United Journal of Pharmacovigilance

# Writing Development Safety Update Reports for an Investigational New Drugs

Pushpraj Prafulla Gawai

Author Biography

**Pushpraj Prafulla Gawai**

Pushpraj Prafulla Gawai is currently a Senior Periodic Safety Reports Writer at Macleods Pharmaceuticals Ltd., Mumbai, India. He received his Masters in Pharmacology from prestigious University Department of Pharmaceutical Sciences, Nagpur University, India. Pushpraj qualified GPAT National level exam (Graduate Pharmacy Aptitude Test) 2013 and 2014 and awarded JRF for Masters from All India Council for Technical Education (AICTE). His post graduate project in collaboration with Creighton University, Omaha, Nebraska, USA involved the 'Antipsychotic - like profile of CIQ isomers in animal models of schizophrenia' published in reputed journal.

His professional experiences includes post-marketing surveillance for vaccines, safety monitoring and evaluation of post-marketing drugs and anticancer investigational new drugs; including authoring, reviewing and submissions of DSUR, PBRER, PSUR, RMP, ACO and ADR reports.

He has published his 05 articles in international journals and 04 based on pharmacovigilance. He continues to explore the field of drug safety for generic as well as branded medications including vaccines. Pushpraj recently received Honorary Membership of London Journals Press.

Corresponding Aurthor:
Pushpraj Prafulla Gawai, Senior Aggregate Reports Writer, India.
Email: pushprajgawai@gmail.com, Phone No: +91 9561217140.

Article Information

Article Type: Review Article
Article Received: 26-11-2020
Article Accepted: 21-12-2020
Article Published:
Vol:1, Issue:1

OPEN ACCESS

Keywords:

Pharmacovigilance, Aggregate report, DSUR, PBRER, investigational drug, Identified Risk and Potential risk.

## Abstract

The Development Safety Update Report (DSUR) is a standard document for periodic reporting covering safety information of drugs, biologicals, vaccines, and combination products under clinical development among the ICH regions. DSUR is also prepared and submitted for marketed drugs that are under further clinical study for another indication. Every investigational drug need to undergo all phases of a clinical trial to prove its safety and efficacy. The DSUR is an important tool to study the safety and risk profile of an investigational drug periodically. The DSUR aims to provide periodic analysis of the emerging safety profile of an investigational drug; actions proposed or being taken, any changes in IB, subject exposure, lack of efficacy from trials and safety findings from non-interventional studies of an investigational drug. In clinical practice, monitoring of subjects is less intensive, broader range of subjects are treated (age, co-morbidities, drugs, genetic abnormalities), and events too rare to occur in clinical trials may be observed. Such factors underlie the need for continuous evaluation of emerging risk, new safety, efficacy, and effectiveness information throughout the development of an investigational drug, and such information should be reported in DSUR periodically. This article gives an overview of the importance, context, purpose, scope, sections, timelines for regulatory submissions of DSUR, which will advantageous to all periodic reports writers and pharmacovigilance professionals.

## Introduction:

During the clinical trials of an investigational drug, timely evaluation of safety data is crucial to the ongoing assessment of risk to trial subjects. It is also important to inform health authorities, ethics committees and IRB at regular intervals about the results of analyses risk and the evolving safety profile of an investigational drug. Currently, laws and regulations of some ICH regions require periodic submission of a DSUR to regulatory authorities to describes the status of ongoing individual investigations, manufacturing changes and overall development status and plans [1].

The main objectives of this report are to provide an assessment of relevant safety, efficacy, and risk data received during the reporting period for the drug under investigation, whether or not it is marketed by To analyze whether the information provided by the sponsor during the reporting period is consistent with prior knowledge of the safety


Citetion: Pushpraj Prafulla Gawai. / United Journal of Pharmacovigilance 1(2020):1-12

of the investigational drug; To identify potential safety problems that may affect the health of subjects in clinical trials; To summaries the current understanding and management of potential and identified risks; To provide an update on the status of clinical investigation/development program and study results [1 , 2].

