Government of Pakistan
Drug Regulatory Authority of Pakistan
Ministry of National Health Services, Regulations and Coordination
****

Islamabad, the April, 2018

NOTIFICATION

S.R.O. (I)/2018. –In exercise of the powers conferred by section 23 of the Drug Regulatory Authority of Pakistan Act, 2012 (XXI of 2012), the Drug Regulatory Authority of Pakistan, with the approval of the Federal Government, is pleased to make the following rules, namely:-

1. Short title, commencement and application. - (1) These rules may be called the Pharmacovigilance Rules, 2018.

(2) They shall come into force at once.

(3) These rules shall also be applicable to perform Pharmacovigilance activities during Clinical Trials, Passive Surveillance, Simulated Reporting, Active Surveillance, Comparative Observational Studies, Targeted clinical investigation and Descriptive studies.

2. Definitions. - In these rules, unless there is anything repugnant in the subject or context;-

(i) "abuse of a therapeutic good" means persistent or sporadic, intentional excessive use of therapeutic good which is accompanied by harmful physical or psychological effects;

(ii) "active surveillance" active surveillance, in contrast to passive surveillance, seeks to ascertain completely the number of adverse events via a continuous pre-organized process. An example of active surveillance is the follow-up of patients treated with a particular drug through a risk management program. It can be achieved through sentinel sites, drug event monitoring and registries;

(iii) "adverse drug reaction" or "ADR" means response to medicines or therapeutic good which is noxious and unintended that occurs at doses normally used for the prophylaxis, diagnosis, or therapy of disease or for the restoration, correction or modification of physiological function;

(iv) "adverse event" or "AE" means any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product or therapeutic good and which does not necessarily have a causal relationship with this treatment;

(v) "adverse event following immunizations" or "AEFI" means any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine**;**

(vi) "causality assessment**"** means the evaluation of the likelihood that a medicine was the causative agent of an observed adverse reaction. Causality assessment is usually made according established algorithms;

(vii) "concerned board" means the board to which the therapeutic good safety regulatory action may be referred which include Drug Registration Board, Medical Devices Board, Health and OTC evaluation and enlistment committee or board, Quality Control Board and Central Licensing Board;

(viii) "data lock point" or " DLP" means the data lock point is the date designated as the cut-off for data to be included in Development Safety Update Report (DSUR) and Periodic Benefits-Risk Evaluation Report (PBRER) based on their Development international birth date (DIBD) and International Birth Date (IBD) respectively;

(ix) "development international birth date" or "DIBD" refers to the date of sponsor's first authorization or approval to conduct a clinical trial in any country worldwide;

(x) "development safety update reports" or "DSUR" is intended to present a comprehensive, thoughtful annual review and evaluation of pertinent safety information collected during the reporting period related to a drug under investigation, whether or not it is marketed, namely:-

a. examining whether the information obtained by the sponsor during the reporting period is in accord with previous knowledge of the investigational drug's safety;

b. describing new safety issues that could have an impact on the protection of clinical trial subjects;

c. summarizing the current understanding and management of identified and potential risks; and

d. providing an update on the status of the clinical investigation or development programme and study results.

(xi) "individual case safety report" or "ICSR" means a report describing a suspected adverse drug reaction related to the administration of one or more medicinal products or therapeutic good to an individual patient;

(xii) "International birth date" or "IBD" refers to the date of the first marketing approval or registration for any product containing the active substance granted to any company in any country in the world;

(xiii) "investigator" means a doctor, health care professional or a person by a profession agreed for investigations because of the scientific background and the experience in patient care it requires. The investigator is responsible for the conduct of a clinical trial at a trial site.

