File No. CDSCO/INS/PV/002/18-DCG(I)

Government of India

Directorate General of Health Service

Central Drugs Standard Control Organization

(Pharmacovigilance Division)

FDA Bhavan, Kotla Rd. New Delhi- 110002.

Date: 27-09-2018

NOTICE

Sub: -- Draft Pharmacovigilance System Inspection Guideline ; -reg.

All stake holders' attentions are hereby invited to the requirements specified in Schedule-Y of Drugs and Cosmetics Rules 1945, envisaging the GSR notification No. 287(E) dated 08th March 2016. This gazetted notification emphasises that all Market Authorization Holders (MAH) i.e the companies holding Licences to manufacture and / or import of "Drugs" for an ultimate motive of marketing medicinal products in India , shall have an established Pharmacovigilance System for collection, processing and reporting of Adverse Drugs reactions (ADR) to the concerned Licencing authorities.

Reference is also invited to Section 28.2 of Schedule-M which mandates that companies holding manufacturing licences are supposed to submit forthwith the reports of serious adverse drug reactions resulting from the use of their drug products along with comments and documents to the concerned licensing authority. Similarly, it is also mandatory in Schedule-D (II) section 2.18 that the Importers of "Drugs" shall submit the detailed PMS study Report for their marketed drug products at the time of renewal application submission.

Therefore this office is currently in the process of examining the current status of PV-systems in companies who are manufacturing and / or importing Drug Products including pharmaceuticals, Phyto-pharmaceuticals, Human Vaccine, Blood products, rDNA technology derived drugs, stem cell therapeutics in the Indian market. Accordingly a comprehensive PV-Guideline has been drafted which will be finalized after deliberations with the stakeholders of such products. Accordingly a meeting of the stake holders was organized on the 24th September 2018 at 2.30 PM in the Conference hall, 5th floor FSSAI, FDA Bhavan, Kotla Road, New Delhi-110002. The meeting was attended by the representatives of Indian Drugs and Pharmaceutical association Forum, Pharmacovigilance Programme of India (IPC), Indian Society for Clinical Research, AEFI secretariat and many pharmaceutical companies. The subject guideline was completely presented, discussed in details with all participants during the meeting.

Now, with the approval of the competent authority, the said guideline is being placed on the official website for public view and further consideration. The stake holders' valuable comments, suggestion are hereby requested for further improvement and finally rolling out a fully functional document. All such feed-back will be acceptable till 31st October, 2018. Contact us at the E-mail: dci@nic.in and pharma.covig@cdsco.nic.in

27/9/2018

(Somnath Basu)

Assistant Drugs Controller (I)

Central Drugs Standard ControlOrganization

Directorate General of Health Services

Ministry of Health and Family Welfare

Government of India

RISK BASED PROGRAMME FOR PHARMACO-VIGILANCE INSPECTIONS OF MARKET AUTHORISATION HOLDERS (MAHs) FOR HUMAN MEDICINAL PRODUCTS

Applies to	**Inspectorate staff deputed by CDSCO**
Summary of Scope	**This document provides harmonized standards on the planning, preparation, conduct and reporting of risk-based pharmacovigilance inspections of market authorization holder (MAHs) for medicinal products, approved for marketing in India.**
Keywords	**Planning, Preparation, Conduct, Reporting, Pharmacovigilance Inspection, PVOI, MAH, Licence, Import, Manufacture.**
Procedure No:	**CDSCO/INS/PV/001/2018**
Supersedes	
Prepared by	
Reviewed by	
Approved by	

ABBREVIATIONS & DEFINITIONS

ADR	Adverse Drugs Reaction
AE	Adverse event
AEFI	Adverse Events following Immunization
ASP	Active Surveillance Plan
CCDS	Company Core Data Sheet
CDSCO	Central Drugs Standard Control Organisation
DCA	Drugs & Cosmetics Act
DCG(I)	Drugs Controller General (India)
DCR	Drugs & Cosmetics Rules
DGHS	Directorate General of Health Services
DCC	Drugs Consultative Committee
DTAB	Drugs Technical Advisory Board
EC	Ethics Committee
EIP	Extended Immunization Programme
FDC	Fixed Dose Combination
ICMR	Indian Council of Medical Research
ICSR	Individual Case Safety Reports
ICMR	Indian Council for medical Research
IPC	Indian Pharmacopeia Commission
ITSU	Immunization Technical Support Unit
MAH	Marketing Authorisation Holder (Manufacturers/Importer)
MoH&FW	Ministry of Health & Family Welfare, Govt. of India
NACO	National AIDS Control Organization
NCC-PvPI	National Coordination Centre for Pharmacovigilance Programme of India
NHSRC	National Health Systems Resource Centre