A DSUR should be precise and concise and provide information to assure health authorities that sponsors are continuously monitoring and evaluating the evolving safety profile of the investigational drug throughout clinical trials. All safety issues observed during the reporting period should be discussed in the DSUR. DSUR main focus on safety and efficacy related data and findings from interventional clinical trials of drugs and biologicals that are under investigation, whether or not they have a marketing approval. After marketing approval for one indication, clinical trials of a drug may continue for another indication, so relevant safety data from post-marketing studies should also be added in the DSUR. The data included in the DSUR based on the investigational drug and provide information on comparator drug when relevant to the safety of trial subjects [1 , 2].

New risk identified during clinical trials communicate with regulatory authority, principal investigators, and ethics committees associate with an investigational drug is carried out using several tools, including the investigators brochure (IB) and expedited reporting of suspected unexpected serious adverse reactions (SUSARs), expedited individual case safety report (ICSR). These safety communication tools may lack in reporting periodicity, data transparency, clarity, or risk message integrity. However, DSUR has accurate periodicity due to its timely data lock point and efficiency in documenting a sponsor's latest comprehensive and integrated perspective on the safety of an investigational drug because its completeness like line listing of recent SUSAR cases from ongoing clinical trials reported during the reporting period in the cumulative tabulation, it also covers all already SUSARs/ ICSRs reported and also have updated IB attached [3].

The preparation of DSUR or PSUR aggregate safety reports usually falls to the pharmacovigilance and maximum safety data required for the preparation of DSUR, including information based on SUSARs and published literature with new safety and efficacy findings, should be readily available to sponsor form company's safety database used for regulatory reporting. Those reports present in the safety database have already been reviewed and analyzed when they were submitted to comply with expedited safety reporting requirements of regulatory authorities [4].

This guidelines document gives important points that are considered during evaluating new safety data in the Evaluation of the Risks (e.g., changes in already identified risk, newly identified safety issues, symptoms, signs, and laboratory evidence). The Benefit-Risk Assessment is an important point in assessing benefits and the identified risks in accords to the previous submitted DSUR. To identify any changes with respect to previous knowledge of safety, efficacy and risks profile, sponsor have to describe how the identified risks have been managed in the clinical trials and detail risk management actions planned to address any emerging safety, and efficacy issues. The Summary of Important Risks, which need to be continuously analyses and updated from DSUR to DSUR, which provide cumulative list of important identified and potential risks [5].

Drugs safety and risk monitoring during clinical development is an essential part of Pharmacovigilance like elixir sulfanilamide tragedy of 1937, and in the late 1950s and early 1960s, more than 10,000 children were born with deformities due to thalidomide as a consequence of inadequate safety and risk data of both drugs from clinical trials. Now the patient safety is one of the important areas during clinical trials [6].

## DISCUSSION

The objective of DSUR:

The main objective of a DSUR is 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, by examining whether the information obtained by the sponsor during the reporting period is in accordance with previous knowledge of the investigational drug's safety describing new safety issues that could have an impact on the protection of clinical trial subjects summarizing the current understanding and management of identified and potential risks providing an update on the status of the clinical investigation/development program and study results [1,2].

### DSUR for single active moiety and combined products:

A single DSUR including safety data from all clinical trials conducted with the drug should be prepared for an investigational drug and includes data from all indications, all dosage forms, all intended populations.

A Single DSUR should be prepared for fixed-dose combination products used in clinical trials (The product contains minimum of two active ingredients in a single dosage form). When the sponsor of trails is conducting clinical trials with individual drugs(s) from the fixed-dose combination, separate DSUR should be prepared and submitted for both individual drugs(s) [1,2].

### The DSUR includes safety information of INDs:

The DSUR included information on the safety of investigational drugs received from all trials conducted during the reporting period. The DSUR should also include significant other findings pertinent to the safety of the investigational drug, including findings from Observational

or epidemiological studies; Nonclinical studies (toxicological and in vitro studies); Data from other DSURs, if applicable to the INDs; any changes of Manufacturing or microbiological data; published clinical studies; lack of efficacy data from Clinical trials; or any other relevant safety findings from drug development process for products in the same therapeutic class; clinical trials conducted by a co-development partner, if permitted by the contractual agreement [1] & [2].