If a trial is conducted by a team of individuals at a trial site, the investigator is the leader responsible for the team and may be called the principal investigator;

(xiv) "investigator's brochure" or "IB" means a compilation of the clinical and non-clinical data on the investigational drug or products which are relevant to the study of the product or products in human subjects;

(xv) **"**medication error" means any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer;

(xvi) "misuse of a therapeutic good" means situations where the therapeutic good or drug is intentionally and inappropriately used not in accordance with the registered therapeutic good information;

(xvii) "National pharmacovigilance centre" or "NPC" means the centre established under rule 3;

(xviii) "occupational exposure to a therapeutic good" for the purpose of reporting cases of suspected adverse reactions, means an exposure to a therapeutic good as a result of one's professional or non-professional occupation;

(xix) "off-label use" refers to the use of an approved medicine under the direction or supervision of a healthcare professional for an unapproved indication, age group, dosage, route or form of administration;

(xx) "overdose of therapeutic good" means administration of a quantity of a therapeutic good given per administration or cumulatively which is above the maximum recommended dose according to the registered therapeutic good information;

(xxi) "passive surveillance" includes spontaneous reporting and case series;

(xxii) "periodic benefit-risk evaluation report" or "PBRER" is intended to present a periodic, comprehensive, concise and critical analysis of new or emerging information on the risks of the health product, and on its benefits in approved indications, to enable an appraisal of the product's overall benefit-risk profile;

(xxiii) "pharmacovigilance" means the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problem;

(xxiv) "pharmacovigilance system" means a system used by the manufacturer or therapeutic good registration holder to fulfil the tasks and responsibilities listed in these rules and designed to monitor the safety of authorized medicinal products and detect any change to their risk-benefit balance;

(xxv) "pharmacovigilance system master file" means a detailed description of the Pharmacovigilance system used by the marketing authorization holder with respect to one or more authorized therapeutic goods;

(xxvi) "post-authorization safety study" or "PASS" means any study relating to a registered drug conducted with the aim of identifying, characterizing or quantifying a safety hazard, confirming the safety profile of the drug, or of measuring the effectiveness of risk management measures;

(xxvii) "risk management plan" or "RMP" means a detailed description of the risk management system which include a set of Pharmacovigilance activities and interventions which are designed to identify, characterize, prevent or minimize risks relating to a medicinal product including the assessment of the effectiveness of these activities and interventions. The RMP consists of a safety overview of the medicinal product, and the proposed Pharmacovigilance activities and risk minimization activities;

(xxviii) "serious adverse reaction" or "serious adverse event " means an untoward medical occurrence that at any dose result in patient death, is life threatening, require in patient hospitalization or result in prolongation of existing hospitalization, result in persistent or significant disability or incapacity, is a congenital anomaly or birth defect or is judge to be medically important event;

(xxix) "signal" means reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information. The publication of a signal usually implies the need for some kind of review or action;

(xxx) "solicited reports" refers to reports derived from organized data collection systems, which include clinical trials, registries, post-approval named patient use programs, other patient support and disease management programs, surveys of patients or healthcare providers, or information gathering on efficacy or patient compliance;

(xxxi) "significant safety issues" includes but are not limited to-

a. modification or removal of an approved indication for safety reasons based on sound scientific evidence which was not scientifically established through clinical trials;
b. addition of a contraindication;

c. major changes to warnings, precautions or adverse reactions statements in the product information for safety reasons in any country where the medicine is marketed;

d. investigations of safety issues or concerns of the medicine other than country of origin medicines regulator (e.g., European Union (EU) referral procedures for safety reasons);

e. withdrawal or suspension of availability of the medicine in another country based on signals indicating seriousness and quality of information;

f. issues identified by the sponsor as a result of the sponsor's own signal management process once assessment has been completed and actions are proposed;

g. significant safety results from post-marketing clinical studies;

h. safety issues due to misinformation in the product information;

i. safety issues related to use outside the terms of the product information or directions for use;

j. safety issues in relation to quality of any raw materials used in the medicine;

k. a lack of efficacy associated with a serious suspected adverse reaction report;

l. quality defect, adulteration, contamination or spurious drugs associated with a serious adverse reaction report; and

m. issues for which the sponsor is considering sending a Dear Healthcare Professional (or DHCP) letter in any country where the medicine is being marketed.

