sign	
Date	03/04/2013	Date	05/04/2013	Date	09/04/2013	Date	10/04/2013

5.2 Following documents shall be submitted in Soft as well as Hard copy by the applicant along with application for issue of "Written Confirmation"for active substances exported to the EU for medicinal products for human use, in accordance with Article 46(2)(b) of Directives No. 2001/83/EC:

Documents required for the application for grant of Written Confirmation Certificate for the first time or reissue or renewal

5.2.1 Covering Letter – The covering letter is an important part of the application and should clearly specify the intent of the application (whether the application is being submitted for the first time, whether the application is for re-issue or for renewal) the list of documents that are being submitted (Index with page no's) as well as any other important and relevant information may be provided in the covering letter. The covering letter should be duly signed and stamped by the authorized signatory, indicating the name & designation of the authorized signatory alongwith the name and address of the firm.

5.2.2 An Authorization letter in original issued by the Director/Company Secretary/Partner of the firm revealing the name & designation of the person authorized to sign (along with the name and address of the firm) on behalf of the firm should be submitted at the time of submission of the application Duly self attested photocopies of the Authorization letter may be submitted at the time of submission of subsequent applications.

5.2.3 Copy of GMP certificate issued as Certificate of Pharmaceutical Product issued as per WHO guidelines, USFDA, EDQM, etc. if any

5.2.4 Copy of Manufacturing License issued by SLA

5.2.5 List of all APIs approved by SLA.

	TITLE	SOP No.	EP-INS-002
	Requirement for submission of application for issue of "Written Confirmation" for active substances exported to the EU for medicinal products for human use, in accordance with Article 46(2)(b) of Directives No. 2001/83/EC	Effective Date	10/04/2013
		Review Date	09/04/2015
		Supersedes	NA
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Prepared By		Checked By		Approved By		Authorized By	
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Designation	Drugs Inspector	Designation	DDC(I)	Designation	DDC(I)	Designation	DCG(I)
Sign		Sign		Sign		Sign	
Date	03/04/2013	Date	05/04/2013	Date	09 /04/2013	Date	10 /04/2013

5.2.6 List of Products applied for issue of "Written Confirmation" for active substances exported to the EU for medicinal products for human use, in accordance with Article 46(2)(b) of Directives No. 2001/83/EC

5.2.7 Summary of Stability data (3 batches) Accelerated/ Real time (as prescribed)

5.2.8 List of Technical staff, their qualification, experience and their approval by SLA.

5.2.9 Validation Master Plan

5.2.10 Summary of Process validation data for 3 batches of each product.

5.2.11 Export data of last 3 years

5.2.12 Good Distribution Practices followed by the firm.

5.2.13 Summary of Annual Product review.

5.2.14 Summary of Market Complaint Review

5.2.15 Summary data of Impurity profiling

5.2.16 Summary data of Analytical Method Validation

5.2.17 Site Master File (as specified under WHO TRS 823)

Documents required for the application for grant of Written Confirmation Certificate for additional Products

5.2.1 Covering Letter – The covering letter is an important part of the application and should clearly specify the intent of the application the list of documents that are being submitted (Index with page no's) as well as any other important and relevant information may be provided in the covering letter. The covering letter should be duly signed and stamped by the authorized signatory, indicating the name & designation of the authorized signatory alongwith the name and address of the firm.

5.2.2 An Authorization letter in original issued by the Director/Company Secretary/Partner of the firm revealing the name & designation of the person authorized to sign (along with the

	TITLE	SOP No.	EP-INS-002
	Requirement for submission of application for issue of "Written Confirmation" for active substances exported to the EU for medicinal products for human use, in accordance with Article 46(2)(b) of Directives No. 2001/83/EC	Effective Date	10/04/2013
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		Supersedes	NA
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Prepared By		Checked By		Approved By		Authorized By	
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Designation	Drugs Inspector	Designation	DDC(I)	Designation	DDC(I)	Designation	DCG(I)
Sign		Sign		Sign		Sign	
Date	03/04/2013	Date	05/04/2013	Date	09/04/2013	Date	10/04/2013

name and address of the firm) on behalf of the firm should be submitted at the time of submission of the application Duly self attested photocopies of the Authorization letter may be submitted at the time of submission of subsequent applications.

5.2.3 Copy of GMP certificate issued as Certificate of Pharmaceutical Product issued as per WHO guidelines, USFDA, EDQM, etc. if any

5.2.4 Copy of Manufacturing License issued by SLA along with the valid Product permission

5.2.5 Copy of valid "Written Confirmation" Certificate.

5.2.6 List of Products applied for issue of "Written Confirmation" for active substances exported to the EU for medicinal products for human use, in accordance with Article 46(2)(b) of Directives No. 2001/83/EC

5.2.7 Summary of Stability data (3 batches) Accelerated/ Real time (as prescribed)

5.2.8 Validation Master Plan

5.2.9 Summary of Process validation data for 3 batches of each product.

5.2.10 Summary of Annual Product review.

5.2.11 Summary of Market Complaint Review

5.2.12 Summary data of Impurity profiling

5.2.13 Summary data of Analytical Method Validation

5.2.14 Site Master File (as specified under WHO TRS 823)

6.0 Annexure / Format

Annexure/Format No.	Title
Annexure 1	WHO TRS 823

7.0 References

	TITLE	SOP No.	EP-INS-002
	Requirement for submission of application for issue of "Written Confirmation" for active substances exported to the EU for medicinal products for human use, in accordance with Article 46(2)(b) of Directives No. 2001/83/EC	Effective Date	10/04/2013
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Prepared By		Checked By		Approved By		Authorized By	
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Designation	Drugs Inspector	Designation	DDC(I)	Designation	DDC(I)	Designation	DCG(I)
Sign		Sign		Sign		Sign	
Date	03/04/2013	Date	05/04/2013	Date	09/04/2013	Date	10/04/2013

Doc. No.	Title
1	WHO TRS 823
2	GMP requirements as per Directives No. 2001/83/EC latest amended vide Directive 2011/62/EU

8.0 Abbreviation

Acronym	Full Form
DCGI	Drugs Controller General India
QA	Quality Assurance
DI	Drug Inspector
CDSCO	Central Drugs Standard Control Organization
DDC (I)	Deputy Drugs Controller, India
ADC (I)	Assistant Drugs Controller, India
SOP	Standard Operating Procedure
INS	Inspection
GMP	Good Manufacturing Practices
IPQC	In-process Quality Control
SLA	State Licensing Authority
OVI	Organic Volatile Impurities
ETP	Effluent Treatment Plant
TRS	Technical Report Series
HVAC	Heating Ventilation and Air Conditioning
MOC	Material of Construction

9.0 Revision History

Revision No.	Reason(s) for Revision
00	Implementation of New Format

	TITLE	SOP No.	EP-INS-003
	Procedure for Planning and Preparation of GMP Inspection for issue of "Written Confirmation" for active substances exported to the EU for medicinal products for human use, in accordance with Article 46(2)(b) of Directives No. 2001/83/EC	Effective Date	10/04/2013
		Review Date	09/04/2015
		Supersedes	NA
Division Name		Revision No.	00
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Designation	Drugs Inspector	Designation	DDC(I)	Designation	DDC(I)	Designation	DCG(I)
Sign		Sign		Sign		Sign	
Date	03/04/2013	Date	05/04/2013	Date	09 /04/2013	Date	10/04/2013

Control Status

1.0 Purpose

To lay down a procedure for planning and preparation of GMP inspection for issue of "Written Confirmation" for active substances exported to the EU for medicinal products for human use, in accordance with Article 46(2)(b) of Directives No. 2001/83/EC.

2.0 Scope

This document is applicable for planning and preparation of inspections for issue of "Written Confirmation" for active substances exported to the EU for medicinal products for human use, in accordance with Article 46(2)(b) of Directives No. 2001/83/EC by the inspectors of CDSCO.

3.0 Responsibility

3.1 The Drugs Inspectors/ADC(I)/DDC(I) of Zones shall be responsible for planning and preparation of inspection.

3.2 The Head of concerned zone shall be responsible for overall compliance of the SOP.

4.0 Accountability

Head of concerned Zone and DCG (I).

5.0 Procedure

5.1 The first written confirmation shall be granted based on valid Certificate of Pharmaceutical Product issued as per WHO guidelines or US FDA or EDQM / TGA certificates (not more than 24 months old). If the company does not have any of these then inspection shall be conducted.

	TITLE	SOP No.	EP-INS-003
	Procedure for Planning and Preparation of GMP Inspection for issue of "Written Confirmation" for active substances exported to the EU for medicinal products for human use, in accordance with Article 46(2)(b) of Directives No. 2001/83/EC	Effective Date	10/04/2013
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Prepared By		Checked By		Approved By		Authorized By	
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Designation	Drugs Inspector	Designation	DDC(I)	Designation	DDC(I)	Designation	DCG(I)
Sign		Sign		Sign		Sign	
Date	03/04/2013	Date	05/04/2013	Date	09/04/2013	Date	10/04/2013

5.2 **Inspection Team**

5.2.1 Composition of the team

One or two inspectors from concerned zonal office of which one trained & qualified Inspector shall be designated as the team leader. One QC expert from CDTL/RDTL/CDL may be included, if required.

5.2.2 Responsibility of the Inspection Team

The responsibility of the Inspection Team shall be as follows:

- To conduct a GMP inspection
- To agree on the inspection's scope
- To discuss and resolve, where possible, any major problems which may occur during the inspection process
- To ensure that all inspectors play an active role in the inspection process
- To make decisions on inspection findings by way of consensus however, where this is not possible, the Team Leader makes the final decision
- To prepare an inspection report

5.2.3 **Responsibility of the Team Leader**

The Team Leader shall be responsible to organize, coordinate, lead during all stages of the inspection and act as spokesperson.

