TRANSFORMING PROMISING IDEAS INTO COMMERCIAL REALITY

# Overview of Periodic Safety Reports For Regulatory Submission

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# Agenda

- **Introduction**
- **Periodic safety reports and its types**
  - Scope
  - Frequency
  - Significance
  - Advantages
  - Various Sample Statistical Reports
- **Various Departments involved**
- **Conclusion**

# Introduction

# Periodic Safety Reports

A periodic report or a recurring report is a written document that summarizes the events that have occurred since the last periodic report was written.

# Investigator's Brochure (IB)



## IB

Comprehensive document summarizing information about an investigational product ("IP" or "study drug") during a drug trial.

- Purpose of the IB is to compile data relevant to studies of the IP in human subjects gathered during preclinical and other clinical trials.

## Significance

Provide the investigator with insights necessary for management of study throughout a clinical trial.

- Dose (of the study drug)
- Frequency of dosing interval
- Methods of administration
- Safety monitoring procedures

## Frequency

- Updated with new information as it becomes available.

# Investigator's Brochure (IB)



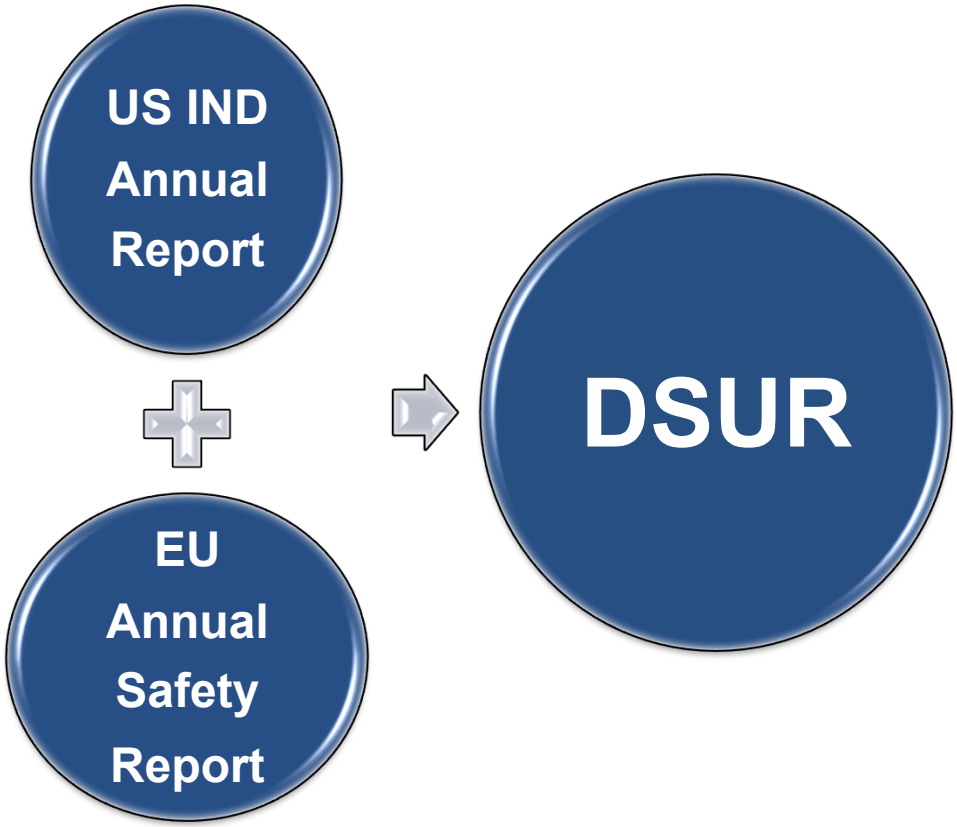
## Inference

- Provide the investigator with a clear understanding of the possible risks and adverse reactions, and of the specific tests, observations, and precautions that may be needed for a clinical trial.
- For post marketing commitment clinical trials, the product label (package insert)  is used.

# Development Safety Update Report



Evaluation of safety information collected in the past year along with a cumulative review of existing safety information.




To identify and evaluate potential risks with the drug and make appropriate adjustments to their clinical development program.

# Development Safety Update Report



## Objective

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.

## Scope

DSUR provides safety information from all ongoing clinical trials or completed trails using an investigational drug whether with or without a marketing approval.

Clinical trials conducted using marketed drugs in approved indication which requires additional monitoring.

Other therapeutic use of an investigational drug and comparability trials.

# Development Safety Update Report

## DSUR Frequency

The first DSUR period should not be longer than 1 year. The DSUR is always submitted on a yearly basis.

# Development Safety Update Report



## Significance

Summarizing, understanding and management of identified and potential risks.

