Government of Pakistan
Drug Regulatory Authority of Pakistan
Ministry of National Health Services, Regulations and Coordination
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Islamabad, the 22nd April, 2022.

NOTIFICATION

S.R.O. 540(I)/2022.– 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 shall be called the Pharmacovigilance Rules, 2022.

(2) They shall come into force at once.

(3) These rules shall be applicable to perform pharmacovigilance activities during passive surveillance, active surveillance and post-authorization 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" is a process that involves, enhanced or targeted monitoring for certain events or therapeutic goods and seeks to ascertain completely the number of adverse events or adverse drug reactions through a continuous pre-planned process;

(iii) "administrative territory" means such states and territories as mentioned in Article I of the Constitution;

(iv) "adverse drug reaction" or "ADR" means response to drug or therapeutic goods 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. A response in this context means that a causal relationship between a therapeutic good and an adverse event is at least a reasonable possibility. An adverse reaction, in contrast to an adverse event, is characterised by the fact that a causal relationship between a therapeutic good and an occurrence is suspected;

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

(vi) "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;

(vii) "causality assessment" means the evaluation of the likelihood that medicine or therapeutic good was the causative agent of an observed adverse reaction;

(viii) "concerned board or committee" means a Board or Committee notified under the Drugs Act, 1976 (XXXI of 1976) and the Drug Regulatory Authority of Pakistan Act, 2012 (XXI of 2012) for the purpose of licensing, registration, enlistment or any other function to which therapeutic good safety related regulatory actions or recommendations may be referred;

(ix) "data lock point" or " DLP" means the cut-off date appointed for data to be included in periodic benefits-risk evaluation report based on their international birth date;

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

(xi) "international birth date" or "IBD" means 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;

(xii) "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 healthcare professional, patient or consumer;

(xiii) "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;

(xiv) "national pharmacovigilance centre" or "NPC" means the national pharmacovigilance centre established under rule 3;

(xv) "occupational exposure to a therapeutic good" means an exposure to a therapeutic good as a result of one's professional or non-professional occupation;

(xvi) "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;

(xvii) "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;

(xviii) "passive surveillance" a process where healthcare professionals or patients send spontaneous reports describing an adverse drug reaction or event after one or more therapeutic goods are administered to the registration holders or regulatory authority;

(xix) "periodic benefit-risk evaluation report" or "PBRER" is a document intended to present a periodic, comprehensive, concise and critical analysis of new or emerging information on the risks of the therapeutic good on its benefits in

approved indications, to enable an appraisal of the therapeutic good overall benefit-risk profile;

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

(xxi) "pharmacovigilance officer" or "PO" means an officer notified under Rule. 6 for the execution of pharmacovigilance activities at different levels;

(xxii) "pharmacovigilance system" means a system used by the registration holder to fulfil the tasks and responsibilities listed in these rules and is designed to monitor the safety of therapeutic goods and detect any change to their risk-benefit balance;

(xxiii) "pharmacovigilance risk assessment expert committee" or "PRAEC" means a committee constituted under rule 9;

(xxiv) "pharmacovigilance system master file" or "PSMF" means a detailed description of the pharmacovigilance system used by the registration holder with respect to one or more authorized therapeutic goods;

(xxv) "provincial pharmacovigilance centre" or "PPC" means the centre established by each provincial government and administrative territory for the execution of pharmacovigilance activities;

(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) "public health programmes" or "PHPs" are the health programmes at the level of National, Provincial or Administrative Territory that are designed for prevention and eradication of disease and prolonging health through organized efforts of the society;

(xxviii) "registration holder" means manufacturer or importer possessing registration or enlistment of therapeutic goods, as the case may be;

(xxix) "risk management plan" or "RMP" means a detailed description of the risk management system which includes a set of pharmacovigilance activities and interventions that are designed to identify, characterize, prevent or minimize risks relating to a drug 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;

(xxx) "safety specification" means safety provision of a therapeutic good defined or compiled by registration holders, submitted initially at the time of registration as part of the dossier and updated accordingly as per international revision of safety specification of the active ingredient or in accordance with national regulatory decisions;

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

(xxxii) "signal" means reported information on a possible causal relationship between an adverse event and a drug or a therapeutic good, 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;

(xxxiii) "significant safety issues" include 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 therapeutic good is marketed;

(d) withdrawal or suspension of availability of the therapeutic good in another country based on signals indicating seriousness and quality of information;

(e) issues identified by the registration holder as a result of their own signal management process once the assessment has been completed and actions are proposed;