## When and Where to submit DSUR:

A DSUR should be prepared after the first authorization of a clinical trial worldwide i.e., DIBD. The first DSUR can be submitted to an earlier than 1 year, but the covered reporting period should not be longer than 1 year. In many countries, the DSUR has submitted annually.

DSUR needs to be submitted for a clinical trial that reached its long-term follow-up phase IV clinical trials. No separate DSUR for a comparator, placebo or Non-IMP is not required. However, relevant safety information of the above-mentioned drug types (comparator, NIMP or placebo) should necessarily be addressed in the DSURs of the investigational drugs.

There is a single, harmonized Developmental International Birth date (DIBD), the date of the first authorization of a clinical trial in any country worldwide for the investigational drug, or an assign date given without authorization to start clinical trials in any country.

The data lock point (DLP) for a DSUR is the last day of the reporting period.

For this process, the company requires the regulatory group to convey this information to all health authorities to a harmonized birth date for submission for DSURs. There is a fixed timeline for submission of DSURs, 60 calendar days after data lock-point. Format and Content of DSUR described in Table 1 [1 , 8].

**Table 1:** Format and Content of DSUR

| Sr. No. | Component of DSUR | Information to be included in DSUR |
|---|---|---|
| | Title page | The title page of the DSUR should include the following information:<br>DSUR number (reports should be numbered sequentially);<br>• Investigational /drug(s);<br>• Reporting period;<br>• Date of the report;<br>• Sponsor(s) name(s) and address(es);<br>• Statement on the confidentiality of the information included in the DSUR;<br>• A cautionary statement that the DSUR includes unblinded information, if applicable. |
| | Executive summary | This section should provide a concise summary of the important information contained in the report. The following information should be included in the Executive Summary:<br>• Introduction – report number and reporting period;<br>• Investigational drug(s) – mode(s) of action, therapeutic class(es), indication(s), dose(s), route(s) of administration, formulation(s);<br>• Estimated cumulative exposure of clinical trial subjects;<br>• Marketing approval(s)? (yes/no) – If yes, number of countries<br>• Summary of overall safety assessment (based on section 18 of the DSUR);<br>• Summary of important risks (based on section 19 of the DSUR);<br>• Actions taken for safety reasons including significant changes to IB;<br>• Conclusions. |
| | Table of contents | |

