DRUG REGULATORY AUTHORITY OF PAKISTAN

Guidelines undertaken for performance of Pharmacovigilance activities

1. Introduction

The DRAP must establish a national pharmacovigilance system for the collection and evaluation of information on therapeutic goods with particular reference to adverse reactions. Furthermore, the DRAP should take all appropriate measures to:

a) Encourage physicians and other healthcare professionals to report suspected adverse reactions to the DRAP and

b) Oblige manufacturer or importer to systematically collect information on risks related to their drugs and to transmit those to the DRAP. The requirements and procedures involved in such a system are described which relates to therapeutic goods marketed in Pakistan and covers collection and evaluation of all information useful in the surveillance of therapeutic goods.

2. Establishment of a Pharmacovigilance System

The DRAP should have in place a system of drug surveillance, (hereafter referred to as "a national pharmacovigilance center") (NPC) for receipt and evaluation of all pharmacovigilance data within Pakistan. Furthermore this center must be in a position to handle these pharmacovigilance data in a way, which is compatible with the procedures undertaken by WHO Collaborating Center for International Drug Monitoring in order that pertinent data may be transferred between the DRAP and WHO center.

3. Management of Pharmacovigilance Data

This section deals with the following procedures:

1. Management of spontaneous reporting programmes.
2. Management of manufacturer/importer derived pharmacovigilance data.
3. Management of pharmacovigilance data from other sources.
4. Procedures for communications and evaluation of pharmacovigilance issues within Pakistan.

3.1 Spontaneous Reporting Systems

3.1.1 Introduction

The DRAP should have in place a system for the collection of spontaneous suspected adverse reaction reports from health care professionals (e.g. free postal or telephone system), and manufacturer/importers marketing authorization holders (hereafter referred to as *MAHs*). The national pharmacovigilance center (NPC) must liaise with the healthcare professionals to increase the awareness of the reporting system, stressing its importance and encouraging reporting (e.g. by the provision of a user friendly system of reporting and provision of feedback after each report as appropriate).

The DRAP should interact with doctors and other healthcare professionals to ensure adequate reporting of adverse reactions to the competent authorities. To this end, it is desirable that the DRAP should ensure the following:

- That reporting of adverse reactions to the designated center is made as simple as possible.
- That all adverse reactions are acknowledged where appropriate and further information is forwarded as requested.
- That regular contact is maintained between the pharmacovigilance center and healthcare professionals for example by:
- The publishing of regular adverse reaction bulletins,
- The sending of "Dear Healthcare Professional" letters, where appropriate, (either by the DRAP and/or the manufacturer/importer),
- The provision of requested information on a one-to-one basis where possible.

3.1.2 General Principles of Spontaneous Reporting Systems (SRS)

The following recommendations concern the spontaneous reporting system procedure:

- A healthcare professional or the manufacturer/importer (marketing authorization holder) reports a suspected adverse drug reaction related to one or more pharmaceutical products, to a national pharmacovigilance center (NPC). Reports are made in writing (e.g. using report forms), by telephone, electronically, or by any other approved way.
- Reports are collected and validated by the pharmacovigilance centre and are usually entered into a database. Serious reactions should be handled with the highest priority. The database is used to identify potential signals and analyze data in order to clarify risk factors, apparent changes in reporting profiles etc.

The procedures of SRS are divided into:

- Case report collection and validation, case report storage,
- Case report processing (evaluation and presentation for transmission), information feedback,
- Protection of data confidentiality and security,
- Data quality control and quality assurance.

3.1.3 Case Report Collection and Validation

This concerns the collection and validation of primary data (i.e. the data transmitted from the reporter to the DRAP). For the validation and management of electronically transmitted reports, the specific operational procedure should be followed.

Case Report Collection

A pharmacovigilance spontaneous report concerns a single case; one patient, one identifiable reporter, one more suspected reaction(s), and one or more suspect pharmaceutical product(s). Only serious cases report by healthcare professionals will be received on an expedited basis in DRAP.