(f) significant safety results from post-marketing clinical studies;

(g) safety issues due to misinformation in the therapeutic good information;

(h) safety issues related to the use outside the terms of the therapeutic good information or directions for use;

(i) safety issues concerning the quality of any raw materials used in the therapeutic good;

(j) a quality defect, adulteration, contamination or spurious therapeutic good associated with a serious adverse reaction report; and

(k) issues for which the registration holder is considering sending a direct healthcare professional communication (DHPC) in any country where the therapeutic good is being marketed;

(xxxiv) "solicited report" means that report which is derived from an organized data collection system, which includes clinical trials, registry, post-approval named patient use program, other patient support and disease management program, surveys of patient or healthcare providers or information gathering on efficacy or patient compliance;

(xxxv) "spontaneous reporting" means,-

(a) a system whereby case reports of adverse drug events are voluntarily submitted from health professionals and registration holders to the national regulatory authority; or

(b) unsolicited communication by a healthcare professional or consumer to a company, regulatory authority or other organization such as World Health Organization, and poison control centre that describes one or more adverse drug reactions in a patient who was given one or more therapeutic goods and that does not derive from a study or any organized data collection scheme;

(xxxvi) "therapeutic good safety alerts" means safety information as an alert for a specific audience issued by NPC or PPC;

(xxxvii) "therapeutic good sale point" means a point of sale of drugs or therapeutic goods, defined in individual Drug Rules of respective Provinces and administrative territories, such as a medical store, pharmacy or wholesale; and

(xxxviii) "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 therapeutic good; or

(b) an adverse reaction, the nature or severity of which is not consistent with the applicable product information or safety specification for a registered therapeutic good.

3. National pharmacovigilance centre.– (1) The Drug Regulatory Authority of Pakistan (DRAP) shall establish and notify the NPC at its headquarters in Islamabad, for the execution of pharmacovigilance activities in the country and for effective coordination at provincial levels and administrative territories levels and at international level including World Health Organization (WHO).

(2) The NPC shall work under the Division of Pharmacy Services, DRAP, having Director, Division of Pharmacy Services as Head of the centre and shall have enough full-time technical staff, infrastructure and technical facility to perform the pharmacovigilance activities.

(3) The NPC shall acquire a national database and shall ensure that the procedure and tools are in place for collection, assessment and investigation of safety issues. The national database shall be linked to World Health Organization Uppsala Monitoring Centre (WHO-UMC) and with PPCs and PHPs as the case may be.

(4) The NPC may have the subscription of online scientific literature databases and of other tools for coding adverse drug reactions and drug interactions. It may also subscribe to other software or tools if desired for its proper functioning.

4. Functions of NPC.– (1) The functions of the NPC shall be to, -

(i) collect and evaluate ADRs and AEs occurring in the context of spontaneous reporting and active surveillance;

(ii) collect pharmacovigilance data of spontaneous reporting from registration holders, PPCs, PHPs as the case may be, from healthcare professionals and consumer or patients directly;

(iii) take such measures to ensure that the minimum criteria for reporting have been fulfilled during the reporting of ADRs, that include an identifiable reporter, an identifiable patient, one or more suspected reactions and one or more suspected therapeutic goods;

(iv) monitor the database to determine whether there are new risks and whether those risks impact the risk-benefit balance of drugs or therapeutic goods;

(v) involve PPCs, PHPs, healthcare professionals and patients or consumers as appropriate, in the follow up of the incomplete ADRs report;

(vi) collect and analyse reports of AEFI from PPCs, PHPs and registration holders;

(vii) ensure that the causality assessment of the AEs has been performed, where possible, before sending reports to WHO-UMC. A mechanism for inclusion or exclusion in this regard may also be developed;

(viii) periodically evaluate the database for new signals and submit these signals to PRAEC and further coordinate with the concerned Board or Committee to take a course of action as per the decision of PRAEC;

(ix) take appropriate measures to encourage PPCs, PHPs, registration holders patients and healthcare professionals to report ADRs and AEs to the NPC;

(x) facilitate patient and healthcare professional reporting through the provision of alternative reporting formats in addition to the hard format of reporting forms;

(xi) ensure that the public is given important information on pharmacovigilance concerns and risks relating to the use of therapeutic goods in a timely manner through one of the following modes i.e. therapeutic goods safety alerts, healthcare advisory or newsletters on a website and through other means of publicly available information as necessary;