| | | |
|---|---|---|
| 1 | Introduction | This section should include:<br>• DIBD or IBD (as applicable);<br>• Reporting period and sequential number of the report; Investigational drug(s) – mode(s) of action, therapeutic class(es), dose(s), route(s) of administration, formulation(s);<br>• A brief description of the indication(s) and population(s) being studied;<br>• A short summary of the scope of the clinical trials covered by the report (e.g., all trials with the investigational drug, indication-specific trials, trials with combination products);<br>• A brief description and explanation of any information that has not been included in the DSUR (e.g., when written agreements with a partner company do not provide for exchange of all safety data);<br>• The rationale for submission of multiple DSURs for the investigational drug, if applicable. |
| 2 | Worldwide Marketing Approval Status | This section should provide a brief narrative overview including: date of first approval, indication(s), approved dose(s), and where approved, if applicable. |
| 3 | Actions Taken in the Reporting Period for Safety Reasons | This section should include a description of significant actions related to safety that have been taken during the reporting period by the sponsor, regulators, data monitoring committees (DMC) or ethics committees that had an impact on the conduct of a specific clinical trial(s) or on the overall clinical development programme. The reason(s) for each action should be provided if known. Relevant updates to previous actions should also be summarised in this section.<br>Actions related to investigational drugs:<br>• Refusal to authorise a clinical trial for ethical or safety reasons;<br>• Partial or complete clinical trial suspension or early termination of an ongoing clinical trial because of safety findings or lack of efficacy;<br>• Recall of investigational drug or comparator;<br>• Failure to obtain marketing approval for a tested indication including voluntary withdrawal of a marketing application;<br>• Risk management activities, |
| 4 | Changes to Reference Safety Information | This section should list any significant safety-related changes to the IB or other reference safety information within the reporting period. Such changes might include information relating to exclusion criteria, contraindications, warnings, precautions, serious adverse drug reactions, adverse events of special interest*, interactions, and any important findings from non-clinical studies (e.g., carcinogenicity studies). Specific information relevant to these changes should be provided in the appropriate sections of the DSUR. |
| 5 | Inventory of Clinical Trials Ongoing and Completed during the Reporting Period | This section should provide a brief overview of the clinical trials ongoing and completed by the sponsor in the reporting period, with detailed information presented in a table as an appendix. Separate tables can be provided by indication, formulation, and study population, if appropriate. The table(s) should include the following information for each clinical trial:<br>• Study ID (e.g., protocol number or other identifier);<br>• Phase (I, II, III, or IV);<br>• Status: Ongoing (clinical trial has begun; has begun but is currently on hold; has concluded but clinical study report has not been finalised); Completed (clinical study report is finalised);<br>• Countries/regions where there is at least one investigational site for the protocol;<br>• Abbreviated study title;<br>• Design (uncontrolled, controlled, open, single blind, double blind, parallel, crossover, etc.);<br>• Dose and regimen of investigational drug and any comparators;<br>• Study population as appropriate (age; sex; indication(s); specific patient groups, e.g., trial subjects with impaired renal function or trial subjects resistant to treatment);<br>• Date of clinical trial start (as defined by the sponsor, e.g., first visit of first patient(FVFP));<br>• Planned enrolment for study as a whole;<br>• Estimates of cumulative numbers of exposed subjects for each treatment arm, where available. The actual enrolment numbers for open or completed trials, and/or an estimate based on the randomisation scheme for blinded trials, should be provided. |

| | | |
|---|---|---|
| 6 | Estimated Cumulative Exposure<br><br>6.1 Cumulative Subject Exposure in the development Programme<br><br><br><br><br><br>6.2 Patient Exposure from Marketing Experience | Sections 6.1 and 6.2 of the DSUR should provide information on cumulative exposure in clinical trials and the marketed setting, respectively. An estimation of cumulative subject exposure can help provide context for the cumulative summary tabulations of serious adverse events (SAEs), and the overall assessment of safety. Tabular format may include in appendices separately.<br><br>This section should include the cumulative number of subjects from ongoing and completed clinical trials; The number exposed to the investigational drug, placebo, and/or active comparator(s) since the DIBD. Sub grouped by age range, sex, and racial group for the development programme when the data are available.<br><br>Cumulative number of subjects exposed to the investigational drug from ongoing and completed clinical trials, sub grouped by age range, sex, and racial group for the development programme when the data are available.<br><br>This section should also include an explanation of the sponsor's rationale for selecting the method to estimate subject exposure, and the limitations of that method.<br><br>If the investigational drug is marketed by the sponsor, the DSUR should include an estimate of the cumulative patient exposure in the marketed setting, based on the information provided in the most recent PSUR or other suitable data source, with an explanation of the method(s) used to determine the estimate. |
| 7 | Data in Line Listings and Summary Tabulations<br><br><br><br>7.1 Reference Information<br><br><br><br>7.2 Line Listings of Serious Adverse Reactions during the Reporting Period<br><br><br><br>7.3 Cumulative Summary Tabulations of Serious Adverse Events | Sections 7.1-7.3 of the DSUR should present important clinical safety information through:<br><br>Interval line listings of the SARs that were reported to the sponsor during the period covered by the DSUR; and Cumulative summary tabulations of serious adverse events that have been reported to the sponsor since the DIBD.<br><br>The line listing and tabulations should include blinded and unblinded Clinical trial data. In general, the tabulation(s) of SAEs should include only those terms that were used in defining the case as serious; they should not include non-serious events.<br><br>This section of the DSUR should specify the version(s) of the coding dictionary (eg: MedDRA) used. If applicable, it should also specify the document and version used as Reference Safety Information for determining expectedness for the tabulations, where required by national or regional laws or regulations.<br><br>This section of the DSUR should summarise how case reports were selected for inclusion in the line listings. This section should not serve to provide analyses or conclusions based on the SARs. The line listings should be provided in an appendix<br><br>Where possible the line listing(s) should include each subject only once regardless of how many SAR terms are reported for the case. If there is more than one reaction, they should all be mentioned but the case should be listed under the most serious adverse reaction (sign, symptom or diagnosis), as judged by the sponsor. It is possible that the same subject could experience different SARs on different occasions (e.g., weeks apart during aW clinical trial). Under such circumstances, the SARs can be listed separately, and a single subject can be included in a line listing more than once.<br><br>This section should refer to an appendix that provides a cumulative summary tabulation of SAEs reported in the sponsor's clinical trials, from the DIBD to the data lock point of the current DSUR. The sponsor should explain any omission of data (e.g., clinical trial data might not be available for products marketed for many years or for products acquired through a business merger). The tabulation(s) should be organised by SOC, for the investigational drug, as well as for the comparator arm(s) (active comparators,<br><br>placebo, and treatment unknown due to blinding) used in the programme. |