5.3 **Preparing for Inspection**

5.3.1 After receiving application of the firm by the deputed inspection team member (s), a review should be made relating to the firm to be visited from the documents available in the office file. This shall include review of following documents:-

5.3.1.1 Covering letter

5.3.1.2 Authorization letter

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		Supersedes	NA
Division Name		Revision No.	00
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Prepared By		Checked By		Approved By		Authorized By	
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Designation	Drugs Inspector	Designation	DDC(I)	Designation	DDC(I)	Designation	DCG(I)
Sign		Sign		Sign		Sign	
Date	03/04/2013	Date	05/04/2013	Date	09/04/2013	Date	10/04/2013

5.3.1.3 Copy of GMP certificate issued as Certificate of Pharmaceutical Product issued as per WHO guidelines, USFDA, EDQM, etc. if any

5.3.1.4 Copy of Manufacturing License issued by SLA

5.3.1.5 List of all APIs approved by SLA.

5.3.1.6 List of Products applied for issue of "Written Confirmation" for active substances exported to the EU for medicinal products for human use, in accordance with Article 46(2)(b) of Directives No. 2001/83/EC

5.3.1.7 List of SOPs and STPs

5.3.1.8 Summary of Stability data (3 batches) Accelerated/ Real time (as prescribed)

5.3.1.9 List of Equipment and Instruments

5.3.1.10 List of Technical staff, their qualification, experience and their approval by SLA.

5.3.1.11 Validation Master Plan

5.3.1.12 Summary of Process validation data for 3 batches of each product.

5.3.1.13 Export data of last 3 years

5.3.1.14 Summary of Annual Product review.

5.3.1.15 Summary of Market Complaint Review

5.3.1.16 Summary data of Impurity profiling

5.3.1.17 Summary data of Analytical Method Validation

5.3.1.18 Site Master File (as specified under WHO TRS 823)

5.3.1.19 Good Distribution Practices followed by the firm.

5.3.1.20 NSQ reports

5.3.1.21 Legal undertaking stating that Inspection/ Investigation reports of any regulatory inspection by Indian regulatory Authority including Show Cause Notices/ Suspensions/ Cancellations

	TITLE	SOP No.	EP-INS-003
Division Name	**Procedure for Planning and Preparation of GMP Inspection for issue of "Written Confirmation" for active substances exported to the EU for medicinal products for human use, in accordance with Article 46(2)(b) of Directives No. 2001/83/EC**	Effective Date	10/04/2013
		Review Date	09/04/2015
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Designation	Drugs Inspector	Designation	DDC(I)	Designation	DDC(I)	Designation	DCG(I)
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if any shall be communicated to "Competent Authority" i.e. DCG(I), CDSCO within 15 working days.

5.3.1.22 Non Conformances pointed out in previous inspection reports.

5.3.2 Any data or information not submitted by the applicant shall be communicated to the firm.

5.3.3 If all the documents are in place, a day wise inspection plan (2-4) days depending on the scope of inspection (Size of the facility, products etc.,) shall be prepared.

5.3.4 The inspection plan may be communicated to the firm at least 7 days before the inspection.

5.3.5 The checklist for inspection shall be given to the firm for filling the self appraisal by the manufacturer at least 7 days before inspection.

6.0 Annexure / Format

Nil

7.0 References

Doc. No.	Title
1	WHO TRS 823
2	GMP requirements as per Directives No. 2001/83/EC latest amended vide Directive 2011/62/EU

8.0 Abbreviation

Acronym	Full Form
QA	Quality Assurance
DI	Drug Inspector
CDSCO	Central Drugs Standard Control Organization
DDC (I)	Deputy Drug Controller, India

	TITLE	SOP No.	EP-INS-003
Division Name: Export Division	**Procedure for Planning and Preparation of GMP Inspection for issue of "Written Confirmation" for active substances exported to the EU for medicinal products for human use, in accordance with Article 46(2)(b) of Directives No. 2001/83/EC**	Effective Date	10/04/2013
		Review Date	09/04/2015
		Supersedes	NA
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Prepared By		Checked By		Approved By		Authorized By	
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Date	03/04/2013	Date	05/04/2013	Date	09/04/2013	Date	10/04/2013

ADC (I)	Assistant Drug Controller, India
SOP	Standard Operating Procedure
INS	Inspection
GMP	Good Manufacturing Practices
WHO	World Health Organization
MFR	Manufacturing Formula Record
BMR	Batch Manufacturing Record
QC	Quality Control
CDTL	Central Drug Testing Laboratory
USFDA	United States Food & Drug Administration
EDQM	European Drug Quality Management
NSQ	Not of Standard Quality
IPQC	In-process Quality Control
RDTL	Regional Drug Testing Laboratory
CDL	Central Drug Laboratory
API	Active Pharmaceutical Ingredient
SLA	State Licensing Authority
STP	Standard Testing Procedure
HVAC	Heating Ventilation and Air Conditioning
TRS	Technical report Series

9.0 Revision History

Revision No.	Reason(s) for Revision
00	Created New

	TITLE	SOP No.	EP-INS-004
Division Name	**Procedure for Conducting GMP Inspection and Report Writing for issue of "Written Confirmation" for active substances exported to the EU for medicinal products for human use, in accordance with Article 46(2)(b) of Directives No. 2001/83/EC**	Effective Date	10/04/2013
Export Division		Review Date	09/04/2015
		Supersedes	NA
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Prepared By		Checked By		Approved By		Authorized By	
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Sign		Sign		Sign		Sign	
Date	03/04/2013	Date	05/04/2013	Date	09/04/2013	Date	10/04/2013

Control Status

1.0 Purpose

To lay down a procedure for conducting GMP inspection and report writingfor issue of "Written Confirmation"for active substances exported to the EU for medicinal products for human use, in accordance with Article 46(2)(b) of Directives No. 2001/83/EC.

2.0 Scope

This document is applicable for inspection for issue of "Written Confirmation"for active substances exported to the EU for medicinal products for human use, in accordance with Article 46(2)(b) of Directives No. 2001/83/ECby the Inspectors of CDSCO.

3.0 Responsibility

3.1 The DI/ADC(I)/DDC(I) of Zonesshall be responsible for conducting GMP inspection and report writing.

3.2 The Head of concerned zone shall be responsible for overall compliance of the SOP.

4.0 Accountability

Head of concerned Zone and DCG (I).

5.0 Procedure

5.1 This procedure takes into account:

5.1.1 ***"Procedure for Planning and Preparation of GMP Inspection for issue of "Written Confirmation" for active substances exported to the EU for medicinal products for human use, in accordance with Article 46(2)(b) of Directives No. 2001/83/EC"***(EP-INS-003), which describes the steps immediately before the conduct of an inspection and particularly the planning and preparation for GMPinspection.

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5.2 Inspection for issue of "Written Confirmation" for active substances exported to the EU for medicinal products for human use, in accordance with Article 46(2)(b) of Directives No. 2001/83/EC

5.2.1 On the basis of adequacy of application a inspection needs to be planned by the inspection team.

5.2.2 Inspections shall be carried out as perGMP requirements as per Directives No. 2001/83/EC latest amended vide Directive 2011/62/EU, orWHO Good Manufacturing Practices (GMP) for active pharmaceutical ingredients stated as per Annex 2- WHO Technical report Series(TRS), No. 957, 2010, orGood Manufacturing Practice guide for Active Pharmaceutical Ingredients ICH Harmonised Triplicate Guideline stated as per ICH Q7utilizing inspection checklist (as annexed).

5.2.3 The inspection team shall examine all portions of premises, plant, and appliances and also inspects the process of manufacture intended to be employed or being employed, standardizing and testing of the drugs to be manufactured or being manufactured and verify into the professional qualification of technical staff to be employed. They shall also examine and verify the statements made in the application in regard to their correctness and the capability of the applicant to comply with the requirements of competent technical staff, manufacturing plant, equipment (Manufacturing & testing) and requirements of GMP.

5.2.4 The inspection team shall conduct an opening meeting with the key personnel of the manufacturing site wherein the scope and purpose of the inspection should be discussed.

5.2.5 Systematic inspection should be carried out by taking rounds, interviewing the personnel, observing the activities and looking into relevant documents. The deficiencies should be

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discussed with the company personnel during the course of inspection for better understanding.

5.2.6 During the course of inspection, inspection team should critically look into following details using risk based approach:

5.2.6.1 Adequacy of Quality Management System.

5.2.6.2 Design and layout of manufacturing areas, flow of personnel and materials, adequacy of segregation.

5.2.6.3 Nature of construction and finishes.

5.2.6.4 Schematic diagram of Air Handling system installed and its recent validation.

5.2.6.5 Schematic diagram of water system installed, its monitoring data and its recent validation.

5.2.6.6 Schematic diagram of steam system installed, its monitoring and its recent validation.

5.2.6.7 Gas pipelines, their color coding and testing and validation of gases.

5.2.6.8 ETP and waste disposal system.

5.2.6.9 Classification of manufacturing areas.

5.2.6.10 Qualification of premises and systems as appropriate.

5.2.6.11 Health, hygiene and gowning requirements for personnel.

5.2.6.12 Adequacy of general GMP training and need based training of the personnel, aseptic practices for aseptic / sterile products.

5.2.6.13 Medical examination record of the personnel.

5.2.6.14 Design and location and suitability of equipment.

5.2.6.15 Preventive maintenance program.

5.2.6.16 Qualification, calibration of equipment BMR & BPR of bulk finished products, sourcing of materials, vendor approvals, etc.

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5.2.6.17 SOP for receipt of Raw Material.

5.2.6.18 Control, storage and handling of materials.

5.2.6.19 Line clearance, labeling and segregation practices.

5.2.6.20 Logging of activities (Specifically for critical manufacturing steps, IPQC steps, cleaning, weighingand environmental monitoring).

5.2.6.21 Transport handling and use of starting materials and packing materials.

5.2.6.22 Monitoring of process operation.

5.2.6.23 Adequacy of change control, deviation control procedures.

5.2.6.24 Sanitation and cleaning.

5.2.6.25 Adequacy of documentation and document control system (Specifications, procedures, records, protocols and reports).

5.2.6.26 Quality Control Practices on RM/PM/FG testing, sampling, quarantine control.

5.2.6.27 Stability studies- SOP, Planand reports.

5.2.6.28 Validation practices- Adequacy of VMP, validation and qualification protocols and reports for premises, system, equipment, processes, cleaning, analytical methods and computer (as applicable).