(xii) take necessary measures to ensure that a registration holder who fails to discharge the obligations laid down in these rules is subject to effective and appropriate regulatory actions as determined by PRAEC;

(xiii) arrange training sessions for POs of PPCs and PHPs for proper reporting of ADRs and AEs through the National database;

(xiv) coordinate with provinces and administrative territories for the establishment of their pharmacovigilance centres at the provincial and hospital level and integration with a central database of NPC;

(xv) take necessary measures for training or capacity building of the POs of NPC regarding data collection, causality assessment, signal detection and risk management etc;

(xvi) frame guidelines of pharmacovigilance for different stakeholders i.e. registration holders, healthcare professionals and patients and shall also develop guidelines for planning, conducting, monitoring and reporting of pharmacovigilance activities;

(xvii) develop standard operating procedures for different processes of pharmacovigilance;

(xviii) conduct good pharmacovigilance practices inspection of registration holders;

(xix) develop ADRs or AEs reporting forms for healthcare professionals, registration holders and patients;

(xx) collaborate with different stakeholders such as PPCs, PHPs and registration holders for effective implementation of pharmacovigilance programme in the country;

(xxi) develop a mechanism for communication with stakeholders on the activities of pharmacovigilance and submit pharmacovigilance data to WHO-UMC;

(xxii) review causality assessment of pharmacovigilance data shared by PPCs and PHPs; and

(xxiii) nominate coordinators for communication with WHO-UMC, PPCs and PHPs etc.

5. Provincial pharmacovigilance centre.– (1) Each Provincial government and administrative territory shall establish a PPC under the respective health department for therapeutic goods safety monitoring and execution of pharmacovigilance activities in the province and territory. The PPC shall have enough full-time technical staff, infrastructure and technical facility to perform the pharmacovigilance activities.

(2) Each provincial government and administrative territory shall nominate a focal person, who shall either be the head or any other PO of the respective PPC for communication and coordination with NPC and hospitals.

(3) Each provincial government and administrative territory shall constitute a provincial pharmacovigilance committee for evaluation of risks associated with the use of therapeutic goods, causality assessment and signal detection etc.

(4) The functions of PPC shall be to-

(a) develop a reporting system for collection of ADRs in line with the reporting system of NPC;

(b) collect pharmacovigilance data from public and private sector hospitals under the respective province and administrative territory;

(c) collect pharmacovigilance data from therapeutic goods sale points;

(d) coordinate with hospitals and collect pharmacovigilance data from their centres;

(e) perform causality assessment of AEs reports submitted to PPC and review causality assessment of collected ADRs reports before submitting the same to NPC;

(f) report to the NPC all serious adverse drug reactions within fifteen calendar days of receiving of a report;

(g) submit to the NPC non-serious ADRs on monthly basis;

(h) arrange awareness sessions, campaigns or take other necessary measures to sensitize healthcare professionals and patients to promote spontaneous reporting culture in the province and administrative territory;

(i) arrange pharmacovigilance training of public sector hospitals of the province and coordinate for their proper functioning;

(j) issue therapeutic good safety alerts within the province and territory and submit to the NPC details of issued alerts within three calendar days;

(k) participate in meetings of PRAEC, if required by NPC;

(l) perform any other function assigned by NPC; and

(m) provide any other information and work in coordination with NPC on matters necessary for the implementation of these rules.

6. Pharmacovigilance officer.– (1) For effective implementation of pharmacovigilance programme in the country, PO having basic qualification of Pharm-D or B-Pharm or MBBS shall be notified by the, -

(a) DRAP in case of NPC;
(b) the respective health department of the Province and administrative territory, in case of PPC and public sector hospitals. In case of Islamabad the notification authority may be Ministry or District Health Office;
(c) respective PHP;
(d) administration of autonomous public sector hospitals; and
(e) administration of private sector hospitals.

(2) POs shall be responsible for effective implementation of pharmacovigilance programme in the country at the National, provincial and administrative territory, public health programme and public and private sector hospitals' levels in accordance with duties assigned to them.

(3) Following functions shall be assigned to the POs at the level of NPC, namely: -

(a) collection, follow-up, validation and assessment of reports followed by the performance of causality assessment of AEs in groups or teams;
(b) Initial signal detections in groups or teams and communication of risk-minimization measures;
(c) processing of therapeutic goods safety alerts;
(d) communication and coordination with WHO-UMC, PPCs, PHPs and registration holders etc.