| | | |
|---|---|---|
| 8 | Significant Findings from Clinical Trials during the Reporting Period | Includes relevant safety information obtained during the reporting interval from MAH sponsored non-interventional studies for the active substance. The information in this section can be provided by indication, when appropriate. |
| | 8.1 Completed Clinical Trials | This section of the DSUR should provide a brief summary of clinically important emerging efficacy and safety findings obtained from clinical trials completed during the reporting period. This information can be presented in narrative format or as a synopsis. It could include information that supports or refutes previously identified safety issues, as well as evidence of new safety signals. |
| | 8.2 Ongoing Clinical Trials | If the sponsor is aware of clinically important information that has arisen from ongoing clinical trials, this section should briefly summarise the issue(s). It could include information that supports or refutes previously identified safety issues, as well as evidence of new safety signals. |
| | 8.3 Long-term Follow-up | This section should provide information from long-term follow-up of subjects from clinical trials of investigational drugs, particularly advanced therapy products (e.g., gene therapy, cell therapy products and tissue engineered products) |
| | 8.4 Other Therapeutic Use of Investigational Drug | This section of the DSUR should include clinically important safety information from other programmes conducted by the sponsor that follow a specific protocol, with solicited reporting as per ICH E2D (e.g., expanded access programmes, compassionate use programmes, particular patient use, single patient INDs and treatment INDs). |
| | 8.5 New Safety Data Related to Combination Therapies | If the DSUR is for an investigational drug that is also under development as a component of a fixed combination product or a multi-drug regimen, this section should summarise important safety findings from the combination therapy DSUR.<br>Conversely, if this DSUR is for a multi-drug therapy or fixed combination product, this section should summarise important safety information arising from trials on the individual components. |