Case Report Validation

If the initial report is oral or made by telephone, it should be confirmed in writing by a healthca professional when several suspected reactions to one or more suspected therapeutic goods occur in o patient, but are considered to be independent reactions, they should be treated as separate reports. considered appropriate, especially in the case of serious or unexpected reactions, data in the repc concerning the patient, the therapeutic goods taken, the reactions, including signs and symptoms a laboratory reports, and the dates should be confirmed by copies of most important and relevant origin documents (e.g. hospital discharge forms, specialist reports, laboratory tests, prescriptions and post morte reports etc.).Completeness of reports should be evaluated according to data required. Incomplete repor especially when concerning serious or unexpected reactions, should be followed up promptly by obtainir further information from the initial reporter or other available sources. In some cases, it would also l appropriate to conduct further follow-up to obtain data on the long-term outcome of the reaction.An adver drug reaction report must contain the following information:

- An identifiable health-care professional,
- An identifiable patient,
- At least one suspected substance/pharmaceutical product/therapeutic good
- At least one suspected reaction.

This is the minimum information which allows the case to be entered onto a database and become availat for signal generation in order to facilitate evaluation of cases. Every effort should be made to obta complete information where appropriate. A reaction is suspected if either the reporting healthca professional or the manufacturer/importer holder believes there is a possible causal relationship between and the therapeutic goods in question. If a reaction is spontaneously reported, this usually implies a positi judgment from the reporter unless the reporter explicitly gives a negative judgment on a causal relationship

3.1.4 Case Report Storage

Initial raw data (paper based) must be stored and treated in the same way as other medical documents, w appropriate respect for confidentiality. Case reports should be stored in a database by the pharmacovigilar centre. Data storage should ensure on-line accessibility of data at all reasonable times.

Recommendations cover individual data entry, audit trail, and correct use of terminologies.

Data Entry

Conformity of stored data with the initial report should be ensured by a quality control procedure which provides for validation against the original data or images thereof.

Audit Trail

Storage should ensure traceability (audit trail) of all data entered or modified, including dates and sources of received data, dates and destinations of transmitted data.

Terminologies

The internationally agreed medical terminology (MedDRA) should be used. This is mandatory for single case reports received electronically and for regulatory reporting of all adverse drug reactions. Reports entered into a database should be coded according to internationally accepted terminologies. Reaction terms should be entered as the closest term available in the terminology, and, if possible, also in the original reporter's words. Use of terminologies should be monitored and validated, either systematically or by regular random evaluation. Data entry staff should be instructed in the use of the terminologies, and their proficiency verified.

3.1.5 Case Report Processing: Evaluation of Seriousness/Expectedness and Presentation for Transmission

Case report processing concerns evaluation of data in individual cases, identification of individual cases requiring specific handling, recognition and processing of alerts, and any other data processing of aggregate cases.

Evaluation of Data in Individual Cases

Data evaluation includes validation of the case report and determination of seriousness, and of expectedness of the suspected reaction. These terms (seriousness and expectedness) have specific meanings in the context of ADR report evaluation. Evaluation of the probability of the causal relationship between therapeutic goods and the suspected reaction(s) is undertaken when considered appropriate. All methods used to evaluate these parameters should be documented. Evaluators should be trained in the methods used and their training verified.

Management of Duplicate Reports

Some cases, especially those which are serious, will probably be reported to DRAP from more than one source or from a single source through more than one channel. The competent authority should make every effort to ensure that case reports contain sufficient information to identify such duplicates, e.g. from patient / reporter initials

(or names if allowed), addresses, date of birth, other dates. Databases should be reviewed regularly to identify duplicates in accordance with DRAP procedures. After identification, duplicates should be flagged as such.

Identification of Individual Cases Requiring Specific Handling

Database management should ensure compliance with regulations, i.e. identification of cases flagged as serious or unexpected and of any other circumstance requiring specific handling or transmission. Procedures should be in place to ensure that cases previously identified and processed are identified as such and not processed or transmitted repeatedly as new cases (see audit trail 3.1.4 above).

Individual Case Presentation for Transmission

Cases sent to other the DRAP or manufacturer/importers (MAHs) should be transmitted according to the approved formats.