NVBDCP	National Vector Born Disease Control Programme
NRA	National Regulatory Authority
PI	Package Inserts
PMS	Post Marketing Surveillance
PSUR	Periodic Safety Update Report
Pv	Pharmacovigilance
RNTCP	Revised National TB Control Programme
RMP	Risk Management Plan
SAE	Serious Adverse Events
SDLA	State Drugs Licensing Authority
SEC	Subject Expert Committee
SEC	Subject Expert Committee.
SUSAR	Serious Unexpected Suspected adverse reaction
UIP	Universal Immunization Programme

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Introduction

CDSCO, under DGHS of MoH&FW is the NRA for medicinal products, Cosmetics and Medical devices in India. This organization as nodal agency, discharges the regulatory functions to ensure safety, efficacy and quality of "Drugs" as defined under Section 3 (b) (i-iv) of Drugs & Cosmetics Act and Rules. CDSCO is headed by the DCG(I) as Licensing Authority defined under Rule 21 in respect of grant of permission for manufacture / import of "New drugs", which is also defined under Rule-122E of DCR.

A. As per **Schedule –Y of DCR,** Point no (3) for studies in special populations, **Para (4)** specifies **Post Marketing Surveillance**; as given below;

1. The applicant shall have a pharmacovigilance system in place for **collecting, processing and forwarding the report to the licensing authority** for information on ADR emerging from the use of the drugs manufactured or marketed by the applicant in the country, vide GSR Notification no. 287(E), dated 08.03.16 (effective:08-03-2016).
2. The system shall be managed by **qualified, trained personnel & the officer in- charge** for collection and processing of data shall be a **medical officer** or **a pharmacist** trained in collection and analysis of ADR reports, vide GSR Notification no. 287(E), dated 08.03.16 (effective:08-03-2016).

3. Subsequent to approval of the product, "N**ew drug" shall be closely monitored for its clinical safety** once it is marketed and the MAH shall have to submit **PSUR every 6 monthly for first 2 years and every year for the next two years.**

B. Also, under **Schedule M of DCR** according to section 28.2, every MAH (the Licencee for manufacture Drugs) shall report serious adverse drug reactions resulting from the use of a drug along with comments and documents to the concerned Licensing Authority (s).

C. Similarly, in Schedule-D (II) of DCR, an MAH (the Licencee for Import of Drugs), it is mandatory in section 2.18 that they should **submit the detailed PMS study Report for marketing period not exceeding five years to the Licensing Authority (s)** for their marketed drug products at the time of submission of renewal application.

In accordance to the above mentioned requirements; every MAHs (Licencees) in the country shall have an established Pv-system in place for collecting, processing and forwarding the report to the Licensing Authority (s).

In compliance with the "**Pharmacovigilance guidance document for marketing authorization holder**" published by NCC-PvPI IPC in collaboration with CDSCO, **the regulatory authorities should determine a program for inspection in relation to marketed pharmaceutical products. These inspections will be prioritized based on the potential risk to public health, the nature of the products, the extent of use, number of products that the MAH marketed.**

The Licensing Authority(s) under the legislative provisions (DCA & DCR) shall ensure by means of repeated inspections, and if necessary unannounced inspections, that the legal

requirements governing medicinal products are complied with. The Licensing Authority(s) may inspect the premises, enquire the records and documents of MAH or any firms employed by the MAH to perform such other activities.

The Licensing Authority(s) of National & State level shall establish written procedure for preparation and revision of guidance documents to impose implementation and supervision of systematic risk-based inspections. The programme shall ensure the extent and frequency of inspections that can be adhered and also sufficient resources must be determined and made available to ensure that the designated program of inspection can be carried out in an appropriate manner. The national level **pharmacovigilance inspection programs** will fulfil the need for the routine inspections. However, based on recommendations from SEC and other statutory bodies (e.g DTAB, DCC), various Government bodies e.g. ICMR, NACO, RNTCP, NVBDCP etc. if necessitate the targeted / triggered inspections will also be reflected in this programme as they may replace the need for a routine inspection.