| | | |
|---|---|---|
| 9 | Safety Findings from Non-interventional Studies | This section should summarise relevant safety information from non-interventional studies that became available to the sponsor during the reporting period (e.g., observational studies, epidemiological studies, registries and active surveillance programmes). |
| 10 | Other Clinical Trial/Study Safety Information | This section should summarise relevant safety information from any other clinical trial/study sources that became available to the sponsor during the reporting period (e.g., results from pooled analyses or meta-analyses of randomised clinical trials, safety information provided by co-development partners or from investigator-initiated trials). |
| 11 | Safety Findings from Marketing Experience | If the investigational drug has been approved for marketing in any country, this section should include a concise summary of key safety findings that have arisen from marketing experience and that became available to the sponsor during the reporting period, particularly if the findings resulted in changes to the product labelling, Investigator's Brochure, informed consent document or amendments to the product's risk management plan.<br><br>This includes not only safety findings relating to approved use but also off-label use, administration to special populations (e.g., pregnant women), medication errors, overdose and abuse. |
| 12 | Non-clinical Data | This section should summarise major safety findings from non-clinical in vivo and in vitro studies ongoing or completed during the reporting period. Implications of these findings should be discussed in the Overall Safety Assessment. |
| 13 | Literature | This section should summarise new and significant safety findings, either published in the scientific literature or available as unpublished manuscripts, relevant to the investigational drug that the sponsor became aware of during the reporting period. This section should include information from non-clinical and clinical studies and, if relevant and applicable, information on drugs of the same class. It should also summarise significant new safety information presented at a scientific meeting and published as an abstract; the sponsor should provide a copy of the abstract, if possible. |
| 14 | Other DSURs | A sponsor should prepare a single DSUR for a single investigational drug. However, if a sponsor prepares multiple DSURs for a single investigational drug (e.g., covering different indications, development programmes, or formulations), this section should summarise significant findings from the other DSURs if they are not presented elsewhere within this report. |
| 15 | Lack of Efficacy | Data indicating lack of efficacy, or lack of efficacy relative to established therapy(ies), for investigational drugs intended to treat serious or life-threatening illnesses could reflect a significant risk to clinical trial subjects and should be summarised in this section. |
| 16 | Region-Specific Information | The information in this section can be used to comply with national or regional requirements and can be provided in appendices to the DSUR.<br><br>Cumulative summary tabulation of serious adverse reactions<br><br>List of subjects who died during reporting period<br><br>List of subjects who dropped out of clinical trial in association with an adverse event<br><br>Significant Phase I protocol modifications<br><br>Significant manufacturing changes<br><br>General investigation plan for the coming year<br><br>Log of outstanding business with respect to US IND |
| 17 | Late-Breaking Information | This section should summarise information on potentially important safety findings that arise after the data lock point but while the DSUR is in preparation. Examples include clinically significant new case reports, important follow-up data, clinically relevant toxicological findings and any action that the sponsor, a DMC, or a regulatory authority has taken for safety reasons. |

| | | |
|---|---|---|
| 18 | Overall Safety Assessment<br><br>18.1. Evaluation of the Risks<br><br>18.2 Benefit-risk Considerations | The overall safety assessment should be a concise, integrated evaluation of all new relevant clinical, non-clinical, and epidemiologic information obtained during the reporting period relative to previous knowledge of the investigational drug. This assessment should consider cumulative experience, new information collected in the period covered by the DSUR and, for investigational drugs with a marketing approval, clinically significant post-marketing data. It should not summarise or repeat information presented in previous sections of the DSUR, but should provide an interpretation of the information and its implications for the clinical trial population and the development programme.<br><br>In this section, particular emphasis should be placed on interpretation of data related to newly identified safety concern or providing significant new information relative to previously identified concern. Relevant points to consider include:<br><br>• Newly identified safety issues (detailed description of adverse events or reactions; associated laboratory values; risk factors; relationship to dose, duration, time course of the treatment; reversibility; factors that could be useful in predicting or preventing reactions);<br><br>• Meaningful changes in previously identified adverse reactions (e.g., increased frequency or severity, outcome, specific at-risk populations);<br><br>• Symptoms, signs, and laboratory evidence of newly and previously identified clinically significant toxicities.<br><br>deaths that are an outcome of an adverse event;<br><br>• Study drug discontinuations because of adverse events, including abnormal laboratory values or investigations;<br><br>• Drug–drug and other interactions;<br><br>• Important non-clinical safety findings;<br><br>• Manufacturing issues that could affect risk;<br><br>• Lack of efficacy where this would place trial participants at risk;<br><br>• Any specific safety issues related to special populations, such as the elderly, children, patients with hepatic or renal impairment, or any other at-risk groups (e.g., slow or fast metabolisers);<br><br>• Pregnancy and lactation exposure and outcomes;<br><br>• Safety findings arising from experience with long-term treatment;<br><br>• Evidence of clinically significant medication errors;<br><br>• Evidence of lack of patient compliance;<br><br>• Experience with overdose and its treatment;<br><br>• Occurrences of drug misuse and abuse.<br><br>This section should provide a succinct statement on the perceived balance between risks that have been identified from cumulative safety data and anticipated efficacy/benefits and should note whether there have been any changes in this balance since the previous DSUR.<br><br>This section is not intended to be a full benefit-risk assessment of the investigational drug. |
| 19 | Summary of Important Risks | This section should provide a concise, cumulative, issue-by-issue list of important identified and potential risks.<br><br>The information in this section could provide the basis for the safety specification of a risk management plan.<br><br>The information can be provided in either narrative or tabular format. |
| 20 | Conclusions | It should briefly describe any changes to the previous knowledge of efficacy and safety resulting from information gained since the last DSUR.<br><br>The conclusion should outline actions that have been or will be taken to address emerging safety issues in the clinical development program. |