5.2.6.29 Adequacy of studies and control procedure followed for product change over.

5.2.6.30 Traceability of activities.

5.2.6.31 SOP on reprocessing, if any.

5.2.6.32 Complaint handling. Check SOP, records and investigation results.

5.2.6.33 Depth and comprehensiveness of Self Audit review.

5.2.6.34 Adequacy of Corrective and Preventive Action system.

5.2.6.35 Trend analysis, risk assessment, annual product review, utilization of alert and action limits in processing and relevant monitoring.

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5.2.6.36 Adequacy of recall system.

5.2.6.37 Handling of rejected material.

5.2.6.38 Adequacy of cold chain management.

5.2.6.39 Animal testing facilities, if any (building with proper HVAC, waste disposal and management etc.)

5.2.6.40 Control system on printed packaging material.

5.2.6.41 Review of compliance of last inspection findings.

5.2.6.42 Good Distribution Practices followed by the firm.

5.2.7 At the end of the inspection, a closing meeting shall be conducted and the observations are to be discussed with the manufacturer.

5.3 Writing of Inspection Report

5.3.1 Inspection report should be prepared by the team giving the details of name of manufacturer, names of inspectors, date of inspection, purpose of inspection and observations made during the inspection along with the recommendations. Checklist should also be filled and the format of the report should include all the elements. Report shall be prepared in a manner or format as annexed.

5.3.2 The observations should include the general description about locations and surroundings, building and premises, HVAC and environmental monitoring, water system, disposal of waste, warehousing area, Production areas, Quality Control areas, Personnel, Health Clothing Sanitation of Worker, Manufacturing operations and controls, Precautions against mix ups and cross contamination, sanitation in manufacturing areas, Raw materials, Equipment's, documentation and records (specification, MFR,BPR, SOP's, distribution records, complaint records, Product recalls, Labels and other printed materials, quality assurance, Self Inspection and

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Quality audits, Quality control system, Validation (process, testing and cleaning), stability studies and Good Distribution Practices followed.

5.3.3 Inspection report should contain the deficiencies pointed out at the time of inspection which may be listed serially.

5.3.4 The deficiencies should be written clearly without ambiguity and may be classified as Critical, Major or Minor as per GMP requirements as per Directives No. 2001/83/EC latest amended vide Directive 2011/62/EU, orWHO Good Manufacturing Practices (GMP) for active pharmaceutical ingredients stated as per Annex 2- WHO Technical report Series(TRS), No. 957, 2010.An attempt should be made to clearly distinguish the non-compliant observations from general observations.

5.3.5 Reference of areas, equipment, documents, system, procedures, personnel etc. need to be cited in the observations as appropriate.

5.3.6 Recommendations should be given on the basis of purpose of inspection and level of GMP compliance and needs to be signed by Inspectors.

5.3.7 The report should be forwarded to the DDC(I) for review.

5.3.8 Complied Inspection report along with previous inspection report along with complete application shall be forwarded to DCG(I) for issuance of "Written Confirmation"for active substances exported to the EU for medicinal products for human use, in accordance with Article 46(2)(b) of Directives No. 2001/83/EC.

5.4 Inspection for Cause/ Un announced Inspection

5.4.1 During the course of complaint investigation in addition to verification of general things as mentioned above specific records with respect to the product in question needs to be verified (BMR, BPR, testing, specification, deviation, changes made, etc.) to see

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whether the subject batch of product is manufactured and tested as per Protocol and GMP requirements.

5.4.2 Control sample of subject product also needs to be verified physically.

5.4.3 Whether the firm has carried out complaint investigation or route cause analysis need to be verified. If any direct or in-direct assignable route cause is detected the impact of that cause on other batches also needs to be verified.

5.4.4 If required samples may be drawn judiciously from the available stocks or control samples and sent for testing or evaluation.

5.4.5 The report of complaint investigation should be written and forwarded to DCG(I) with specific comments.

5.5 Inspection for Changes made after issue of "Written Confirmation" for active substances exported to the EU for medicinal products for human use, in accordance with Article 46(2)(b) of Directives No. 2001/83/EC

5.5.1 Inspection to verify the suitability of changes if required for routine adoption.

5.5.2 In case of changes like;

5.5.2.1 Major up gradation of production facilities.

5.5.2.2 Major change in equipment.

Routine inspection may be carried out to see the suitability of steps taken to handle the change.

5.5.3 Suitability validation of the process for following changes and detailed comments by the inspecting team should be made in the report.

5.5.4 The report for change verification is compiled and forwarded to DCG(I) with clear comments on due diligence taken by the manufacturer for justification of change.

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5.5.5. Any other inspection may be carried out as directed by Competent Authorityon the lines ofEU directives No. 2001/83/ECassessment inspection carried out for issue of "Written Confirmation"for active substances exported to the EU for medicinal products for human use, in accordance with Article 46(2)(b) of Directives No. 2001/83/ECwith specific emphasis on any issue in question and reported accordingly.

5.6 Review

5.6.1 Review of the inspection reports shall be done by Zonal Heads.

6.0 Annexure / Format

Annexure/Format No.	Title
Annexure 1	GMP Checklists

7.0 References

Doc. No.	Title
1	GMP requirements as per Directives No. 2001/83/EC latest amended vide Directive 2011/62/EU
2	WHO Good Manufacturing Practices (GMP) for active pharmaceutical ingredients stated as per Annex 2- WHO Technical report Series(TRS), No. 957, 2010
3	Good Manufacturing Practice guide for Active Pharmaceutical Ingredients ICH Harmonised Triplicate Guideline stated as per ICH Q7

8.0 Abbreviation

Acronym	Full Form
QA	Quality Assurance
DI	Drug Inspector
CDSCO	Central Drugs Standard Control Organization

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DDC (I)	Deputy Drug Controller, India
ADC (I)	Assistant Drug Controller, India
SOP	Standard Operating Procedure
INS	Inspection
GMP	Good Manufacturing Practices
MFR	Master Formula Record
BMR	Batch Manufacturing Record
BPR	Batch Packing Record
RM	Raw Material
PM	Packing Material
FG	Finished Goods
NSQ	Not of Standard Quality
IPQC	In-process Quality Control
ETP	Effluent Treatment Plant
HVAC	Heating Ventilation and Air Conditioner
EU	European Union
EC	European Council
TRS	Technical Report Series
VMP	Validation Master Plan

9.0 Revision History

Revision No.	Reason(s) for Revision
00	Implementation of New Format

	TITLE	SOP No.	EP-INS-005
Division Name	**Review of Inspection Report and issue of "Written Confirmation' for active substances exported to the EU for medicinal products for human use, in accordance with Article 46(2)(b) of Directives No. 2001/83/EC**	Effective Date	10/04/2013
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Control Status

1.0 Purpose

To lay down a procedure for review of Inspection Report and issue of "Written Confirmation' for active substances exported to the EU for medicinal products for human use, in accordance with Article 46(2)(b) of Directives No. 2001/83/EC.

2.0 Scope

This document is applicable toreview of inspection report.

3.0 Responsibility:

3.1 The personnel at a level of DI shall review the inspection report.

3.2 The ADC (I) shall be responsible for implementation of the SOP.

3.3 DDC (I) shall be responsible for the regular monitoring of compliance of this SOP.

3.4 DCG(I) shall be the "Competent Authority" to issue "Written Confirmation"for active substances exported to the EU for medicinal products for human use, in accordance with Article 46(2)(b) of Directives No. 2001/83/EC.

4.0 Accountability

DDC (I) of concerned zone and DCG(I)

5.0 Procedure

5.1 On the basis of recommendations of inspection report or investigation report submitted, need to be initiated as follows.

5.1.1 If deficiencies are pointed out for compliance, it is to be communicated to the firm for compliance. The Zonal officer shall be responsible for verification of compliance, once the compliance report is submitted by the firm.

5.1.2 If deficiencies are pointed out and application is rejected, it needs to be informed to the applicant with reasons.

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Division Name	**Review of Inspection Report and issue of "Written Confirmation' for active substances exported to the EU for medicinal products for human use, in accordance with Article 46(2)(b) of Directives No. 2001/83/EC**	Effective Date	10/04/2013
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5.1.3 Review the report and categorize the deficiencies as critical or major or minor under the criteria as given below.

CRITICAL DEFICIENCY	A deficiency which has a direct impact on quality of the product and which could result injurious to the patient or animal. Some of these defects are evidences of potential contamination and cross contamination issues, mix-up issues, falsification of data etc
MAJOR DEFICIENCY	A non-critical deficiency that may have an impact on the quality of the product and adversely affect the quality of the product. Some these defects are evidences of non-compliances of GMP of non-critical norms, failure to carry out satisfactory procedures for release of batches etc.
MINOR DEFICIENCY	A deficiency which cannot be classified as either critical or major, but which indicates a departure from good manufacturing practice

5.1.4 If "Written Confirmation" is already issued, Critical or Major GMP non-compliance observed during surveillance audit or Inspection for Cause/ Un announced Inspectionor Inspection for Changes made after issue of "Written Confirmation" for active substances exported to the EU for medicinal products for human use, in accordance with Article 46(2)(b) of Directives No. 2001/83/ECat a manufacturer should be sent to EU as per SOP EP-INS-006 "Procedure for reporting of Non Compliances to EU

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5.1.5 On the basis of review of criticalities of deficiencies regulatory action needs to be taken like:

5.1.5.1 Show cause notice need to be issued to the manufacturer stating that why such an order should not be passed and ask the manufacturer to reply within ten days of receipt of the copy of the order by the Concerned Zonal office and a copy in hard and soft shall be sent to the office of DCGI.

5.1.5.2 Then based on the reply, if required, a suitable action may be recommended to SLA. For any violation under the Drugs & Cosmetics Act and Rules the "Written Confirmation' for active substances exported to the EU for medicinal products for human use, in accordance with Article 46(2)(b) of Directives No. 2001/83/EC issued by the Competent Authority may be suspended or cancelled and a copy in hard and soft shall be sent to the office of DCGI.

5.1.6 Manufacturer, if complies with the deficiencies and inform to the Competent Authority, the compliance report and document need to be scrutinized and on the strengths of compliance report further inspection may be carried out.