Purpose

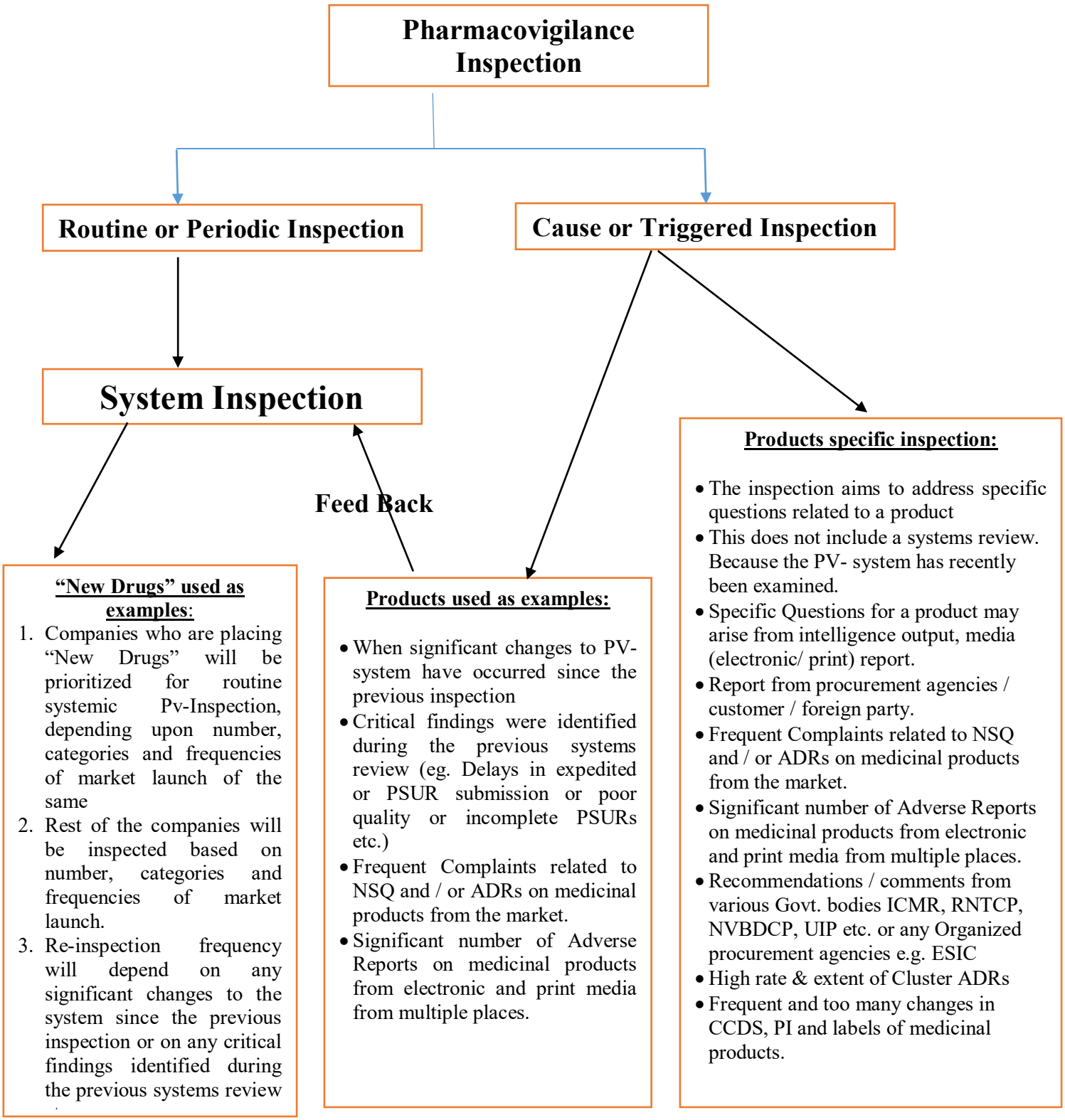
This guidance document provides the procedure for a risk-based planning of routine pharmacovigilance inspections schedule which shall present the list of companies and list of products which are prioritised based on criteria, as per Annexure-1, although considerations should be given to inspection early post authorisation and to introduce a random element to the inspection programme at an early stage.