(xxxii) "spontaneous reporting" means;-

a. system whereby case reports of adverse drug events are voluntarily submitted from health professionals and pharmaceutical manufacturers to the national regulatory authority; or

b. a spontaneous report is an unsolicited communication by a healthcare professional or consumer to a company, regulatory authority or other organization (e.g. World Health Organization, Regional Centres, Poison Control Centre) that describes one or more adverse drug reactions in a patient who was given one or more medicinal products and that does not derive from a study or any organized data collection scheme;

(xxxiii) "sponsor" means an individual, company, institution or organization which takes responsibility for the initiation, management and financing of a clinical trial; and

(xxxiv) "unexpected adverse reaction" means;-

(a) an adverse reaction, the nature or severity of which is not consistent with domestic labelling or market authorization, or expected from characteristics of the drug; or
(b) an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unauthorized or unregistered investigational drug or summary of product characteristics for a registered drug).

3. National Pharmacovigilance Centre. - (1) The Drug Regulatory Authority of Pakistan (DRAP) shall establish NPC at Islamabad for the therapeutic goods safety monitoring, signal management and effective coordination at Provincial levels and with international level including World Health Organization (WHO).

(2) NPC shall work under the Division of Pharmacy Services, DRAP, having Additional Director as an in-charge of the centre and shall have enough technical staff, logistics and technical facility to perform the pharmacovigilance activities.

(3) NPC shall acquire a National database and shall ensure that the procedure and tools are in place for collection, assessment, and investigation of safety issue. The National database shall be linked to World Health Organization, Uppsala Monitoring Centre (WHO-UMC) and with the Regional or Provincial centres.

(4) NPC shall have subscription of scientific literature and of others tools for coding adverse drug reactions, drug interactions and of any other software or tool that it desired for its proper functioning.

4. Functions of National Pharmacovigilance Centre. - (1) The functions of the NPC shall be as follows, namely:-

(i) collect and evaluate adverse event or adverse drug reactions occurring in the context of clinical trials, safety and efficacy studies and spontaneous reporting;

(ii) NPC shall collect spontaneous adverse drug reactions reporting forms relating to the use of therapeutic goods from manufacturer or therapeutic good registration holder, Provincial pharmacovigilance centres as the case may be from health care professional, pharmacist and the consumer directly;

(iii) technical staff at NPC shall ensure that the minimum criteria for reporting is met during reporting, that include an identifiable reporter, an identifiable patient, one or more suspected reaction and one or more suspected therapeutic goods;

(iv) shall ensure that the reports are submitted according to timelines provided under these rules for smooth running of the centre;

(v) monitor the database to determine whether there are new risks or whether risks have changed and whether those risks impact on the risk-benefit balance;

(vi) in case of incomplete reports NPC shall involve patients and healthcare professionals as appropriate, in the follow up of the report and shall collaborate with manufacturer or therapeutic good registration holders in the detection of duplicate report;

(vii) shall collect and analyse the ICSR of all AEFI and spontaneous serious and non-serious adverse reactions from the hospital, health care professional, pharmacists and manufacturer or therapeutic good registration holder;

(viii) shall ensure that proper causality assessment of the adverse drug reactions have been performed before sending these to WHO-UMC;

(ix) shall periodically evaluate the database for new signals, and submit these signals to Pharmacovigilance risk assessment expert group (PRAEG) for further action;

(x) submit the quarterly review of the adverse drug reactions to PRAEG constituted under rule 5 to further coordinate with concerned board to take further course of action;

(xi) take all appropriate measures to encourage patients, doctors, pharmacists and other healthcare professionals to report suspected adverse reactions to the NPC.

For these tasks, organizations representing consumers, patients and healthcare professionals may be involved as appropriate;

(xii) facilitate patient reporting through the provision of alternative reporting formats in addition to web-based formats;

(xiii) take all appropriate measures to obtain accurate and verifiable data for the scientific evaluation of suspected adverse reaction reports;

(xiv) ensure that the public is given important information on pharmacovigilance concerns relating to the use of a therapeutic goods in a timely manner through publication i.e. safety communication, health care advisory, news bulletin on the web-portal and through other means of publicly available information as necessary;