5.1.7 If the satisfactory compliance is reported then the application may be forwarded for issue of "Written Confirmation"for active substances exported to the EU for medicinal products for human use, in accordance with Article 46(2)(b) of Directives No. 2001/83/ECand the same may be communicated to the EU.

6.0 Annexure

NIL

7.0 References

Doc. No.	Title
1	GMP requirements as per Directives No. 2001/83/EC latest

	TITLE	SOP No.	EP-INS-005
	Review of Inspection Report and issue of "Written Confirmation' for active substances exported to the EU for medicinal products for human use, in accordance with Article 46(2)(b) of Directives No. 2001/83/EC	Effective Date	10/04/2013
		Review Date	09/04/2015
		Supersedes	NA
Division Name		Revision No.	00
Export Division		Page No.	4 of 4

Prepared By		Checked By		Approved By		Authorized By	
Name	Sidharth Sahai Malhotra	Name	P. Venkateshwarlu	Name	Dr. S. Eswara Reddy	Name	Dr. G. N. Singh
Designation	Drugs Inspector	Designation	DDC(I)	Designation	DDC(I)	Designation	DCG(I)
Sign		Sign		Sign		Sign	
Date	03/04/2013	Date	05/04/2013	Date	09/04/2013	Date	10/04/2013

	amended vide Directive 2011/62/EU

8.0 Abbreviation

Acronym	Full Form
QA	Quality Assurance
ADC (I)	Assistant Drug Controller, India
DI	Drug Inspector
DCG(I)	Drugs Controller General, India
DDC (I)	Deputy Drugs Controller,India
SOP	Standard Operating Procedure
SLA	State Licensing Authority
INS	Inspection

9.0 Revision History

Revision No.	Reason(s) for Revision
00	Implementation of New Format

	TITLE		SOP No.	EP-INS-006
	Procedure for forwarding of Non Compliances to EU		Effective Date	10/04/2013
			Review Date	09/04/2015
			Supersedes	NA
Division Name			Revision No.	00
Export Division			Page No.	1 of 3

Prepared By		Checked By		Approved By		Authorized By	
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Sign		Sign		Sign		Sign	
Date	03/04/2013	Date	05/04/2013	Date	09/04/2013	Date	10/04/2013

Control Status

1.0 Purpose

To lay down a procedure for forwarding of Non Compliances to EU.

2.0 Scope

This document is applicable toforwarding of Non Compliances to EU for the manufacturers to whom "Written Confirmation" for active substances exported to the EU for medicinal products for human use, in accordance with Article 46(2)(b) of Directives No. 2001/83/EC have already been issued.

3.0 Responsibility:

3.1 The personnel at a level of DI shall review the inspection report.

3.2 The ADC (I) shall be responsible for implementation of the SOP.

3.3 DDC (I) shall be responsible for the regular monitoring of compliance of this SOP.

3.4 DCG(I) shall be the "Competent Authority" to forward Non Compliances to EU.

4.0 Accountability

DDC (I) of concerned zoneand DCG (I)

5.0 Procedure

5.1 The inspection or investigation report shall be reviewed and Non Compliances shall as categorized as per SOP EP-INS-005 "Procedure for review of Inspection Report and issue of "Written Confirmation' for active substances exported to the EU for medicinal products for human use, in accordance with Article 46(2)(b) of Directives No. 2001/83/EC".

5.2 Critical and Major Non Compliances shall be forwarded to EU.

5.3 Details of Show Cause issued and any suitable action, if taken, shall be forwarded to EU.

5.4 The following information needs to be submitted to the EU:

- Contact details of the notifying authority

	TITLE		SOP No.	EP-INS-006
	Procedure for forwarding of Non Compliances to EU		Effective Date	10/04/2013
			Review Date	09/04/2015
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Export Division			Page No.	2 of 3

Prepared By		Checked By		Approved By		Authorized By	
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Designation	Drugs Inspector	Designation	DDC(I)	Designation	DDC(I)	Designation	DCG(I)
Sign		Sign		Sign		Sign	
Date	03/04/2013	Date	05/04/2013	Date	09/04/2013	Date	10/04/2013

- Manufacturer name and address
- Product-related information
  - Human / Veterinary / IMP / API / export only
  - Products / dosage forms / buildings / lines affected
- Non-compliance issues
  - EU GMP non-compliances
  - Exporting country GMP non-compliances

5.5 In case a "Written Confirmation" is suspended or cancelled, after successful compliance of Non Compliances observed during inspection by the firm the "Written Confirmation" shall be re issued and same shall be informed to EU.

5.6 EU shall be informed by e-mail at qdefect@ema.europa.eu or by mail at the following address"Commission europeénne/EuropeseCommissie, Helath and Consumers Directorate-General, 1049 Bruxelles/Brussel, BELGIQUE/BELGIË".

6.0 Annexure

NIL

7.0 References

Doc. No.	Title
1	GMP requirements as per Directives No. 2001/83/EC latest amended vide Directive 2011/62/EU

8.0 Abbreviation

Acronym	Full Form
DCGI	Drugs Controller General, India
QA	Quality Assurance

	TITLE		SOP No.	EP-INS-006
	Procedure for forwarding of Non Compliances to EU		Effective Date	10/04/2013
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Division Name			Revision No.	00
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Date	03/04/2013	Date	05/04/2013	Date	09/04/2013	Date	10/04/2013

ADC (I)	Assistant Drug Controller, India
DI	Drug Inspector
DDC (I)	Deputy Drug Controller,India
SOP	Standard Operating Procedure
EU	European Union
INS	Inspection
EC	European Council
IMP	Innovative Pharmaceutical Molecule
API	Active Pharmaceutical Ingredient

9.0 Revision History

Revision No.	Reason(s) for Revision
00	Implementation of New Format

GMP CHECKLIST

(Based on WHO Good Manufacturing Practices (GMP) for active pharmaceutical ingredients stated as per Annex 2- WHO Technical report Series(TRS), No. 957, 2010; Good Manufacturing Practice guide for Active Pharmaceutical Ingredients ICH Harmonised Triplicate Guideline stated as per ICH Q9; and GMP requirements as per Directives No. 2001/83/EC latest amended vide Directive 2011/62/EU)

1	***Location and surroundings:***	**Self appraisal to be filled by the manufacturer along with all details (yes or no type reply will not be acceptable)**	**Observations to be noted by the inspecting team at the time of inspection**	**Remarks**
1.1	How factory building is situated and controlled to avoid risk of contamination from external environment including open sewage, drain, public lavatory or any other factory which produces disagreeable or obnoxious, odors, fumes, excessive soot, dust, and smoke, chemical or biological emissions. *Pls specify industries / establishments adjoining manufacturing site.*			
2	**Building and premises: -**			
2.1	How the building has been designed constructed and maintained to suit the manufacturing operations so as to produce drugs under hygienic conditions. *Pls specify nature of construction used in the facility in respect of its maintenance and hygienic conditions.*			
2.2	Whether the building confirm to the conditions laid down in the Factories Act, 1948 *Pls attach valid factory certificate/ license issued by the competent authority.*			
2.3	Specify how the premises used for manufacturing operations and testing purpose prevents contaminations and cross contamination is: a) Compatible with other drug manufacturing operations that may be carried out in the same or adjacent area. Pls specify any special criteria for			

	the product manufacturered. e.g. temperature, humidity, air class requirements maintained for aseptic products, etc.			
2.4	b) Whether adequate working space is provided to allow orderly and logical placement of equipment, materials and movement of personnel so as to avoid risk of mix-up between different categories of drugs and to avoid possibility of the contamination by suitable mechanism. Pls specify space left around the machines. Pls attach equipment lay out, men and material movement, waste movement if applicable.			
2.5	c) Describe the pest, insects, birds and rodents control system followed in the premises. Attach copy of pest / rodent control schedule along with contract agreement if any.			
2.6	d) What measures have been taken to make Interior surface of (walls, floors, and ceilings) smooth and free from cracks, and to permit easy cleaning *Specify material of construction and finish for walls, ceiling, floor, coving etc. i.e. whether Epoxy or PU coated, kota / granite stone with epoxy sealed joints, solid / GI / gypsum / cal. Silicate board ceiling with epoxy, PU or any other pre-fabricated panel (GRP, powder coated SS or Aluminum etc.) paint.*			
2.7	e) What measures have been taken so that the production and dispensing areas are well lighted and effectively ventilated, with air control facilities. Pls specify the lux level maintained in various parts of the premise.			
2.8	Pls specify the air handling system used in various areas like stores, production, packing, QC areas etc.			

2.9	f) Specify drainage system which prevents back flow and entry of insects and rodents into the premises. Drains should be of adequate size and should be provided with an air break or a suitable device to prevent back-siphonage *(pls specify number and location of drains installed)*			
2.10	Containment area: Any production activities (including weighing, milling or packaging) of highly toxic non-pharmaceutical materials such as herbicides and pesticides should not be conducted using the buildings and/or equipment being used for the production of APIs. Handling and storage of these highly toxic non-pharmaceutical materials should be separate from APIs.			
3	**Water system: -**			
3.1	Whether the unit has validated system for treatment of water drawn from own or any other source to render it potable in accordance with standards specified by BIS or local municipal norms. Pls specify source of raw water and give details of treatment processes, sampling points, distribution and storage system for raw and purified water.			
3.2	How bio burden in purified water controlled / reduced.			
3.3	How water tank are cleaned periodically and records maintained thereof. How water distribution system is sanitized to control microbial contaminations.			
4	**Disposal of waste: -**			
4.1	Specify the system of disposal of sewage, and effluents (solid, liquid, and gas) from the manufacturing site. (Enclosed the copy of NOC obtained from State Pollution Control Board in this regard).			