Aggregate Case Processing and Alert Identification

Database management should enable users to identify case aggregates or trends indicating a signal. Once a possible signal has been identified, the possibility of a causal relationship should be assessed. In these cases, all adverse drug reaction reports should be classified according to national preferences or requirements, using nationally or internationally accepted methodologies. All reports fulfilling the minimum information requirement must be included in the overall analysis. Certain analyses (for example those concerning the role of risk factors) may be confined to cases where enough information is available, but it should be made clear that this is a subset of the data. Aggregate case processing should allow case grouping by accepted terms (see Terminologies 3.1.4 above). The terminology used for case aggregation should be specified. DRAP and manufacturer/importer (MAHs) should inform each other of identified signals which may impact on the risk benefit profile of the pharmaceutical product/therapeutic goods.

3.1.6 Information

The DRAP should ensure that the reporter(s) of a case is informed of its receipt and provided with the allocated reference number if appropriate, and additional information, if requested. The DRAP should ensure that ADR data are transmitted to the manufacturer/importer (MAHs) as required . The DRAP should also ensure that healthcare professionals (and when necessary, treated patients) are informed of any significant changes where appropriate in the pharmaceutical product information and of any suspected hazards requiring vigilance. The DRAP should ensure that proper and timely information is provided to international bodies, in particular the World Health Organization (WHO).

3.1.7 Quality Control and Quality Assurance

Quality control and quality assurance concern every step in the processes described above. Quality control and quality assurance should be ensured by DRAP, which should devise and implement the necessary procedures.

3.1.8 Confidentiality and Security

Confidentiality of patients' records including their personal identity, if given, should always be maintained; where possible, identifiable personal details of reporting healthcare professionals should be kept in confidence, as appropriate and in keeping with national legislation. At each stage of storage and processing of pharmacovigilance data, all care must be taken to ensure data security and confidentiality. This involves strict control of access to documents and to databases to authorized personnel sharing the medical and administrative confidentiality of the data. This security extends to the complete data path. Case report information should only be provided in an anonymous form. In addition, procedures should be taken to ensure security and non corruption of data during data transfers.

3.2 Manufacturer/importer Derived Pharmacovigilance Data Introduction

Manufacturer/importer introduce any therapeutic goods in the market must ensure that he has an appropriate system of pharmacovigilance in place in order to ensure responsibility and liability for his product on the market and to ensure that appropriate action can be taken, when necessary. Manufacturer/importer derived pharmacovigilance will be in one of the following formats:

1. Individual adverse reaction reports
2. Periodic safety update reports (PSURs)
3. Manufacturer/importer sponsored post-marketing safety studies.

This section deals with the procedures, to be undertaken by the Pharmacovigilance center, for handling manufacturer/importer-derived pharmacovigilance data.

3.2.1 Individual Adverse Reaction Reports

The national pharmacovigilance center (NPC) should ensure that all reports submitted by the manufacturer/importer conform with the requirements as laid out in these guidelines, in order to ensure conformity of reporting of adverse reactions by manufacturer/importer. Further more, the national pharmacovigilance center must ensure the validation and verification of all data included in these case reports as far as possible. Finally, for centre should ensure that these reports are followed up by the manufacturer/importer where appropriate, in order to improve the quality of data available and to facilitate causality assessment. The DRAP should ensure that they have the capability to send and receive ADR reports electronically and to encourage manufacturer/importer to do so in a defined format.

3.2.2 Periodic Safety Update Reports (PSURs)

A periodic safety update report (PSUR) is intended to provide an update of the worldwide safety experience of a therapeutic goods to The DRAP at defined times post-marketing. In the case of registered products, any major action (e.g. variation, suspension or withdrawal of a marketing authorization) considered necessary as a result of such evaluation out side Pakistan should be notified to the DRAP.

3.2.3 Manufacturer/importer Sponsored Post-Marketing Safety Studies

These studies are normally conducted to assess the clinical safety of marketed medicines in routine clinical practice; they may be either hypothesis-generating or hypothesis-testing. Manufacturer/importer (MAHs) proposing to perform such studies have been advised to discuss the draft protocol with the DRAP. The NPC may review studies, which are taking place within its jurisdiction on a regular basis. All serious adverse reactions, resulting from these studies, should be submitted in the usual way by the Manufacturer/importer (MAHs) /investigator and should be dealt with as outlined below. On completion of each study, the final report should be evaluated and, in the case of nationally authorized therapeutic goods, all relevant data (e.g. showing significant changes in the frequency of known adverse reactions, the development of unexpected adverse reactions, new interactions etc.) should be incorporated into the Summary of Product Characteristics (SPC) and notified to DRAP.