(xv) take the necessary measures to ensure that a manufacturer or therapeutic good registration holder who fails to discharge the obligations laid down in these rules is subject to effective, appropriate and dissuasive penalties as determined by PRAEG;

(xvi) communicate and liaise with Pakistan Medical and Dental council (PMDC), Pakistan Nursing Council, Pharmacy councils and Provincial Governments to impose specific obligations on Doctors, Nurses, Pharmacists and other health care professionals working in the district headquarters hospitals and tertiary care hospitals of the Provinces to develop the suspected adverse drug reactions reporting trend in the country;

(xvii) conduct training of the health care professionals for proper reporting of adverse drug reactions reporting as per WHO protocols;

(xviii) help Provinces to establish their Pharmacovigilance centre at the Provincial and Regional level and connect their database with the central database of NPC;

(xix) ensure that manufacturer or therapeutic good registration holders inform the NPC in the event of new risks or risks that have changed, or changes to the risk-benefit balance have been detected;

(xx) conduct training or capacity building of the technical staff of NPC regards to causality assessment, signal detection, and risk management etc. For this purpose it shall develop training plan and update it at least once a year and maintain records of staff training;

(xxi) frame guidelines of pharmacovigilance for different stakeholders (manufacturer or therapeutic good registration holder, health care professional and sponsor), pharmacovigilance planning, (recording, monitoring, and conducting);

(xxii) develop standard operating procedures (SOP) for the different processes of pharmacovigilance and implementation of National pharmacovigilance programme;

(xxiii) conduct Good Pharmacovigilance Practice (GVP) inspection of manufacturer or therapeutic goods' registration holder;

(xxiv) develop adverse drug reactions or adverse event reporting forms for health care professionals, manufacturer or therapeutic goods' registration holder;

(xxv) collaborate with different stake holders i.e. public and private hospitals, medical colleges, pharmacy faculty or department of universities, non-governmental organization and prime minister health programs for effective implementation of pharmacovigilance program in the country;

(xxvi) develop mechanism for regular feedback to all stakeholders on the activities of pharmacovigilance, and shall ensure that pharmacovigilance activities and feedback are properly communicated to the public; and

(xxvii) share pharmacovigilance data and findings with relevant regional and international partners.

5. Pharmacovigilance Risk Assessment Expert Group. - (1) The Authority shall constitute PRAEG for evaluation of risks associated with the use of therapeutic goods, signal detection, causality assessment, risk management, risk minimization, failure mode effect analysis and evaluation of periodic reports.

(2) PRAEG shall ensure that risks associated with use of therapeutic goods are detected as early as possible and take necessary steps to minimize these risks, coordination with public and health care professional and give recommendation to concerned board for further regulatory actions.

(3**)**PRAEG shall consist of the following members:-

(a) Director Pharmacy Services who shall be its ex-officio Chairman;
(b) Additional Director Pharmacy Services or Pharmacovigilance who shall be its ex-officio Secretary;
(c) one professor of clinical pharmacy/pharmacy practice to be nominated by DRAP (member);
(d) one professor of toxicology to be nominated by DRAP (member);
(e) one representative from Pharmaceutical Evaluation and Registration Division, DRAP (member);
(f) one representative from Quality Control and Lab Testing Division, DRAP (member);
(g) one representative from Medical Devices and Medicated Cosmetics Division, DRAP (member);
(h) one representative from Health and OTC Division, DRAP (member);
(i) one representative from Biological Drug Division, DRAP (member); and
(j) maximum eight expert members to be nominated by DRAP having at least five years' experience in the field of Clinical Pharmacology, Clinical Pharmacist, Physician, Epidemiology, Toxicology, Pharmacovigilance, Clinical Trials (drug research), and Biological safety.

(4) The members of the PRAEG, other than its ex officio members, shall hold office for three years and shall be eligible for re-nomination.

(5) The group may opt representative from professional bodies like Pakistan Pharmaceutical Manufacturers' association, Pakistan Chemists' and Druggists'' association, Medical Devices association, Pharma Bureau etc. as observer and comments.

(6) The meetings of the PRAEG may held at such time as the group may deem fit and, due to risks of therapeutic goods as a course of evaluation of database, the Chairman may at any time call a meeting if there is any important matter for its consideration.