4.2	Whether provision for disposal of bio-medical waste made as per the provisions of the Bio Medical Waste (Management and Handling) Rules 1996.			
5	***Warehousing Area: -***			
5.1	Whether adequate areas have been allocated for warehousing of Raw Materials, intermediates, Packaging Material, products in quarantine, finish products, rejected or returned products. How these areas marked or segregated. Please specify the total area provided for warehousing.			
5.2	How the warehousing areas being maintained to have good storage conditions. Are they clean and dry and maintained within acceptable temperature limits?			
5.3	Specify the storage arrangement provided for materials which sensitive to temperature, humidity and light and how the parameters are monitored. Is cold room or deep freezers required for storage of goods? If yes, how the temperature is monitored.			
5.4	Whether proper racks, bins and platforms have been provided for the storage.			
5.5	Whether receiving and dispatch bays are maintained to protect in coming and out going materials.			
5.6	How incoming materials are treated and cleaned before entry into the plant. Please specify the cleaning system for the outer surface of the container.			
5.7	How quarantined materials are segregated from other materials. How access to quarantined area is restricted.			
5.8	Whether separate sampling area for active Raw Materials and Excipients is provided and maintained. If yes, what is the control on entry of material and men into the sampling area. Whether reverse LAF have			

	been provided for sampling. Whether log book for sampling booth maintained. If not what provision has been made for sampling so as to prevent contamination, cross contamination and mix-ups at a time of sampling.			
5.9	Specify the arrangements provided to sample the primary packaging materials foils, bottles, etc which are used as such.			
5.10	Pls specify sampling plan used. Which type of sampling tools are used and how they are cleaned, dried and maintained.			
5.11	How containers are cleaned before and after sampling. Who carries out the sampling? (Pls specify whether the sampling is carried out as per the current SOP).			
5.12	What precautions are taken during sampling of photosensitive, hygroscopic materials?			
5.13	What provisions have been made for segregated storage of rejected, recalled or returned materials or products. How is the access to these areas restricted.			
5.14	How highly hazardous, poisonous and explosive materials, narcotics, and psychotropic drugs are handled and stored. How these areas are safe and secure. Is there certification from competent authority for handling of explosives etc. If any. Pls attach the certificate issued by the competent authority.			
5.15	How printed secondary packaging materials are stored in safe, separate and secure manner.			
5.16	Specify the arrangement provided for dispensing of starting materials. What is the control on entry of material and men into the dispensing area? Whether reverse LAF have been provided for dispensing with back ground clean air supply. Whether pressure differential is maintained between the dispensing and adjacent areas.			

5.17	Which type of dispensing tools are used and how they are cleaned, dried and maintained. How containers are cleaned before and after dispensing. Who carries out the dispensing? (Pls specify whether the dispensing is carried out as per the current SOP).			
5.18	How and where sampling of sterile materials carried out.			
5.19	What steps are taken against spillage, breakage and leakage of containers?			
5.20	What provisions have been made to prevent the entry of rodents, insects, birds. Which substance is used for pest control and how it is handled. (Pls specify whether the pest control is carried out as per the SOP).			
5.21	Whether record of master labels is maintained for comparision to issued labels?			
6	***Production Area: -***			
6.1	Please specify the design of the manufacturing area which allow uni-flow and logical sequence of operations so as to prevent product contamination/ mix ups. Is there any criss cross of flow of materials and men. Specify the position of IPQC lab in the manufacturing area . Please specify whether non storage areas used for storage of any material.			
6.2	Whether separate dedicated and self-contained facilities have been provided for the production of sensitive pharmaceutical product like Penicillin, Biological preparation with like micro-organism, Beta lactam, Sex Hormones and Cytotoxic substances. If yes pls explain how and attach copy of plan of premises of each category of drug.			

6.3	Please specify the provisions of storage of dirty, washed and cleaned equipment parts, tool room, in process storage areas etc. Which provide sequential / logical manner so as to prevent contamination and cross contamination?			
6.4	Please specify how service lines like pipe work, electrical fittings, ventilation openings etc. are identified by colors for nature of supply and direction of the flow. Whether service lines in production areas are through service pendants. If not, how they are placed so as to avoid accumulation of dust.			
7	***Ancillary areas: -***			
7.1	Please specify the position of rest and refreshment rooms and mention whether they are separate and not leading directly to the manufacturing and warehouse areas.			
7.2	Are there general change rooms in plant? Are toilets, change room separate from mfg. Area? Pls specify number of washing station & toilets provided for number of users. Whether change facilities separated for both sexes. How many sets of protective garments provided for each personnel entering production area. Is there in house general laundry for garment washing / cleaning? If not how garments washing are carried out and monitored			
7.3	Whether maintenance workshop is separate and away from production.			
7.4	Whether animals for production or testing are housed in the facility if so whether areas housing animals are isolated from other areas. Please specify the provision of air conditioned and ventilation system for the animal house. How quarantined, under test and tested animals housed and controlled. How animal carcass are disposed of. Pls attach copy of CPCSEA.			

8	**Quality Control Area: -**			
8.1	Whether QC area is independent of production area. Whether QC carries out its own: □ physico-chemical testing, □ biological testing, □ microbiological testing & sterility testing and □ Instrumental testing. Whether firm is outsourcing testing. If yes names of the testing laboratories contacted or approved. Pls give list of test currently outsourced. In case of contractual testing what are the responsibilities of contract giver and contract acceptor. (Copy of the contract should be enclosed) Are there safety installation such as shower, eye washer, fire extinguisher etc in the laboratory. Is there separate area for humidity chambers for stability studies. How many humidity chambers have been provided. Pls attach stability calendar.			
8.2	Please specify the arrangement provided for handling and storage of test samples, retained samples, reference standards / cultures, reagents. Whether retained samples are stored for a period of 1 year after expiry or 3 years after distribution whichever is earlier? Whether separate area for storage of reagents and glassware provided. Whether separate records room is provided.			
8.3	How hazardous or poisonous materials are stored and handled.			
8.4	How environmental conditions are met during the course of storage and testing of samples.			
8.5	Which grade of glassware are used in assay procedures.			
8.6	Whether separate AHU's are provided for biological, microbiological and radio iso-topes testing areas with HEPA filter arrangement.			

8.7	Whether separate areas provided for sterility testing within microbiology lab. Whether support areas are under AHU. Whether double door autoclave provided for sterilization of materials.			
8.8	Whether entry to the sterility area is through three air lock systems. What is the air class of these testing areas and whether pressure difference is maintained in these areas?			
8.9	Which types of workbenches are provided in these areas for testing? When was the last filter integrity tests performed on HEPA filters			
8.10	How waste (cultures etc) disposed of. Whether in case of antibiotic potency testing, statistical proof of the determination of potency and validity of the test carried out.			
9	***Personnel: -***			
9.1	Whether the manufacturing and testing of drugs is conducted under approved technical staff Names of Technical Staff alongwith qualification & experience For Manufacturing: - For Analysis:			
9.2	Please specify whether head of Q.C. is independent of manufacturing unit			
9.3	Name, qualification and experience of the personnel responsible for Quality Assurance function.			
9.4	Whether responsibilities for production and QC laid down and followed.			
9.5	Whether adequate number of personnel employed in direct proportion to the work load.			
9.6	What is the firm‟s policy on training of personnel at various levels?			
9.7	How is Periodic assessment of the training checked?			
10	***Health, clothing and sanitation of workers: -***			

10.1	Whether personnel handling Beta lactam antibiotics are tested for penicillin sensitivity before employment.			
10.2	Whether personnel involved in handling of sex hormones, cytotoxic and other portent drugs are periodically examined for adverse effect. (Pls specify whether the current SOP is followed or not).			
10.3	Whether all personnel prior to employment have undergone medical examination including eye examination and all free from Tuberculosis, skin and other communicable or contagious diseases			
10.4	Whether there is a SOP for medical examination.			
10.5	Pls give name and qualification of contracted medical officer for medical examination.			
10.6	Whether investigational reports, films of X rays etc. preserved. Whether records of such medical examination are maintained thereof			
10.7	Whether all personnel are trained to ensure high level of personal hygiene. Pls attach training calendar of last two years.			
10.8	Whether proper uniforms and adequate facilities for personal cleanliness are provided. Pls specify nature and type of dress used by the personnel in various areas of operation. How many dress/footwear have been provided to each personnel. Please specify whether cross over bench is in place in the change room and if so whether it rule out the possibility of entering dust particle to the clean side. Whether arrangements provided for cleaning of outside dust and dirt from foot Please specify whether hands are disinfected before entering the production area Whether for sterile garments in			

	house clean laundry has been provided.			
11	***Manufacturing Operations and Controls: -***			
11.1	Whether the contents of all vessels and containers used in manufacture and storage is conspicuously labeled with the name of the products. Batch no, Batch Size, and stage of manufacture along with signature of technical staff.			
11.2	Whether the products not prepared under aseptic conditions are free from pathogens like Salmonella, Escherichia coli, Pyocyanea etc.			
11.3	If yes, pls give brief account of measures taken to assure freedom from pathogens.			
11.4	*Precautions against mix-up and cross-contamination: -*			
11.4.1	Whether proper AHU, pressure differential, segregation, status labeling have been provided to prevent mix-up and cross-contamination in manufacturing area			
11.4.2	Pls specify the areas of dust generation and mechanism involved in controlling the dust.			
11.4.3	Do all the areas have their own independent air locks separately for men and material entry.			
11.4.4	What criteria of pressure differential have been set for production v/s adjoining areas.			
11.4.5	Whether various operations are carried out in segregated areas.			
11.4.6	Whether processing of sensitive drugs like Beta lactum Antibiotics and Sex Hormones is done in segregated areas with independent AHU and proper pressure differentials alongwith demonstration of effective segregation of these areas with records.			
11.4.7	Please specify what measures has been taken to prevent contamination of products with Beta Lactum Antibiotics, Sex harmons and cyto toxic substances			

11.4.8	What measures has been taken to prevent mix-ups during various stages of production.			
11.4.9	Whether equipments use for production are labeled with their current status.			
11.4.10	What is the policy for the use of Recovery material?			
11.4.11	Whether packaging lines are independent and adequately segregated.			
11.4.12	How line clearance is performed. Whether records of line clearance is maintained according to appropriate checklist			
11.4.13	Whether separate coding area has been provided or online coding is performed How coding procedure is controlled.			
11.4.14	Please specify how temperature, humidity and air filtration are controlled in the areas where raw material and/or products are exposed and handled.			
11.4.15	How access of authorized persons to manufacturing areas including packaging is controlled.			
11.4.16	Whether separate gowning provision is follows before entering into the procedure.			
11.4.17	Whether segregated secured areas for recall or rejected materials or for such material which are to be processed or recovered are provided. Please specify the room No. of such areas in the plant.			
11.5	***Sanitation in the Manufacturing areas:-***			
11.5.1	Specify the cleaning procedure of the manufacturing areas. Whether cleaning procedure is validated. Please specify validation protocol No. of the same.			
11.5.2	Whether the manufacturing areas are used as the general thoroughfare and storage of materials not under process.			