The programme will be separated from any targeted / triggered inspection, but if a targeted inspection has been or will be conducted in a similar timeframe it may replace the planned routine inspection and for this reason it will remain reflected in the programme with a new scheduled year for that inspection. Specific triggers for targeted inspection are listed in Annexure-2.

Scope

- This procedure shall cover the PV-inspection (Routine) of MAHs who are placing human medicinal products in Indian market based on approval from the LA (CDSCO and / or SDLA) as defined in Section-21 of DCA for manufacture and import. National PV-inspection programmes (NPVIP) is expected to fulfil the need for regulatory compliances by routine inspections and if required targeted /triggered Inspections.
- Therefore, when a Competent Authority has carried out, or intends to carry out an inspection covering the scope of that requested within the required timeframe, the inspection results will be made available to the DCG(I) for further reviewing by a committee constituted by the DCG(I) at CDSCO (HQ).
- If such situations arise that PV-inspections would be specifically requested by any committee appointed by Govt. of India e.g. SEC, DTAB, DCC, the focus of such inspections would be to determine whether the MAH has the personnel, systems and facilities in place to meet their regulatory PV-obligations for "Drugs" placed by them in the Domestic & overseas market.
- These inspections will be requested as system inspections with one or more specific products selected as examples, for which specific information can be traced and verified through various processes. This shall provide a practical evidence for the functioning of the MAH's PV-system and their compliance with the regulatory requirements.
- The timing of the first inspection and any further inspection will be determined on the basis of prioritisation criteria described in this procedure but as a principle, re-inspections will take place based on risk assessment criteria. A four-year inspection cycle will be used but may be shortened or lengthened based on the risk assessment. This process and the methodology should be revised as appropriate.

Flow Diagram of systematic risk based pharmacovigilance program



Procedure

- Based on the dynamic List of "New Drugs" approved by the DCG(I), the pharmacovigilance section in CDSCO (HQ) will prepare a 4-yearly program for routine PV-inspections.
- This 4-yearly program will be revised on year-to-year basis.
- The preparation and revision of this program will be initiated 12 months in advance of the implementation of the first year of such program and allow for having always a consecutive four-yearly program
- For example, considering a 2018-21 program, during the implementation of the 2018 program, the new 2019 program should be prepared in order to have the consecutive 2019-2022 four-yearly program).
- The periodicity of re-inspections will be determined by various risk factors associated with the Medicinal products, functioning of the MAH.

Gathering Information

- At least twice per year, CDSCO will gather information from the MAH e.g. changes in the location of the PVOI, changes in data base system, too many changes proposing in product label & package inserts, too many & frequent Post-approval Changes and also information on any new MAHs add on the market force with New drug to be included in the program.
- In addition, previous information available on inspections or inspections conducted / planned at national level will also be taken into

consideration (e.g. the re-inspection dates proposed by the inspectors and / or review committee, if any, after conduct of the inspections proposed in this program).

- Other necessary tools will be identified and implemented to facilitate the collection and exchange of information on risk factors / triggers for inspections like the "Template for collecting information on PV issues for the attention of the inspectors/assessors".

Preparation and revision of the program

This document envisages a programme covering composite PV-inspections plan for rolling out a 4-year cycle with revision by 12 months in advance. Thus the first year of such programme will replace that year and allow for a consecutive 4-yearly programme to be in place and further revisions in order to introduce any necessary changes to the programme.

Thus a dynamic, rolling on 4-year cycle programme shall be revised each year to reflect the inspections already performed, the revised priorities, new MAHs, New drugs joining the system, new signals of ADR, Cluster ADRs.

The PV section in CDSCO (HQ) will prepare first 4yearly programme based on the information gathered from the official website of CDSCO and prioritising "MAHs" and "specific Drugs" to be inspected, as per "primary prioritisation factors" (Annexure-1). The priority list in this first programme will be in principle established based on the number of prioritisation factors

that concur at the same time for a particular MAH. Once a preliminary selection has been made, the "secondary prioritisation factors" (see annex 1),may be used in order to refine this selection.