(7) In the absence of the Chairman, the group may elect one of its members to preside over a meeting.

(8) The quorum to constitute a meeting of the group shall be one third of its total membership.

6. Functions of Pharmacovigilance Risk Assessment Expert Group. - (1) The functions of PRAEG shall be as follows, namely:-

(a) perform the initial analysis and prioritization of signals of new risks or risks that have changed or changes to the risk-benefit balance. Where it considers that follow-up action may be necessary, the assessment of those signals and agreement on any subsequent action concerning registration shall be conducted in a time-scale commensurate with the extent and seriousness of the issue;

(b) on the basis of concerns resulting from the evaluation of data from Pharmacovigilance activities ,recommend the NPC to inform the Provincial Health Departments, PMDC, Pakistan Medical Association, or general public through web base safety announcement and health care advisory, where it considers necessary that a new contraindication, a reduction in the recommended dose or a restriction to the indication of therapeutic goods is necessary;

(c) verify whether the safety concern relates to therapeutic goods other than the one covered by the information, or whether it is common to all products belonging to the same range or therapeutic class and if identifies that safety concerns relates to more therapeutic goods than those which are covered by the information or that is common to all therapeutic goods belonging to the same range or therapeutic class, it shall extent the scope of procedure accordingly;

(d) evaluate and assess DSUR, PBRER and RMP or nominate a penal of expert or appoint rapporteur for this purpose;

(e) on the basis of assessment and evaluation of database, or due to detection of new signals if it is found that risks of therapeutic goods outweigh its benefits, it shall recommend a regulatory or necessary remedial action to the concerned board for variation, suspension, revocation, market withdrawal or any other action which it considers appropriate to ensure therapeutic good safety;

(f) recommend to Drug Registration Board to impose obligation on manufacturer or therapeutic good registration holder to conduct post authorization or registration safety or efficacy studies, if it is found that during the evaluation of data, there is safety concern with use of drug;

(g) in the case of assessment and evaluation of PBRER, DSUR, RMP and final report PASS and post authorization efficacy study or report of rapporteur, if it is found that there is risk associated with the drug, PRAEG may recommends regulatory action to the Drug Registration Board which may include suspension of license, revocation and cancellation of registration, market withdrawal, imposition of or label change or summary of product characteristics;

(h) establish Pakistan reference dates list for PBRER and DSUR submission; and

(i) nominate a team for GVP inspection of manufacturer or therapeutic goods' registration holders.

(2) If the opinion of concerned board differs from the recommendations of the PRAEG, it shall attach to its opinion a detailed explanation of the scientific grounds for the difference together with recommendations.

7. Obligations of manufacturer or therapeutic good registration holder to perform pharmacovigilance activities.- (1)Manufacturer or therapeutic good registration holder shall operate a pharmacovigilance system for fulfilment of his pharmacovigilance activities in accordance with directives of NPC and evaluate all information scientifically, consider options for risk minimization or prevention and take appropriate measures as necessary. Manufacturer or

therapeutic good registration holder shall collect, record, store, maintain, and analyse the adverse event or adverse drug reactions of the therapeutic goods registered in their name in order to monitor their safety and report to NPC.

(2) Manufacturer or therapeutic good registration holder shall appoint an appropriately qualified person having such experience and qualification, responsible for pharmacovigilance system on permanent basis, who shall reside and operate in the country and shall be responsible for establishment and maintenance of the pharmacovigilance system. Manufacturer or therapeutic good registration holders shall submit name and contact details of the qualified person to NPC.

(3) Manufacturer or therapeutic good registration holder shall collect adverse event or adverse drug reactions and report to NPC in the following conditions, namely:-

(i) passive surveillance;
(ii) stimulated reporting;
(iii) active surveillance;
(iv) comparative observational studies (cross sectional study, case control study, and cohort study);
(v) targeted clinical investigations; and
(vi) descriptive studies (nature history of disease and drug utilization study).