11.5.3	Whether a routine sanitation program is in place. Please specify detailed account of sanitation proramme specific to various areas, equipment.			
11.5.3	Dose the location facilitate cleaning of equipment as well as the cleaning of the areas in which they are installed.			
11.5.4	Whether production area is adequately lit. If yes. Please give lux levels provided in production, visual inspect			
12	***Raw Materials: -***			
12.1	Whether the hard copies of records of Raw Materials are maintained.			
12.2	Please specify the procedures followed receiving and processing of in-coming materials (Starting materials and packing material).			
12.3	Whether first in / first out or first expiry principal has been adopted.			
12.4	How they are labeled and stored as per their status – Under Test, Approved and Rejected			
12.5	Whether incoming materials are purchased from approved sources.			
12.6	What is the procedure for approving the source for incoming materials.			
12.7	Whether the raw materials are directly purchased from the manufacturers.			
12.8	Whether list of approved vendors is available to the user.			
12.9	How damaged containers are identified recorded and segregated.			
12.10	How damaged containers are identified recorded and segregated.			
12.11	Whether all the containers of each batch of starting materials is sampled for identification test.			
12.12	Whether labels of raw material in the storage area have information like (a) designated name of the product and the internal code reference, where applicable, and analytical reference number; (b) manufacturer‘s name, address and batch number; (c) the status of the contents (e.g.			

	quarantine, under test, released, approved, rejected); and (d) the manufacturing date, expiry date and re-test date.			
12.13	Whether separate areas are provided for under test, approved and rejected materials.			
12.14	How control on temperature and humidity conditions, wherever necessary, maintained in these storage areas.			
12.15	How the containers from which samples have been drawn labeled.			
12.16	Please specify the procedures by which it is ensured that the raw materials which has been released by the Quality Control Department and which are within their shelf life are going to be used in the product.			
12.17	How materials are stacked in the Stores i.e on Pallets, racks etc.			
13	***Equipment: -***			
13.1	Whether the equipments are designed aiming to minimize risk of error and permit effective cleaning in order to avoid cross contamination, build up of dust			
13.2	Whether all equipment are provided with log book.			
13.3	Please specify the procedures to clean the equipment after each batch production.			
13.4	Whether validity period for use after the cleaning of equipment is specified.			
13.5	Whether separate area is provided for storage of machine parts etc.			
13.6	Whether balances and other measuring equipments with appropriate range are available in the Raw Material stores & production areas and they are calibrated in accordance with SOP maintained. Specify the calibration schedule of the balances.			

13.7	Please specify material of construction of contact parts of the production equipments.			
13.8	Which types of lubricants are used in the equipment. Specify the quality and control reference No. of these lubricants.			
13.9	Specify the procedures to remove defective equipments from production areas.			
14	***Documentation and Records: -***			
14.1	How the documents are designed, prepared, reviewed and controlled to provide an audit trail. Whether documents are approved signed and dated by appropriate and authorized person. Whether documents are approved signed and dated by appropriate and authorized person. Whether documents specify title, nature and purpose. Whether documents are regularly reviewed and kept up to date. If yes. Please specify review period. Please attached the list of documents maintained by the firm			
14.2	Whether the records are made at the time of each operation in such a way that all significant activities concerning to the production are traceable.			
14.3	Whether data is recorded by electronic data processing system or by other means. If by electronic data processing system then how access is controlled to enter, modify etc. the data.			
14.4	Whether master formula and detailed operating procedures are maintained as hard copy.			
14.5	Who is responsible for maintenance of these records.			
15	***Labels and Other Printed Materials:***			
15.1	Whether the printing is in bright colour and legible on labels and other printed materials.			
15.2	How printed labels (art work) are approved. Is there any SOP for this if yes please give current SOP No.			

15.3	Which colour coding system is used to indicate the status of a product and equipment.			
15.4	How printed packaging materials, product leaflets etc. are stored separately to avoid chances of mix-up.			
15.5	How labels cartons boxes circulars inserts and leaflets are controlled.			
15.6	Whether the samples from the bulk are drawn tested, approved and released prior to packaging and labeling. How carryout the sampling			
15.7	How records of receipt of all labeling and packaging materials are maintained.			
15.8	Whether re-conciliation of used packaging materials is maintained. Whether unused packaging materials return to the store or destroyed.			
15.9	How returned/unused packaging material like foils is controlled so as to prevent contamination and cross-contamination.			
15.10	How the labels of reference standard and culture maintained.			
16	***Quality Assurance: -***			
16.1	Specify the comprehensive quality assurance system maintained by the firm *Inter-alia* to cover deviation, reporting, investigation and change control. How the products are designed and developed in accordance with GMP.			
16.2	Please specify the arrangements provided to ensure that correct starting and packaging materials are used for manufacture.			
16.3	Please specify the mechanism by which all control like IP QC Calibration, Validation etc. are ensured.			
16.4	Please specify the mechanisms to ensure that the finished product has been correctly processed and checked in accordance with the established procedures.			
16.5	Please specify the mechanisms to ensure that Pharmaceuticals products are released for sale by authorization person.			

17	***Self Inspection and Quality Audit: -***			
17.1	Whether the firm has constituted a self inspection team supplemented with a quality audit procedure to evaluate that GMP is being followed. If no. How internal audits are carried out.			
17.2	What is the system of monitoring, evaluation of self inspection.			
17.3	How conclusion and recommended correcting actions are followed and adopted.			
17.4	What is the frequency of self-inspection.			
17.5	Is there any proforma for carrying out the self-inspection. Please indicate the date of last self-inspection.			
18	***Quality Control System: -***			
18.1	Please specify the details of quality control system of the unit.			
18.2	How the reference standards are stored, evaluated and maintained. Please provide list of reference standard and reference impurities procured from the authentic sources.			
18.3	Please specify the procedures of preparation of working standard from the reference standards.			
18.4	Whether SOPs for sampling, inspecting, testing of Raw Materials, Finish products, Packing Materials and for monitoring environmental conditions are available.			
18.5	Whether approved specifications for different materials, products, reagents, solvents including test of identity content, purity and quality available.			
18.6	How reference samples from each batch of the products are maintained.			
18.7	Who releases batch of the products for sale			
18.8	Whether there is check list for release of a batch. Please specify current SOP No. for batch release.			
18.9	Please specify the sampling procedures from various stages of production.			
18.10	How it is ensured that the sample collected are representative of the whole batch.			

18.11	Please specify the procedures for carrying out the stability studies.			
18.12	Under what condition stability studies of the products are tested. How many stability chambers have been provided.			
18.13	How self life is assigned to a product. Please give current stability protocol No.			
18.14	Whether records of stability studies are maintained.			
18.15	Please attach stability calendar of last year.			
18.16	How complaints are investigated.			
18.17	How instruments are calibrated and at which interval.			
18.18	How testing procedure validated before they are adopted for routine testing.			
18.19	Specify the validation procedure is responsible for validation of procedures.			
18.20	How validation procedures are documented (Please indicate various protocols/ recoding system applied during validation).			
18.21	Whether specifications for raw materials intermediates final products and packaging materials are available.			
18.22	Whether periodic revision of these specifications are carried out. Please specify No. of STPs being maintained by the firm.			
18.23	Which pharmacopoeias in original are available in the plant.			
19	***Specifications: -***			
19.1	Whether specification of raw material include. (a) the designated name and internal code reference; (b) reference, if any, to a pharmacopoeial monograph; (c) qualitative and quantitative requirements with acceptance limits; (d) name and address of manufacturer or supplier and original manufacturer of the material; (e) specimen of printed material; (f) directions for sampling and testing or reference to procedures;			

	(g) storage conditions; and (h) Maximum period of storage before re-testing. Whether specification of finished product include (a) the designated name of the product and the code reference; (b) the formula or a reference to the formula and the pharmacopoeial reference; (c) directions for sampling and testing or a reference to procedures; (d) a description of the dosage form and package details; (e) the qualitative and quantitative requirements, with the acceptance limits for release; (f) the storage conditions and precautions, where applicable, and (g) the shelf-life.			
19.2	Whether the container and closures meet the pharmacopial specifications. Whether second hand or used containers and closures used.			
20	**Master Formula Records: -**			
20.1	How master formula records are prepared, authorized and controlled.			
20.2	Whether head of production, quality control and quality assurance unit endorse this documents. Whether master formula is batch size specific.			
20.3	Whether all products have master formula containing. (a) the name of the product together with product reference code relating to its specifications; (b) the patent or proprietary name of the product along with the generic name, a description of the dosage form, strength, composition of the product and batch size; (c) name, quantity, and reference number of all the starting materials to be used. Mention shall be made of any substance that may „disappear" in the course of processing. (d) a statement of the expected final yield with the acceptable limits, and of relevant intermediate yields, where applicable. (e) a statement of the processing			

	location and the principal equipment to be used. (f) the methods, or reference to the methods, to be used for preparing the critical equipments including cleaning, assembling, calibrating, sterilizing; (g) detailed stepwise processing instructions and the time taken for each step; (h) the instructions for in-process control with their limits; (i) the requirements for storage conditions of the products, including the container, labeling and special storage conditions where applicable; (j) any special precautions to be observed; (k) packing details and specimen labels.			
21	**Packaging Records: -**			
21.1	Whether authorized packaging instructions for each products, pack size and type are maintained and complied with. Whether following are included in the packaging instructions. (a) Name of the product; (b) the pack size expressed in terms of the weight or volume of the product in the final container; (d) complete list of all the packaging materials required for a standard batch size, including quantities, sizes and types with the code or reference number relating to the specifications of each packaging material.; (e) reproduction of the relevant printed packaging materials and specimens indicating where batch number and expiry date of the product have been applied; (f) special precautions to be observed, including a careful examination of the area and equipment in order to ascertain the line clearance before the operations begin. (g) description of the packaging operation, including any significant subsidiary operations and equipment to be used;			