| | | |
|---|---|---|
| | Appendices to the DSUR | The DSUR should be accompanied by the following appendices, as appropriate, numbered as follows:<br>Investigator's Brochure (if required by national or regional laws or requirements);<br>Cumulative Table of Important Regulatory Requests;<br>Status of Ongoing and Completed Clinical Trials;<br>Cumulative Summary Tabulations of Demographic Data;<br>Line Listings of Serious Adverse Reactions;<br>Cumulative Summary Tabulation of Serious Adverse Events;<br>Scientific Abstracts (if relevant).<br>The DSUR should also be accompanied by the following Regional Appendices, as appropriate:<br>Cumulative summary tabulation of serious adverse reactions;<br>List of subjects who died during the reporting period;<br>List of subjects who dropped out of studies during the reporting period;<br>Significant Phase I protocol modifications with respect to a US IND;<br>Significant manufacturing changes;<br>Description of the general investigation plan for the coming year with respect to a US IND; |

## Recipients of DSUR:

Regulatory Authorities: DSUR should be submitted within 60 calendar days from the DIBD

Ethical Committee/IRB, if required: Executive Summary (plus line listing of SAEs)

Final DSUR in a Territory: will be notified with a cover letter[1 , 2].

## Relation between DSUR and PBRER:

When any product gets approval for marketing and clinical trials continue for another indication, both DSUR and PBRER/PSUR are needed to be submitting separately. The CIOMS VII Working Group "think about to align the DSUR with the PSUR as same as possible.

In such situation to avoid unnecessary duplication of works and to promote consistency, the DSUR data lock point (DIBD) can coincide with the PBRER/PSUR International Birth Date (IBD) if desired by the sponsor so that the DSUR and the PSUR can be synchronized as 13 sections of DSUR and PBRER is same, and the sponsor may interchange this information in both reports. Table 2. Shows common sections shared between DSUR and PBRER [1, 7, 9 , 10].

**Table 2:** List of DSUR Sections Shared with PBRER.

| | | |
|---|---|---|
| 1 | Worldwide Marketing Approval Status | Same as PBRER |
| 2 | Actions Taken in the Reporting Interval for Safety Reasons | Same as PBRER |
| 3 | Cumulative Subject Exposure in Clinical Trials | Same as PBRER |
| 4 | Cumulative and Interval Patient Exposure from Marketing Experience | Same as PBRER |
| 5 | Cumulative Summary Tabulations of Serious Adverse Events from Clinical Trials | Same as PBRER |
| 6 | Summaries of Significant Findings from Clinical Trials during the Reporting Period; Completed CT, Ongoing CT, Long-Term Follow-up, Other Therapeutic Use of Medicinal Product and New Safety Data Related to Combination Therapies | Same as PBRER |
| 7 | Findings from Non-Interventional Studies | Same as PBRER |
| 8 | Information from Other Clinical Trials and Sources | Same as PBRER |
| 9 | Non-Clinical Data | Same as PBRER |
| 10 | Literature | Same as PBRER |
| 11 | Lack of Efficacy in Controlled Clinical Trials | Same as PBRER |
| 12 | Late-Breaking Information | Same as PBRER if both have same DLP |
| 13 | Conclusions and Actions | Same as PBRER |

**Identified risk:** An untoward occurrence for which there is adequate evidence of an association with the medicinal product of interest.