Updated status of the clinical investigation/development program and study results.

## Advantages

Additional level of protection for subjects in clinical trials.

Harmonised report sent to regulators in the three ICH regions.

DSUR should be concise and in turn; assure regulators that adequately monitoring and evaluating the safety profile of the investigational drug.



Much more Ahead

# Benefit- Risk Balance

During the marketing authorization process, pharmaceutical companies need to establish and demonstrate the benefits and the risks of the medicinal product.

Regulators need to assess those benefits and risks.

When a new product is authorized for marketing, that decision is based on a benefit-risk balance.

With the information available at that specific moment, products are authorized if it is considered that the benefits are greater than the risks.

“Positive benefit-risk balance” .

# Periodic Safety Update Reports

# PSUR, PBRER and PADER



**PSUR**

- Periodic Safety Update Report

**PBRER**

- Periodic Benefit-Risk Evaluation Report

**PADER**

- Periodic Adverse Drug Experience Report

## Objective

To present a comprehensive and critical analysis of the risk-benefit balance of the product taking into account new or emerging safety information in the context of cumulative information on risk and benefits.

# PSUR Versus PADER

## PSUR

- Approved worldwide.
- Adverse events occurring around the world .
- Overall safety evaluations with specific highlighting.
- Cumulative data is analyzed for assessing benefit risk balance.

## PADER

- Approved by US FDA.
- Adverse events occurring in the U.S. (especially 15 day report).
- Non-Serious Adverse Events can be exempted.
- Specific periodic data is analyzed for assessing benefit risk balance.

# PSUR Versus PBRER

## PSUR

- No Benefit evaluation.
- Risk evaluation (risk minimization procedures for limited products).
- No integrated risk benefit analysis.

## PBRER

- Benefit evaluation
- Risk evaluation (risk minimization procedures for all significant risks associated with all products).
- Integrated risk benefit analysis.

# PSUR, PBRER and PADER



## SCOPE

Examine whether new information is in **accord with previous knowledge** of the benefit risk profile

Summarizes relevant new safety **information that may impact the benefit risk profile**

Summarizes any **important new efficacy and effectiveness** information

Conduct an integrated B/R evaluation (where **new important safety** information has emerged)

# PSUR, PBRER and PADER



## Frequency

**EMA**

Every 6 months for 2 years.
Annually for the 3 following years.
Every 3 years (at the time of renewal of registration).

**PMDA**

Every 6 months for 3 years.
Annually thereafter.

**FDA**

PADERs quarterly during the first 3 years.
Annually thereafter.

# PSUR, PBRER and PADER



## SIGNIFICANCE

- Benefit risk decision- making tools
- An effective means of risk communication to regulatory authorities
- To consider whether any action concerning the marketing authorization for medicinal product is necessary.
- Related safety data to patient exposure
- Considers changes to product information to optimize the product use
- An indicator for the need for risk management initiatives, as well as a tracking mechanism monitoring the effectiveness of such initiatives

# Orphan Drug Reports



## Orphan Drug

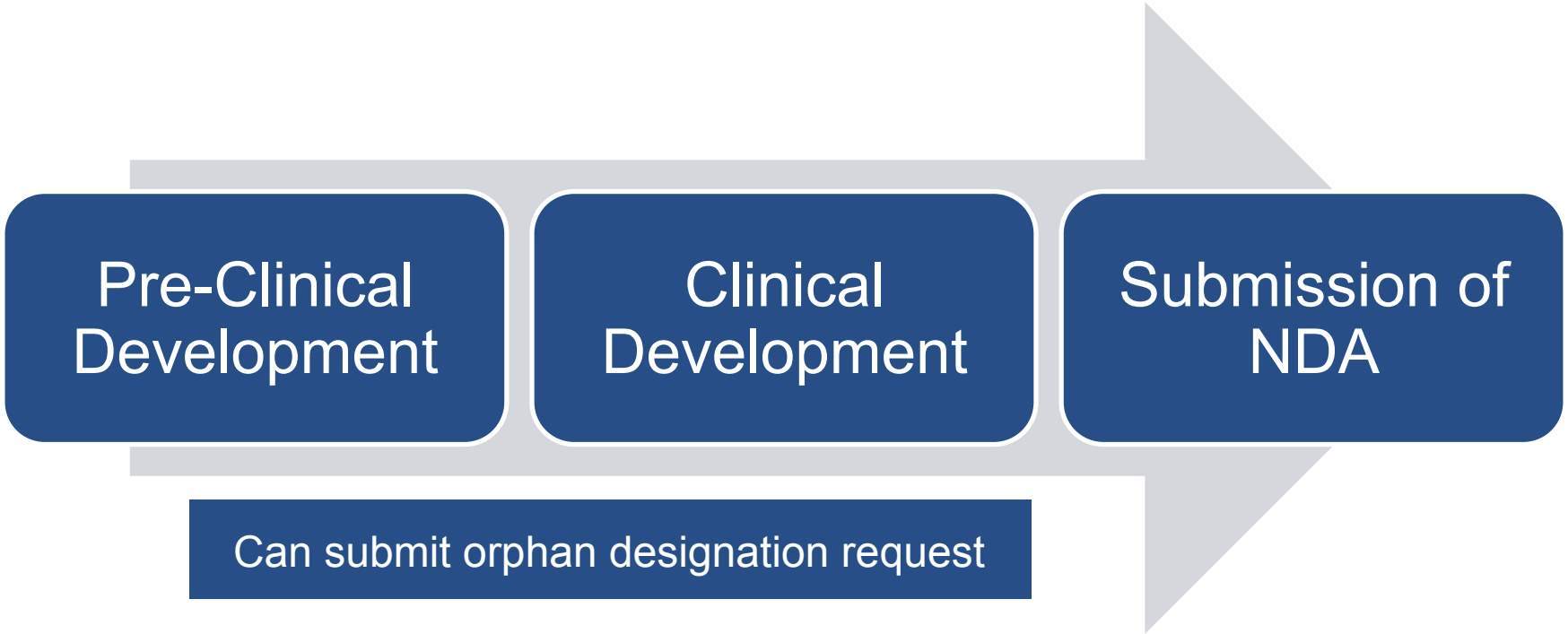
Drug (or biological product) used for the prevention, diagnosis or treatment of a **Rare Disease** or diagnosis of a disease that is life-threatening or chronically debilitating.