	(h) details of in-process controls with instructions for sampling and acceptance; and (i) Re-conciliation after completion of the packing and labeling operation. (j) Whether line clearance records are part of batch packing records.			
22	***Batch Processing Records*** **(BPR)**			
22.1	Whether BPR are based on current master formula record.			
22.2	How BPR are designed to avoid transcription errors. Whether the Batch Processing Records for each product on the basis of currently approved master formula is being maintained. Whether following information are recorded in BPR (a) the name of the product, (b) the number of the batch being manufactured, (c) dates and time of commencement, significant intermediate stages and completion of production. (d) initials of the operator of different significant steps of production and where appropriate, of the person who checked each of these operations, (e) the batch number and/or analytical control number as well as the quantities of each starting material actually weighed, (f) any relevant processing operation or event and major equipment used, (g) a record of the in-process controls and the initials of the person(s) carrying them out,and the results obtained, (h) the amount of product obtained after different and critical stages of manufacture (yield), (i) comments or explanations for significant deviations from the expected yield limits shall be given, (j) notes on special problems including details, with signed authorization, for any deviation from the Master Formula, (k) Addition of any recovered or			

	reprocessed material with reference to recovery or reprocessing stages. Specify the procedures for all the entries made in BPR‟s. (l) Procedure for reprocessing and policy of the firm for adding of recovery.			
23	**Standard Operating Procedure and Records: -**			
	Whether SOPs and records are being maintained and complied for the following. SOP for receipt of in coming material (a) SOP for Internal labelling, quarantine, storage, packaging material and other materials (b) SOP for each instrument and Equipment (c) SOP for sampling (d) SOP for batch numbering (e) SOP for testing (f) SOP for equipment assembly and validation (g) SOP for Analytical apparatus and calibration (h) SOP for maintenance, cleaning and sanitation (i) SOP for training and hygiene for the personal (j) SOP for retaining reference Samples (k) SOP for handling, re-processing and recoveries (l) SOP for distribution of the product (m) SOP for warehousing of products. Whether applicable SOPs are available in each area where they are required. Whether recording formats are referred in SOP. Is there SOP for writing an SOP.			
24	**Reference Samples**			
24.1	Specify the procedures for collection of reference samples of active ingredients and finished formulations and how they are stored and maintained.			
25	**Reprocessing and Recoveries**			
25.1	Is appropriate Validation of recoveries and reprocessing done is			

	being performed?			
26	**Distribution records**			
26.1	Whether pre dispatch inspections are carried out before release.			
26.2	Whether periodic audits of distribution center are carried out to access warehousing practices			
26.3	Whether distribution records are part of the batch record. If not how batch wise distribution record up to retail levels are maintained.			
26.4	Whether instruction for warehousing and stocking of products like LVPs, Heat sensitive etc are available in store.			
26.5	Whether Good Distribution Practices followed			
27	**Validation and Process Validation: -**			
27.1	Specify the validation policy of the company. Whether validation master plan has been prepared.			
27.2	Whether validation studies of processing, testing and cleaning procedures are conducted as per pre defined protocol.			
27.3	How records and conclusion of such validation studies are prepared and maintained.			
27.4	Whether master formula is based on approved process validation.			
27.5	Specify how significant changes to the manufacturing process equipments material etc are controlled.			
27.6	Whether DQ,IQ,OQ & PQ are in place for all major equipment and facility.			
27.7	Whether validation records of all utilities and major equipments are available.			
28	***Product Recalls: -***			
28.1	Specify the product recall system followed by the firm. How promptly recall operation at the level of each distribution channel up-to the retail level can be carried out. Whether there is a SOP for recall of products clearly defining responsibility, procedure, reporting,			

	re-conciliation etc.			
29	***Complaints and Adverse Reactions:***			
29.1	Specify the review system for complaints concerning the quality of products.			
29.2	How records of complaint maintained.			
29.3	Whether reports of serious complaints with comments and documents immediately sent to Licensing Authority			
29.4	Is there any criteria for action to be taken on the basis of nature of complaint.			
30	***Site Master file: -***			
30.1	Whether all the relevant information have been included in the site master file.			
30.2	Whether quality policy has been included in the site master file. Please attach the current version			
30.3	Is there a master plan (Master validation plan) covering:			
30.4	Resources and those responsible for its implementation.			
30.5	Identification of the systems and processes to be validated			
30.6	Documentation and standard operating procedures (SOPs), Work Instructions and Standards (applicable national and international standards)			
30.7	Validation list: facilities, processes (e.g. aseptic filling), products			
30.8	Key approval criteria			
30.9	Protocol format			
30.10	Each validation activity, including re-validation and reasonable unforeseen events (power failures, system crash and recovery, filter integrity failurer. Please attach validation calendar.			
30.11	Pls specify whether the critical processes validated Prospectively, retrospectively or concurrently.			
30.12	Whether validation of following performed and documented: Analytical methods, Production and assay equipment, Sterile production processes, Non-sterile production processes, Cleaning procedures, Critical support systems (purified			

	water, water for injections, air, vapor, etc.), Facilities			
30.13	Please list reasons considered important for validation or re-validation.			
30.14	In case electronic data processing systems are used, are these validated? Please specify whether periodical challenge tests performed on the system to verify reliability.			
30.15	Are the validation studies performed according to pre-defined protocols? Is a written report summarized, results and conclusions prepared and maintained? Is the validity of the critical processes and procedures established based on a validation study?			
30.16	Are criteria established to assess the changes originating a revalidation? Are trend analyses performed to assess the need to re-validate in order to assure the processes and procedures continue to obtain the desired results?			
31	**WATER SYSTEM PURIFIED WATER WATER FOR INJECTIONS**			
31.1	Please specify whether waster system qualification (IQ, OQ and PQ) has been carried out as per protocol and repots have been prepared and maintained.			
31.2	Whether IQ protocol include at least facility review, equipment specification vs. design, welding roughness testing on pipelines, absence of dead points / section in the pipelines, pipe and tank passivation, drawings, SOP for operations, cleaning, sanitation, maintenance and calibration of gadgets. Whether its report includes Conclusion / Summary, description of the performed assay, Data tables, Results, Conclusions, Protocol reference, Revision and approval signatures.			
31.3	Whether OQ protocol include at least System production capacity (L/min), Flow type and water rate, Valve operation, Alarm system			

	operation and Controls operation?			
31.4	Whether its report includes Conclusion / Summary, description of the performed assay, Data tables, Results, Conclusions, Protocol reference, Revision and approval signatures.			
31.5	Please specify the water whether Phase 1, Phase 2 and Phase 3 studies carried out in at PQ stages?			
31.5.1	Phase 1 : Whether the operations parameters, cleaning and sanitation procedures & frequencies defined. Whether daily sampling records for every pretreatment point and usage point for a period of 2 to 4 weeks maintained and SOP‘s prepared.			
31.5.2	PHASE 2 : Whether daily sampling records for every pretreatment point and usage point for a period of 4 to 5 weeks after Phase 1 maintained and reviewed.			
31.5.3	PHASE 3 : Whether weekly sampling records available of every usage point for a one-year period. In the case of water for injections systems, are the daily sampling records of at least one usage point available, with all the usage points sampled weekly? Whether results of these records summarized to show suitability. Are there personnel training records?			
32	**EQUIPMENT**			
32.1	Are the equipment installation Qualification (IQ) protocols contains followings: Introduction, Installation description, Responsibilities, Performed tests/assays, Qualification acceptance criteria and Data recording and reporting?			
32.2	Whether report contains Summary, Description of performed tests/assays, Obtained data tables, Results, Conclusions, Installation diagrams, Revision and approval signatures.			
32.3	Whether the equipment operation qualification (OQ) protocols contains following: Introduction, Equipment description, Description of the equipment operation steps			

	(SOP‘s), Responsibilities, Qualification acceptance criteria, Data recording and reporting. Whether report contains Summary, Description of performed tests/assays, Obtained data tables, Results, Conclusions, Revision and approval signatures.			
32.4	Whether equipment performance qualification (PQ) protocols contains followings: Introduction, Responsibilities, Performed assays, Qualification acceptance criteria, Data recording and reporting.			
32.5	Whether report contains Summary, Description of performed tests/assays, Obtained data tables, Results, Conclusions, Revision and approval signatures.			
32.6	Whether Preventive Maintenance Schedule of the equipments is followed and records available?			
33	**Analytical Method Validation**			
33.1	Please specify whether following Characteristics are considered during validation of analytical methods: — specificity — linearity — range — accuracy — precision — detection limit — quantitation limit — Robustness.			
33.2	Whether Paharmocopial methods are also validated. If yes, how.			
33.3	Whether system suitable testing is included in testing protocols e.g. HPLC, GC etc.			
33.4	Whether the procedure covers all aspects of impurity profiling required			
33.5	Whether procedure covers all aspects of Organic Volatile Impurities detection and quantification			
34	**CLEANING**			
34.1	Is a validation performed to confirm cleaning effectiveness?			
34.2	Does the protocol define the selection criteria for products or			

	groups of products subject to cleaning validation?			
34.3	Is data produced supporting the conclusion that residues were removed to an acceptable level?			
34.4	Please specify whether the validation is implemented to verify cleaning of: Surfaces in contact with the product, After a change in product, Between shift batches.			
34.5	Please specify whether the Validation Strategy include contamination risks, equipment storage time, the need to store equipment dry and sterilize and free of pyrogens if necessary?			
34.6	Whether the cleaning Validation Protocol include: a. Interval between the end of production and the beginning of the cleaning SOP‘s. b. Cleaning SOP‘s to be used. c. Any monitoring equipment to be used. d. Number of consecutive cleaning cycles performed? e. Clearly defined sampling points.			
34.7	Whether Quality Control responsible of the sampling for cleaning verification?			
34.8	Whether personnel engaged in cleaning, sampling etc. trained.			
34.9	Please specify whether acceptance limits been set for cleaning verification and are based on following criteria: a. Visually clean. b. 10 ppm in another product c. 0.1% of the therapeutic dose?			
34.10	Please specify whether detergent residues investigated and degradation products verified during validation.			
34.11	Whether validation records include Recovery study data, Analytical methods including Detection Limits and Quantification Limits, Acceptance Criteria, Signatures of the Quality Assurance Manager, employee in charge of cleaning and the verification from Production and Quality Control.			