The preparation / revision of further 4-yearly programmes will be made as per the following rules:

- For new MAH to be included in the program, the feedback from the inspectorates on when they plan to inspect these MAHs will be considered. This proposal may need to change based on the prioritising factors in Annex-1.
- The conduct of an inspection early post authorisation and/or the introduction of a random element to the inspection program may be used as well to refine the selection.
- For the MAHs already included in the program, the inspectorates will be asked to confirm whether or not a change is needed, ensuring that these CAP inspections fit in with CDSCO's national PV-Inspection programs.
- CDSCO may trigger inspection of a particular "MAH" and "Drug" based on feedback from the assessors (e.g. SEC)/PVPI/Immunization division (MOHFW) /SDLA/ Institutional procurement agencies.
- Re-inspections will be determined by risk factors and will be focused on addressing critical findings observed in previous inspections, changes in the system or any product specific issues of concern for the assessors.

- The preparation & revision of further 4-yearly programs will take place at least twice per year i.e. 1Q and 3Q of 2018.
- The program should at least include the below details:

(i) Full name of The MAH

(ii) Registered / corporate Office address of MAH

(iii) Contact person, e-mail and telephone (Land & Mobile) No.

(iv) PVOI and his organogram

(v) Work Station of the PVOI and his team.

(vi) Name Contact Phone No. & addresses of the hired Service providors

(vii) List of all "New Drugs" approved in previous 4-year

(viii) Licences / permission granted for manufacture and / or Import of such "New drugs"

(ix) Brand name and INN of such "New drugs"

(x) Routine or triggered Inspection

(xi) If triggered, the entity of requestor

(xii) Inspected sites, dates of inspection will be tracked in other working documents e.g Inspection Trackers, Inspection Reports, Ad-memoir etc.

Adoption of Program

This four-yearly programme should be concurred and duly approved by the DCG(I) before its implementation. As this programme will be a live document requiring periodic revision through the year, it is expected to be circulated to the appropriate persons for review at least twice, in the 2Q and 4Q of the year.

Implementation of the program

The nominated inspectorate should ensure that these inspections take place as agreed and approved by the DCG(I). The inspectors should submit a summary report along with the critical and major findings on the concluding day of Inspection to DCG(I) by official e-mail. The final elaborated inspection report including how these substantial issues are to be addressed may be submitted within 15-calender days of the concluding day of inspection. For those inspections requested by the SEC the specific recommendation should be followed.

A flow diagram on the circulation of the inspection reports related to this programme is available in Annexure-3.

Re-inspection

The calculation of the next inspection date should result from the last inspection date and the risk assessment process. In principle a 4-year inspection cycle will be used but may be shortened or lengthened based on this risk assessment.

Summary of Procedure

Steps for the preparation of the 2018-2021; CDSCO routine pharmacovigilance program

Sl No	Steps	Sources	Responsibility	Time Line
1	**Gathering information for making PV-Inspection plan / calendar**	**i. CDSCO website ii. PvPI iii. Immunization Division iv. Market complaints. v. Print/ Electronic Media vi. Peer review journals / Periodicals vii. State drugs Control Deptt viii. PSUR**	**Pharmacovigilance division in CDSCO (HQ)**	**At least 1Q & 3Q 200(X-1) e.g For 2019, do it in 1st& 3rd quarter of 2018**
2	**Preparation and revision of the Programme 200X-200(X+3) e.g. 2019-2022**	**i. CDSCO website ii. PvPI iii. Immunization Division iv. Market complaints. ix. Print/ Electronic Media x. Peer review journals / Periodicals v. State drugs Control Deptt. vi. PSUR**	**Pharmacovigilance division in CDSCO HQRS, Inspectors deputed by DCG(I)**	**At least 1Q & 3Q 200(X-1) To be done in 2018**
3	**Adoption of the program 200X-200(X+3)**	**i. CDSCO website ii. PvPI iii. Immunization Division iv. Market complaints. xi. Print/ Electronic Media xii. Peer review journals/ Periodicals v. State drugs Control Deptt. vi. PSUR**	**Pharmacovigilance division in CDSCO HQRS, Inspectors deputed by DCG(I)**	**At least 3Q &4Q 200(X-1)**