(4) Following functions shall be assigned to the POs at the level of PPCs namely:

(a) collection, follow-up, validation, and assessment of reports followed by causality assessment of AEs in groups or teams;
(b) Initial signal detection in groups or teams and communication of risk-minimization measures;
(c) processing of therapeutic goods safety alerts;
(d) communication and coordination with NPC and public and private sector hospitals of the province and administrative territory.

(5) POs at the level of secondary and tertiary care public and private sector hospitals shall perform the functions of collection, completeness, follow-up, causality assessment and reporting of AEs and ADRs.

(6) POs at PHPs shall perform functions of collection, completeness, follow-up, causality assessment and reporting of ADRs, AEs or AEFI and shall also participate in pharmacoepidemiological studies and cohort event monitoring.

7. Pharmacovigilance activities in public health programmes or PHPs.– (1) Each PHP shall establish a pharmacovigilance centre at the National level, which shall be integrated within provincial and administrative territory chapter of that programme.

(2) PHP shall nominate focal persons for communication and coordination with NPC and with the provincial chapter and administrative territory of the PHP.

(3) Enough and full-time POs must be notified at National, provincial and site levels.

(4) PHP shall constitute an expert safety review panel (ESRP) at the National level, which shall comprise pharmacists, physicians, disease experts and other members which it may desire. The ESRP shall perform functions of drugs or therapeutic goods safety monitoring, reviewing causality assessment of ADRs and AEFI, signal detection and shall establish procedures for pharmacoepidemiological studies and cohort event monitoring.

(5) PHP shall develop a system of active surveillance for all new drugs and other drugs that are specific to that PHP and are associated with risks i.e. priority drugs.

(6) PHP shall conduct or arrange specific training of the POs and other staff involved in pharmacovigilance in respect of data collection, causality assessment, active surveillance, risk-minimization, cohort event monitoring and pharmacoepidemiological studies. In addition, PHPs shall organize awareness campaigns and develop educational material for patients, to facilitate patients' reporting to the prescribers.

(7) PHP shall submit to the NPC the pharmacovigilance data as per the following frequencies, namely, -

(a) non-serious AEs, ADRs and AEFIs shall be submitted on monthly basis; and
(b) serious AEs, ADRs and AEFIs shall be submitted within fifteen calendar days.

8. Pharmacovigilance in public and private sector hospitals.– (1) At each secondary and tertiary care public and private sector hospital, a pharmacovigilance centre shall be established by the health department of the respective province or administrative territory or by the administration of public and private hospitals as the case may be.

(2) At least one PO must be notified at the level of a two hundred bedded hospital. The number of POs may be increased based on the size of the hospital i.e. number of beds.

(3) A pharmacovigilance committee shall be constituted in the hospital, which shall at least comprise a medical specialist, a pharmacist, a physician and a nurse. The committee may opt disease experts of the hospitals on case to case basis. The purpose of this committee shall be drug or therapeutic goods safety monitoring and causality assessment of AEs. This committee shall develop spontaneous reporting trends and culture in the hospitals by sensitizing health care professionals, medical students and patients.

(4) Secondary and tertiary care public and private sector hospitals shall submit to PPC the pharmacovigilance data as per the following frequencies, namely, -

(a) non-serious AEs and ADRs shall be submitted on monthly basis; and
(b) serious AEs and ADRs shall be submitted within fifteen calendar days.

9. Pharmacovigilance risk assessment expert committee (PRAEC).– (1) The DRAP shall notify PRAEC for risk management associated with the use of therapeutic goods, i.e. signal detection, causality assessment, risk minimization, communication related to risk of adverse events and evaluation of periodic reports etc.

(2) PRAEC shall ensure that risks associated with the use of therapeutic goods are detected as early as possible and take necessary steps to minimize these risks and give recommendations to the concerned Board or Committee for further regulatory actions.

(3) PRAEC shall consist of the following, namely: -

(a) To be notified by DRAP from the members of PRAEC for three years i.e. tenure of the committee;	*Chairman*
(b) Director, Division of Pharmacy Services, ex-officio Co-Chair;	*Co-Chair*
(c) Additional Director or Deputy Director, Division of Pharmacy Services, or Pharmacovigilance to be	*Member cum-Secretary*

nominated by Authority who shall be its ex-officio Secretary;