3.2.4 Communication between Manufacturer/importer and DRAP

The DRAP should ensure that they communicate with MAH according to existing legislation and guidelines.

3.3 Pharmacovigilance Data from Other Sources

3.3.1 Intensive Monitoring Schemes

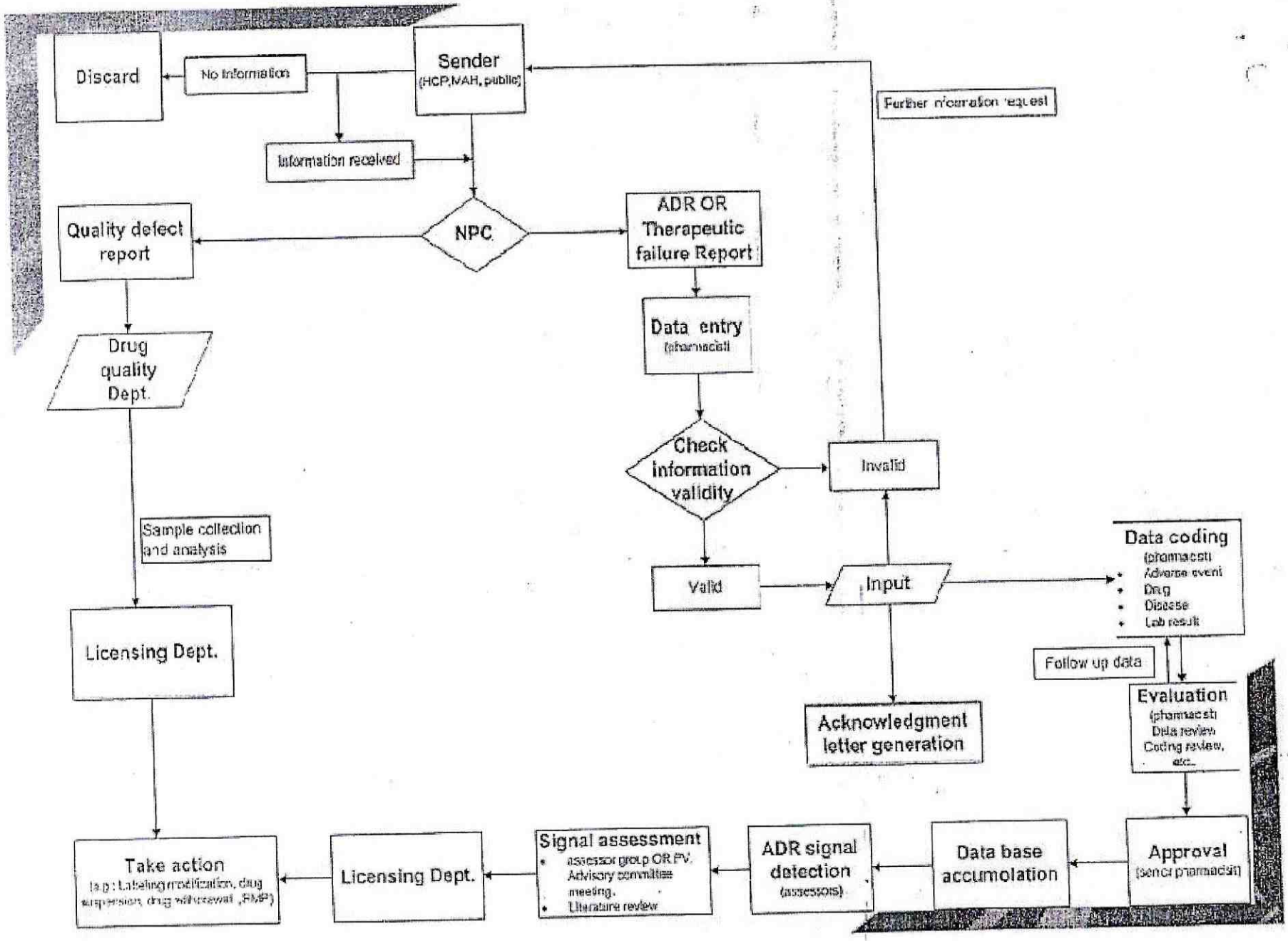
Intensive Monitoring is defined as a system of record collation in designated areas e.g. hospital units or by specific physicians. The DRAP may be involved in the drawing up of the protocol to undertake this collection of data or will be informed that such monitoring is taking place. Furthermore, it may be considered appropriate in the authorization of certain therapeutic goods to impose specific requirements in respect of reporting serious or unexpected reactions on the prescribing physician and to make these requirements a condition of use of the product under the terms of the registration. The national pharmacovigilance centre should ensure that data and reports are collected at agreed intervals and in an appropriate format.