Examples of identified risks include:

An adverse reaction adequately described in non-clinical studies and confirmed by available clinical data;

An adverse reaction observed in well-designed clinical trials or epidemiological studies for which the magnitude of the difference compared with the comparator group (placebo or active substance) on a parameter of interest suggests a causal relationship;

An adverse reaction is suggested by a number of well-documented spontaneous reports where causality is strongly supported by temporal relationship and biological plausibility, such as anaphylactic reactions or application site reactions [1].

**Potential risk:** An untoward occurrence for which there is some basis for suspicion of an association with the medicinal product of interest but where this association has not been confirmed.

## Examples of potential risks include:

Non-clinical safety concerns that have not been observed or resolved in clinical studies;

Adverse events observed in clinical trials or epidemiological studies for which the magnitude of the difference, compared with the comparator group (placebo or active substance, or unexposed group), the data is available but not sufficient to prove causality between risk and suspect drug.

A signal arising from a spontaneous adverse reaction reporting system;

An event that is known to be associated with other products of the same class or which could be expected to occur based on the properties of the medicinal product.

**Important identified risk and important potential risk:** An identified risk or potential risk that could have an impact on the risk-benefit balance of the product [1] .

## When to stop submitting a DSUR:

In the EU region, DSUR submission stop when the trial ends (CT) to the Member States in whose territory the CT is being conducted (Clinical Trial Directive 2001/20 Article 17(2)).

DSUR needs to be submitted until the final clinical study report is completed and its summary submitted to these European Member States. DSUR should be submitted until the last visit of the last patient in the MS concerned. The DSUR is a more or less harmonized document now accepted in most countries of the world. It is a more complex and analytical document than the old-style annual safety reports. If a clinical trial has been started and ended within a time period shorter than 1 year, it will not be subject to the submission of DSUR. However, for the multiple performed short trials for one IMP it is recommended to consider submitting a DSUR [8].

## Conclusions:

The DSURs contain not only an evaluation of safety information collected during one year reporting period but also includes a cumulative review of existing safety efficacy and risk-related data. This evaluation gives an idea to the sponsors for identification and evaluation of identified and potential risks with the drug to make appropriate decision with their clinical development of drug. Not a single article is published yet describing details about the importance, context, purpose, scope, timelines, and an important point is what information to be added in all 20 sections during the preparation of DSUR. This article gives an overview and idea to all periodic reports writer and pharmacovigilance professionals for which information need to add in all sections during preparation of DSUR.

## References:

[1]. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH guideline E2F on development safety update report. 2008.

[2]. Guidance for Industry E2F Development Safety Update Report. 2011.

[3]. Urushihara H, Kawakami K. Development Safety Update Reports and Proposals for Effective and Efficient Risk Communication. 2010; 33(5): 341-352.

[4]. Geary S. The Development Safety Update Report A Critical Review. Pharm Med. 2010; 24 (5): 271-279.

[5]. Davis B. The Development Safety Update Report What can We Expect?. Pharm Med 2009; 23 (1): 19-24.

[6]. Gawai PP. Introduction and evaluation of Pharmacovigilance for beginners. Int J Sci Rep 2020; 6(10): 425-32.

[7]. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Periodic Benefit-Risk Evaluation Report: ICH guideline E2C (R2) on periodic benefit-risk evaluationreport. Current step 5, 2013

[8]. Questions and Answers to the Annual Safety Report, Frequently asked questions regarding the Development Safety Update Report (DSUR); Clinical Trial Facilitation Group. 2011.

[9]. Maheshwari D G, Parmar R G. Regulatory aspects of safety report in pharmaceuticals. World Journal of Pharmaceutical Research. 2018; 7 (2): 279-289.

[10]. CIOMS VII Working Group Report. Development Safety Update Report (DSUR): harmonizing the format and content for periodic safety reporting during clinical trials. Geneva CIOMS. 2006; 85.