4	**Implementation of the program 200X-200(X+3)**	**i. Pharmacovigilancework station of the MAH,** **ii. SOPs and Guidelines;** **iii. Work Instructions,** **iv. Computerized Data base System** **v. Contract agreements with hired services parties** **vi. ICSR and ADR Formats** **vii. QMS- manual** **viii. Line Listing of SAE/AE,** **ix. Minutes of Pv-deptt of MAH.** **x. PSUR, if any** **xi. Follow-up Letters, mail communications with Doctors,/ HCPs/ Customers / regulators etc.** **xii. Archeivals , Library for Journals**	**Lead Inspector, his team, concerned DDC(I) of DCSO(Zone Office), Concerned SLA DCG(I)**	**At least 1Q & 3Q 200(X+3)**
5	**Re-inspections**	**i. Previous Inspection Reports,** **ii. Meeting Minutes within time lag** **iii. CAPA adopted**	**Lead Inspector, his team, concerned DDC(I) of CDSCO(Zone Office), Concerned SLA DCG(I)**	**Four year cycle unless considered to be performed later/earlier**

Annexure-1

Factors to be considered on deciding a routine pharmacovigilance inspection

Primary Prioritisation Factors

- When and how many times MAH was inspected (PV-inspection)
- What were the critical findings in such inspections;
- Whether MAH has any product with additional Risk Minimization /Management Activities;
- The MAH has never been inspected;
- Number and categories of New Drugs placed by the MAH in the market.
- Whether MAH is out sourcing entire or partial PV activities with one or multiple licensing partners;
- Sale Volume and Patient exposure
- Quantum and frequency of CCDS & Package insert update
- Whether re-inspection recommended in previous inspection report.
- If CDSCO receives too many and frequent post-approval changes on marketed medicinal products.
- If CDSCO receives feed-back, recommendation, specific alert/ information about product related complaints, ADRs from various Govt. bodies, organizational procurement agencies.

Secondary Prioritisation Factors (the following situations / issues may be considered)

- If CDSCO has information that MAH has recently been or is involved in a merger or takeover process;
- If CDSCO has information that MAH has changed their system significantly (e.g. new data base system, contracting out of reporting activities);
- If CDSCO has information that MAH has changed the sub contracted PV activities partner.
- Critical results of previous inspections (GCP, GMP, GLP);
- If CDSCO has information that Adverse comments / safety concerns from agencies/bodies outside India.
- If CDSCO has information that MAH has established PV system only to address third country regulations;
- If MAH has changed the PVOI since the last inspection;
- Whether MAH has many products in the market, covering many active ingredients;
- If MAH has only one New drug in the market;
- Size of the MAH (Large/ medium/ small);
- Non-availability of Detailed Description of the PV System (DDPS) in respect of any New drug
- Whether the MAH has many products with large sales volume;

Annexure-2

Triggers to be considered when deciding on a targeted pharmacovigilance inspection

- Delays in carrying out or failure to carry out specific obligations or follow-up measures relating to the monitoring of product safety, identified at the time of the marketing authorisation;
- Delays in expedited or periodic reporting;
- Incomplete reporting;
- Submission of poor quality or incomplete PSURs;
- Inconsistencies between reports and other information sources;
- Change in risk-benefit balance;
- Failure to communicate change in risk-benefit balance;
- Previous inspection experience;
- Information received from other authorities;
- Poor follow-up to requests for information from the Competent Authorities;
- Communication of information on PV concerns to the general public without giving prior or simultaneous notification to the Competent Authorities or Agency as applicable;
- Product withdrawal in other foreign market with little or no advance notice to CDSCO

Annexure-3

Procedures to be adopted by CDSCO

- The Inspectorate Team will prepare the Preliminary Report (PIR) of PV inspection with salient observations on the concluding day of Inspection.
- In case of routine PV-Inspection, this PIR will be forwarded to the DCG(I) through e-mail with copy to company
- In case of for-cause / triggered inspection, the PIR will be directly sent to the DCG(I) through e-mail on the same day.
- In both cases the detailed reports shall be prepared within 5- working days from the concluding day of Inspection and submitted to the DCG(I).
- The concerned division in CDSCO (HQ) will follow-up the matter for further regulatory action
- Such regulatory actions arranged in chronological manner will be incorporated as major contributing factor in planning for the 4-year cycle of PV-Inspection program.

********** **END OF INSPECTION GUIDELINE**********