35	**Air Handling System**			
35.1	Please specify whether following parameters have been qualified: — temperature — relative humidity — supply air quantities for all diffusers — return air or exhaust air quantities — room air change rates — room pressures (pressure differentials) — room airflow patterns — unidirectional flow velocities — containment system velocities —filter penetration tests (HEPA) — room particle counts — room clean-up rates — microbiological air and surface counts where appropriate — operation of de-dusting — warning/alarm systems where applicable.			
35.2	Whether strategic tests like Particle count, air pressure differential, air flow volume, air flow velocity etc. included in Air Handling System qualification.			
36	**Media fill test**			
36.1	Whether medial fill tests carried out twice in a year during normal working conditions.			
36.2	Pls give date of last such test.			
36.3	How many units are filled and tested.			
36.4	What is the criterion for qualification of this test?			
36.5	In case of failure of media fill test, what precautions or actions are taken.			
37	**Product Information**			
37.1	Name of product			
37.2	Whether validated master formula is available?			
37.3	Whether specific SOP for product processing is available?			
37.4	Comments on the above SOP			
37.5	Process Validation performed for the product covers all aspects and the approach is Risk Based			
37.6	No. of Batches Produced			
37.7	Stability studies (i) Accelerated			

	(ii) Real Time (iii) Whether the expiry date assigned on the basis of stability study?			
37.8	Whether trend analysis was carried out and interpretation thereof?			
37.9	Whether Annual product review (APR) is carried out? Whether the following parameters considered in the Annual product review? 1 critical in-process control and critical API test results 2 all batches that failed to meet established specification(s) 3 all critical deviations or non-conformances and related investigations 4 any changes carried out to the processes or analytical methods 5 results of the stability monitoring programme 6 quality-related returns, complaints and recalls and adequacy of corrective actions			
37.10	Is there any complaint received for the product and If any, whether the investigation report along with ATR is maintained?			

F. No:7-5/2019/Misc/101
Government of India
Directorate General of Health Services
Central Drugs Standard Control Organization
(International Cell)

FDA Bhawan, Kotla Road,
New Delhi - 110002
Dated:- 4/3/2020

To
All Zonal /Sub Zonal offices of CDSCO

Circular

Subject: Disposal of the applications of "Written Confirmation" for active substances exported to the EU for medicinal Products for Human use in accordance with Article 46(2) (b) of Directives no. 2001/83/EC – Reg.

In order to streamline the process of issuance of Written Confirmation (WC) Certificate through a uniform procedure of inspection and review of documents, it has been decided to adopt following updated procedures by the inspectorate in CDSCO Zonal/Sub-Zonal offices with primary focus towards quality compliance for Active Pharmaceutical ingredients (API).

For issuance of WC for the purpose of grant/renewal or issuance of additional product:

A. - The applicant shall submit the application along with supporting document & details given in checklist (**Annexure A)** & Checklist for additional Product (**Annexure B)**, as per the guidance in the SOP no. EP-INS-001 (Procedure for issue of "Written Confirmation" for active substances exported to the EU for medicinal Products for Human use in accordance with Article 46(2) (b) of Directives no. 2001/83/EC)

Checklist (Annexure-A):

a) Application from Manufacture
b) Site master file (as specified under WHO TRS 961, Annexure 14)
c) An Authorization letter in original issued by the Director/Secretary/Partner of the firm
d) Copy of GMP certificate issued as Certificate of Pharmaceutical product issued as per WHO guidelines, USFDA, EDQM etc., if any
e) Copy of Manufacturing license.
f) List of Approved APIs .
g) List of APIs applied for issuance of WC.
h) List of SOPs and STPs

i) Stability studies of 3 batches for minimum 06 months for accelerated and real time studies along with stability protocol and commitment List of equipment and Instruments

j) List of Technical Staff, their Qualification, Experience and approval status& Organogram.

k) List of Equipment and Instruments

l) Manufacturing Layout Plan.

m) Validation Master Plan.

n) Process Validation for 3 batches of each Product.

o) Annual Product Review for last 3 years

p) Export data for last 3 years

q) Good Distribution Practices followed by the firm.

r) Analytical Method Validation

s) Market Complaint Review.

t) Data of impurity profiling.

u) NSQ reports, if any.

v) Legal undertaking

Checklist for additional Product:(Annexure-B)

a) Application from Manufacturer for additional product

b) An Authorization letter in original issued by the Director/Secretary/Partner of the firm

c) Name of the applied API

d) List of API approved

e) Stability studies of 3 batches for minimum 06 months for accelerated and real time studies along with stability protocol and commitment.

f) Process Validation for 3 batches of Product

g) Analytical Method Validation.

h) Annual product review for last 3 years.

i) Export data for last 3 years

j) Market Complaint Review.

k) Data of impurity profiling.

l) NSQ reports, if any.

B. Disposal of application: - From the date receipt of complete application submitted to CDSCO Zonal or Sub-zonal offices

i. Recommendation for issuance/further compliance /rejection of WC by the CDSCO Zonal or Sub-zonal office shall be forwarded to CDSCO(HQ) as per the following timeline:

a. When no inspection is required – 07 days of receipt of complete application

b. When inspection is required – 15 days of receipt of complete application

ii. Based on the recommendations of Zonal/Sub Zonal Heads, CDSCO (HQ) shall issue WC within 5 working days of the receipt of the recommendation.

C. First time Applicant for WC certificate:

No inspection is required, if firm is holding valid Certificate of Pharmaceutical Product issued as per WHO guidelines or US FDA or EDQM/TGA certificates (not more than 24 months old). If the company does not have any of these, then inspection to be conducted.

Inspection shall be planned by officers of Zonal or Sub-zonal as per SOP no. EP-INS-005 after review of documents submitted under Annexure A.

Inspection shall be carried out as per the guidelines laid down in SOPs and checklist in accordance with Article 46(2)(b) of Directives No. 2001/83/EC: GMP requirements as per Directives 2001/83/EC or WHO Good Manufacturing Practices (GMP) for Active Pharmaceutical Ingredients or Good Manufacturing Practice for Active Pharmaceutical Ingredients as per ICH guideline and report shall be prepared as per SOP no. EP-INS-004.

WC certificate shall be issued when the firm had made necessary compliance to the deficiencies observed during such inspection, (if any) as per procedures laid down in SOP no. EP-INS-005.

iii. Application for additional product to the WC Certificate:

For those firms which have been previously inspected within two years by officers of CDSCO zonal or sub-zonal and found to comply with requirements of Article 46(2)(b) of Directives No. 2001/83/EC: GMP requirements as per Directives 2001/83/EC or WHO Good Manufacturing Practices (GMP) for Active Pharmaceutical Ingredients or Good Manufacturing Practice for Active Pharmaceutical Ingredients as per ICH guideline, WC certificate shall be issued on providing the complete data of products as mentioned in **Annexure B**.

This circular/document is to be treated as dynamic for updation as per development in this area.

Your faithfully,

(Dr. V. G. Somani)
Drugs Controller General (India)

Copy for information to :

1. Stakeholders

CC: Joint Secretary (R), MoHFW, Govt. of India, Nirman Bhawan, New Delhi

F. No. 7-5/2013/DCGI/WC (EU)
CENTRAL DRUGS STANDARD CONTROL ORGANISATION
DIRECTORATE GENERAL OF HEALTH SERVICES
OFFICE OF DRUGS CONTROLLER GENERAL (INDIA)

FDA Bhawan, Kotla Road,
New Delhi-110002
Dated 22 OCT 2013

CIRCULAR

European Union has mandated through Directives No. 2001/83/EC dated 8th June, 2011 that every consignment of Active Pharmaceutical Ingredient (API) from non-EU/ non-listed countries must be supported by a "Written Confirmation" Certificate issued by the Competent Authority of that country, stating that the consignment conforms to standards of Good Manufacturing Practices (GMP) as laid down in the EU guidelines or equivalent thereof. This is effective from 2nd July, 2013.

This Directorate issues Written Confirmation Certificate on the basis of recommendation from the concerned CDSCO zonal office and the standards shall be applicable for issue of "Written Confirmation Certificate" for active substances exported to the EU for medicinal products for human use, in accordance with Article 46(2)(b) of Directives No. 2001/83/EC and the documents required should be as per: "Good Manufacturing Practices guide for Active Pharmaceutical Ingredients ICH Harmonized Triplicate Guideline stated as per ICH Q7".

This office has been receiving recommendation from CDSCO Zonal offices for the grant of Written Confirmation wherein long term stability data and accelerated stability data submitted by the firm is lesser than the period of 12 months and 6 months respectively. The matter has been examined in detail. While renewing our commitment to the spirit of the GMP and also keeping in regard the International Practices, it has been decided that applications containing 6 months accelerated and 6 months long term stability data on 3 batches and if no major changes from the specifications have been observed, issue of Written Confirmation Certificate to such API's would be considered subject to the following conditions:

1. The firm shall submit the Stability protocol along with the undertaking or a stability commitment, that an ongoing stability program is in place and they shall submit the data covering the retest period/shelf life of the API within 30 days on completion of the studies to the concerned Zonal Office.

2. The firm should assign retest/expiry date of the API based on available stability data or as per the procedure laid down in the ICH Guidelines. The firm shall provide a commitment regarding the retest period/ shelf life of the API.

In view of the above all the applicants seeking Written Confirmation Certificate with 6 month stability data should submit an undertaking as mentioned above along with their application.

(Dr. G. N. Singh)
Drugs Controller General (I)

To,

1. All Stake Holders
2. All Zonal and sub-Zonal Office, CDSCO.

Copy To:

1. US (Drugs)
2. Guard file.