3.3.2 Data onMisuse/Abuse of Drugs/therapeutic goods

Reports of suspected adverse reactions due to misuse and abuse of therapeutic goods which are received by the national pharmacovigilance centers (via spontaneous reports, manufacturer/importer/importers reports etc.) should be handled in the same way as for the other types of reactions.

3.3.3 Other Pharmacovigilance Data

These data include drug usage figures, published adverse reaction reports, pharmacoepidemiology studies conducted by organizations other than the Manufacturer/importer, pre-clinical studies or significant quality data and reports on products not currently marketed in Pakistan. These are important for determining frequency, occurrence of unexpected adverse reactions, new interactions etc. and overall risk/benefit analysis. In those cases (e.g. from pharmacoepidemiology studies) where significant data are received from these sources, these findings may be transmitted to the DRAP and the Agency, as part of a routine exchange of pharmacovigilance information, with a view to taking action as appropriate.


Discard
No information
Sender
(HCP,MAH, public)
Further information request
Information received
Quality defect report
NPC
ADR OR Therapeutic failure Report
Data entry
(pharmacist)
Drug quality Dept.
Check information validity
Invalid
Sample collection and analysis
Valid
Input
Data coding
(pharmacist)
Adverse event
Drug
Disease
Lab result
Licensing Dept.
Follow up data
Acknowledgment letter generation
Evaluation
(pharmacist)
Data review
Coding review,
etc..
Take action
Licensing Dept.
Signal assessment
assessor group OR PV Advisory committee meeting.
Literature review
ADR signal detection
(assessors)
Data base accumolation
Approval
(senior pharmacist)

DRUG REGULATORY AUTHORITY OF PAKISTAN

SUSPECTED ADVERSE DRUG REACTIONS

If you suspect an adverse reaction may be related to one or more drugs/vaccines/complementary remedies.
Do not be put off reporting because some details are not known.

PATIENT DETAILS Patient Initials:_____ Sex: M / F Ethnicity:_____ Weight if known (kg):_____

Age (at time of reaction):_____ Identification number (e.g. Your Practice or Hospital Ref):_____

SUSPECTED DRUG(S)/VACCINE(S)

Drug/Vaccine (Brand if known)	Batch	Route	Dosage	Date started	Date stopped	Prescribed for

SUSPECTED REACTION(S) Please describe the reaction(s) and any treatment given:

Outcome
- Recovered ☐
- Recovering ☐
- Continuing ☐
- Other ☐

Date reaction(s) started:_____ Date reaction(s) stopped:_____

Do you consider the reactions to be serious? Yes / No

If yes, please indicate why the reaction is considered to be serious (please tick all that apply):

- Patient died due to reaction ☐
- Life threatening ☐
- Congenital abnormality ☐
- Involved or prolonged inpatient hospitalisation ☐
- Involved persistent or significant disability or incapacity ☐
- Medically significant; please give details:_____

OTHER DRUG(S) (including self-medication and complementary remedies)

Did the patient take any other medicines/vaccines/complementary remedies in the last 3 months prior to the reaction? Yes / No

If yes, please give the following information if known:

Drug/Vaccine (Brand if known)	Batch	Route	Dosage	Date started	Date stopped	Prescribed for

Additional relevant information e.g. medical history, test results, known allergies, rechallenge (if performed), suspect drug interactions. For congenital abnormalities please state all other drugs taken during pregnancy and the last menstrual period.

Please list any medicines obtained from the internet:_____

REPORTER DETAILS

Name and Professional Address:_____

Postcode:_____ Tel No:_____

Email:_____

Speciality:_____

Signature:_____ Date:_____

CLINICIAN (if not the reporter)

Name and Professional Address:_____

Postcode:_____ Tel No:_____

Email:_____

Speciality:_____

Date:_____