(4) Manufacturer or therapeutic good registration holder shall maintain and make available on request pharmacovigilance system master file, which shall include following contents, namely;-

(i) details of the qualified person responsible for pharmacovigilance;
(ii) details of the organization structure of the company that actually holds the registration;
(iii) details of all the sources of the relevant safety data;
(iv) details of all electronic (computerized) systems and databases;
(v) details of all pharmacovigilance processes;
(vi) details of the performance of all drug safety systems; and
(vii) details of all quality control systems.

(5) Manufacturer or therapeutic good registration holder shall record all adverse events or adverse drug reactions with therapeutic goods registered on their name in the country which are brought to their attention, whether reported spontaneously by patient or health care professional, or occurring in the context of a post-authorization study and shall not refuse to consider reports of suspected serious and non-serious adverse reaction received through email or by telephone from patients and health care professionals and shall report as under to NPC as per following timeline, namely;-

(i) submit to NPC database serious suspected adverse reactions within fifteen calendar days following the day on which manufacturer or therapeutic good registration holder concerned gained knowledge of the event;
(ii) submit to NPC database non-serious suspected adverse reactions that occur in the country, within ninety calendar days following the day on which the manufacturer or therapeutic good registration holder concerned gained knowledge of the event; and

(iii) Manufacturer or therapeutic good registration holder shall not be required report to NPC database the adverse reactions recorded in the listed medical literature, but they shall monitor all other literature and report any suspected adverse reaction.

(6) Manufacturer or therapeutic good registration holders shall establish procedures in order obtain accurate and verifiable data for scientific evaluation of suspected adverse reaction reports, shall collect follow-up information on these reports and submit to NPC database. Manufacturer or therapeutic good registration holders shall collaborate with NPC in detection of duplicates reports of suspected adverse reactions.

(7) Manufacturer or drug registration holder shall conduct voluntarily non-interventional specific studies on the efficacy and safety if it is found that there is risk associate with the drug or if it is imposed by the registration board on the recommendation of PRAEG. Post authorization safety and efficacy study can also be initiated in the case if it is laid down as a condition of registration for the specific drugs.

(8) Manufacturer or drug registration holder shall submit PBRER for all new drugs after registration as per the following frequency, namely;-

(i) every six month for the first two years;
(ii) annually for the subsequent two years; and
(iii) at three years intervals thereafter.

(9) Manufacturer or drug registration holder shall submit PBRER as per the following timelines, namely;-

(i) PBRER covering intervals of six or twelve months is to be submitted within seventy calendar days of DLP. The DLP of PBRER is based on IBD of the said drug;
(ii) PBRER covering intervals in excess of twelve months within ninety calendar days of DLP ; and
(iii) adhoc PBRER within ninety calendar days of DLP, unless otherwise specified in the ad-hoc request. Ad-hoc PBRER are reports outside the routine reporting requirements, and may be requested by Drug Registration Board or NPC due to safety risk or any other reason. Where an ad-hoc report is requested and a PBRER has not been prepared for a number of years, it is likely that a completely new report will need to be prepared by the manufacturer or therapeutic good registration holder.

(10) By way of derogation from sub-rule (8) the manufacturer or therapeutic good registration holder shall submit PBRER for generic drugs, drugs that have well established use, alternative medicines and medical devices only if such obligation is laid down as a condition of registration or when required by concerned board or NPC on the basis of concern relating to pharmacovigilance or due to lack of periodic safety reports relating to an active substance after the registration has been granted, otherwise there is no need to submit PBRER in case of these therapeutic goods.

(11) Manufacturer or drug registration holder shall submit to the Drug Registration Board RMP for all new drugs along with drug registration application. The PRAEG may request manufacturer or drug registration holder to submit RMP other than new drugs registration application, if there are safety risk with its use after registration, or at time of revision of drug prescribing information.

(12) Sponsor or manufacturer or therapeutic good registration holder shall report any identified significant safety issue as soon as possible within seventy-two hours of the awareness of the issue by sponsor or manufacturer or therapeutic good registration holder to NPC and concerned board.