(d) One professor of pharmacy practice, to be nominated by DRAP;	*Member*
(e) Expert in basic pharmacology having at least ten-year experience to be nominated by DRAP;	*Member*
(f) Expert of clinical pharmacology having at least ten-year experience to be nominated by DRAP;	*Member*
(g) Expert of clinical pharmacy or clinical pharmacist having at least ten-year experience in a hospital to be notified by DRAP;	*Member*
(h) Expert of medicine or medical specialist having at least ten-year experience in a hospital to be nominated by DRAP;	*Member*
(i) Expert of epidemiology or pharmacoepidemiology having at least ten-year experience to be nominated by DRAP;	*Member*
(j) Expert of toxicology or forensic medicines having at least ten-year experience to be nominated by DRAP;	*Member*
(k) Expert of pharmacovigilance at least ten-year experience in the conduct of pharmacovigilance activities to be nominated by DRAP;	*Member*
(l) Expert of clinical trials or drug research having at least ten-year experience to be nominated by DRAP;	*Member*
(m) Expert of biologicals having at least ten-year experience to be nominated by DRAP; and	*Member*
(n) Expert of biostatistics having at least ten-year experience to be nominated by DRAP.	*Member*

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

(5) The committee may opt experts of any speciality for a specific meeting, to assess any particular case, as and when required.

(6) The meeting of the PRAEC may be held at such time as the committee may deem appropriate or on a quarterly basis due to the detection of risk associated with the use of therapeutic goods. The Secretary may also coordinate with the Chairman, who may at any time call a meeting if there is an important matter/emergency for its consideration.

(7) In case of such risks arising from the use of therapeutic goods having a major impact on the public at large or the in case of a public health emergency, the meeting of PRAEC may be called within 24 hours through any means for the initial assessment of the risk and to take appropriate risk minimization measures to prevent the public from harm.

(8) In absence of the Chairman, the Co-Chair will preside over the meeting.

(9) The quorum for holding a meeting of the committee shall be one-third of its total membership.

10. Functions of PRAEC.– (1) The functions of PRAEC shall be as follows, namely:-

(a) Cover all aspects of risk management associated with the use of therapeutic goods, i.e. signal detection, assessment, risk minimization and communication related to risks of adverse drug reaction, Perform the initial analysis and prioritization of signals which are detected and validated by NPC.

(b) on the basis of concerns resulting from the evaluation of data from pharmacovigilance activities, recommend to NPC to inform pharmacovigilance stakeholders through available means, where it considers necessary that a new contraindication, a reduction in the recommended dose or a restriction to the indication of therapeutic goods etc. is necessary;

(c) verify whether the safety concern relates to a therapeutic good or its whole class, it shall extend the scope of procedures accordingly;

(d) evaluate and assess PBRER and RMP or nominate a panel of experts or appoint a rapporteur for this purpose. A rapporteur shall be appointed by the PRAEC from amongst its members or from the relevant field of expertise to prepare recommendations or advice, as applicable, together with an assessment report, if appropriate, on the relevant issue raised to the PRAEC;

(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, Committee or Division for variation, suspension, revocation, market withdrawal, change in safety specification or any other action which it considers appropriate;

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

(g) in the case of assessment and evaluation of PBRER, RMP and final report of PASS and post-authorization efficacy study or report of the rapporteur, if it is found that there is risk associated with the drug, PRAEC may recommend a regulatory action to the concerned board, committee or division, which may include suspension of licence, revocation and cancellation of registration, market withdrawal, change in label or safety specification or any other action which it considers appropriate;

(h) shall consider or recognize and if deemed appropriate shall implement within Pakistan the pharmacovigilance relevant decisions of other countries and of regional and international bodies of the following nature, namely:-

(i) modification or removal of an approved indication of therapeutic good due to safety reasons;
(ii) addition of contraindications;
(iii) imposition of post-authorization safety or efficacy studies due to safety reasons;
(iv) major changes in the statements of warning, precaution or adverse reactions in the product information;
(v) withdrawal or suspension of therapeutic good in other countries due to safety reasons; and
(vi) any other safety information or decision which it considers appropriate, for ensuring the safety of the public;

(i) whenever possible, give consensus on scientific recommendation/advice. If such a consensus cannot be reached, the scientific recommendations/advice shall be adopted if supported by an absolute majority of the members of the PRAEC (i.e. favourable votes by at least half of the total members eligible to vote plus one). The members expressing divergent positions shall provide in writing, stating clearly the reasons on which they are based.

(j) Approve nomination of a team for good pharmacovigilance practices inspection of registration holders.

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

11. Obligations of registration holders.– (1) Every registration holder shall establish a pharmacovigilance system for the fulfilment of pharmacovigilance activities in accordance with the directives of NPC. They shall evaluate all information scientifically, consider options for risk minimization or prevention and take appropriate measures. The registration holder shall collect, record, store, maintain and analyse the AEs, AEFI and ADRs of all therapeutic goods registered in its name, to monitor their safety. Registration holder shall report to NPC pharmacovigilance data including zero events as per format approved by DRAP and timelines provided in these rules.

(2) The registration holder shall appoint a qualified person for pharmacovigilance (QPPV), having such experience and qualification as defined by DRAP, who shall be responsible for pharmacovigilance system and shall reside and operate in the country, and shall also be responsible for establishment and maintenance of the pharmacovigilance system. In the case of a multinational registration holder, the nomination of a local safety officer will also be accepted, who shall reside and operate in the country. The registration holder shall submit the name and contact details of the qualified person to NPC.

(3) The registration holder shall collect ADRs, AEFIs and AEs and report to NPC in the following conditions, namely:-

(a) passive surveillance;
(b) active surveillance; and
(c) post-authorization studies.

(4) Registration holder shall maintain the pharmacovigilance system master file (PSMF) on a format approved by DRAP and submit it to NPC within forty-five calendar days when directed. The PSMF shall also be actively submitted to NPC when there is an update.

(5) Registration holder shall record all AEs, ADRs and AEFIs with therapeutic goods registered on its name in the country which is brought to its attention, whether reported spontaneously by a patient or healthcare professional or occurring in the context of a post-authorization study and shall not refuse to consider reports of suspected serious and non-serious ADRs received through email or by telephone from patients and healthcare professionals and shall report to NPC on a format approved by DRAP and as per the following timeline, namely:-

(a) submit to NPC database domestic serious AEs, ADRs and AEFIs within fifteen calendar days following the day on which registration holder concerned gained knowledge of the event;
(b) submit to NPC database non-serious AEs, ADRs and AEFIs that occur in the country, within ninety calendar days following the day on which the registration holder concerned gained knowledge of the event;
(c) submit to NPC database zero event report within ninety calendar days; and
(d) registration holder shall monitor all medical literature and report any domestic ADRs within fifteen or ninety calendar days based on its seriousness.

(6) Registration holder shall establish procedures in order to obtain accurate and verifiable data for the scientific evaluation of suspected adverse reaction reports, shall collect follow-up information on these reports and shall submit to NPC database.

(7) Registration holder shall conduct voluntarily non-interventional specific studies on the efficacy and safety if it is found that there is risk associated with the drug or if it is imposed by the Registration Board on the recommendation of PRAEC. 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) Registration holder shall submit PBRER for all new drugs as per International Council on Harmonization (ICH) format, after its registration in Pakistan in line with the international frequency that is based on its IBD.

(9) Registration holder shall submit PBRER as per the following timelines, namely:-

(a) 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;

(b) PBRER covering intervals in excess of twelve months within ninety calendar days of DLP; and
(c) adhoc PBRER within ninety calendar days of DLP, unless otherwise specified in the adhoc request. Adhoc PBRER are reports outside the routine reporting requirements and may be requested by Registration Board or NPC due to safety risk or any other reason. Where an adhoc 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 registration holder.

(10) By way of derogation from sub-rule (8), the 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 committee or NPC on the basis of concerns 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) Registration holder shall submit to the Registration Board RMP for all new drugs along with drug registration application. Moreover, ad hoc RMP may be submitted by the registration holder either voluntarily or if directed by NPC or PRAEC in case of a specific safety issue.

(12) Registration holder shall report to NPC and concerned board or committee any identified significant safety issue as soon as possible within fifteen calendar days of the awareness of the issue. Registration holder shall also inform the NPC in the event of new risks or risks that have changed or changes to the risk-benefit balance have been detected

(13) Registration holder shall forward to NPC within fifteen calendar days of its awareness on format approved by DRAP those reports which are associated with adverse outcomes as a result of an overdose, abuse, misuse, off-label use, occupational exposure and medication error of therapeutic goods.

(14) Lack of therapeutic efficacy in case of vaccines, contraceptives, antimicrobials and drugs used in critical conditions or life-threatening situations shall be reported to NPC within fifteen calendar days on format approved by DRAP.

(15) Registration holder shall issue direct healthcare professional communication (DHPC) to inform the health professionals about new risks that may affect the patient which has come to its knowledge either due to its self-assessment or detected by NPC.

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AAMAR LATIF,
Deputy Director (Legal Affairs).