(13) Sponsor or manufacturer or therapeutic good registration holder shall forward to NPC valid serious reports which are associated with adverse outcomes as result of overdose, abuse, misuse, occupational exposure and medication error of therapeutic goods within fifteen calendar days of its awareness.

(14) Sponsor or manufacturer or therapeutic good registration holder shall submit adverse drugs reaction reports of medicines when used off-label.

(15) Lack of therapeutic efficacy in case of vaccines, contraceptives, antibiotics, and medicines used in critical conditions or life-threatening situations shall be reported to NPC within fifteen calendar days.

8. Pharmacovigilance activities during the clinical trials. - (1) The sponsor shall bound the investigator to report all serious adverse events immediately to him except for those that the protocol or investigator's brochure identifies as not requiring immediate reporting. The immediate report shall be followed by detailed, written reports. The immediate and follow-up reports shall identify subjects by unique code numbers assigned to the latter.

(2) Adverse events and laboratory abnormalities identified in the protocol as critical to safety evaluations shall be reported to the sponsor according to the reporting requirements and within the time periods specified in the protocol.

(3) For reported deaths of a subject, the investigator shall supply the sponsor and the Ethics Committee with any additional information requested.

(4)The sponsor shall keep detailed records of all adverse events which are reported to him by the investigator or investigators. These records shall be submitted to the NPC.

(5) The NPC shall ensure that all suspected unexpected serious adverse reactions to an investigational drug which are brought to its attention are recorded.

(6) Sponsor shall reports adverse event occurring during the clinical trials to the NPC as per following timelines, namely;-

(a) the sponsor shall ensure that all relevant information about suspected serious unexpected adverse reactions or adverse event occurring in clinical investigation, that are fatal or life-threatening are recorded and reported as soon as possible to the NPC, and to the Ethics Committee, and in any case no later than seven calendar days after knowledge by the sponsor of such a case, and the relevant follow-up information is subsequently communicated within additional eight calendar days;

(b) all other suspected serious unexpected adverse reactions shall be reported to the NPC and to the Ethics Committee concerned as soon as possible but within a maximum of fifteen calendar days of first knowledge by the sponsor;

(c) once a year throughout the clinical trial, the sponsor shall provide to the NPC and the Ethics Committee with a listing of all suspected serious adverse reactions which have occurred over this period and a report of the subjects' safety; and
(d) non-serious AEs or ADRs shall not be reported on expedite basis but shall be included in the periodic reports.

(7) Sponsor shall submit DSUR for as long as the sponsor conducts clinical trials with the investigational drug. For the ease of manufacturer or drug registration holder or sponsor, the DSUR shall be submitted for all ongoing clinical trials that the sponsor is conducting or has completed during the review period including,-

(a) clinical trials conducted using an investigational drug whether with or without a registration, i.e., human pharmacology, therapeutic exploratory and therapeutic confirmatory trials (Phase I – III);
(b) clinical trials conducted using marketed or registered drugs in approved indications, i.e., therapeutic use trials (Phase IV);
(c) other therapeutic use of an investigational drug (e.g., expanded access programmes, compassionate use programmes, particular patient use, single patient investigational new drugs, and treatment investigational new drugs);and
(d) comparability trials conducted to support changes in the manufacturing process of drug.

(8) The DSUR shall be submitted annually no later than sixty calendar days from the DSUR's DLP. The DLP of the DSUR should be based on DIBD.

(9) If the investigational drug has received accelerated approval or registration, and clinical trials continue or are initiated, both a PBRER and a DSUR should be prepared in accordance with directions from NPC. The sponsor shall change the DSUR's DLP to coincide with the IBD so that the DSUR and the PBRER can be synchronized. In synchronizing the DLP for the DSUR and PBRER, the period covered by the next DSUR should be no longer than one year.

(10) When submission of an annual DSUR report is no longer required, the sponsor should indicate that the final DSUR serves as the last annual report for the investigational drug. The sponsor should also indicate whether or not clinical trials are continuing elsewhere.

[No. F.9-5/2017-DD(PS)]

AAMAR LATIF
Deputy Director (Legal Affairs)
Drug Regulatory Authority of Pakistan