- Not be more than 5 in 10,000 people in EU

–<200K people in the US

# Orphan Designation Request






- No IND required

Once designated, sponsor is required to submit annual reports with-in 14 months and annually until drug is approved.

# Scope of Orphan Annual Reports

- Progress of drug development(pre-clinical and clinical studies).
- Investigational plan for the coming year.
- Anticipated difficulties in development, testing, and marketing.
- Any changes that may affect the orphan-drug status of the product.

# Various Statistical Reports

## TABLE 1 - EXAMPLES OF TABLE HEADINGS FOR CLINICAL TRIAL STATUS LISTINGS

### STATUS OF ONGOING AND COMPLETED CLINICAL TRIALS
### OVERVIEW OF ONGOING [study drug] STUDIES

| Study ID | Phase | Country | Study Title | Study design | Dosing regimen | Study population | FVFP* | Planned enrollment | Subject exposure** |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | |

* FVFP = first visit first patient
** based upon total number of patients recruited as of [date] and applied randomisation schemes

### OVERVIEW OF [study drug] STUDIES COMPLETED DURING THE DSUR PERIOD

| Study ID | Phase | Country | Study Title | Study design | Dosing regimen | Subject population | Subject/patient exposure per treatment arm (M/F) |
|---|---|---|---|---|---|---|---|
| | | | | | | | |

# Various Statistical Reports

**TABLE 2 - EXAMPLES OF DEMOGRAPHIC DATA TABLES**
**CUMULATIVE SUMMARY TABULATIONS OF DEMOGRAPHIC DATA**
**Estimated cumulative subject exposure to [study drug] clinical studies by age and gender***

| | Number of subjects | | |
|---|---|---|---|
| **Age (yr)** | **Male** | **Female** | **Total** |
| <16 | | | |
| 16 - 25 | | | |
| 26 - 35 | | | |
| 36 – 45 | | | |
| 46 – 55 | | | |
| 56 – 65 | | | |
| 66 – 75 | | | |
| >75 | | | |
| **Total** | | | |

* data from completed studies as of [date]

**Estimated cumulative subject exposure to [study drug] in all clinical studies by ethnic origin***

| **Ethnic origin** | **Number of subjects** |
|---|---|
| Caucasian | |
| Black | |
| Oriental | |
| Other | |
| **Total** | |

* data from completed studies as of [date]

# Various Statistical Reports

**TABLE 3 - EXAMPLES OF HEADINGS FOR INTERVAL LINE LISTINGS OF SERIOUS ADVERSE REACTIONS**

**INTERVAL LINE LISTINGS OF SERIOUS ADVERSE REACTIONS (SARs)**

| Study ID EudraCT number | Case ID/ Subject number* | Country Gender Age | Serious ADR(s) | Outcome | Date of Onset** Time to Onset** | Suspect Drug | Daily dose Route Formulation | Dates of treatment Treatment duration | Comments | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | |
| | -------- | -------- | ------- | -------- | -------- | -------- | -------- | -------- | -------- | |

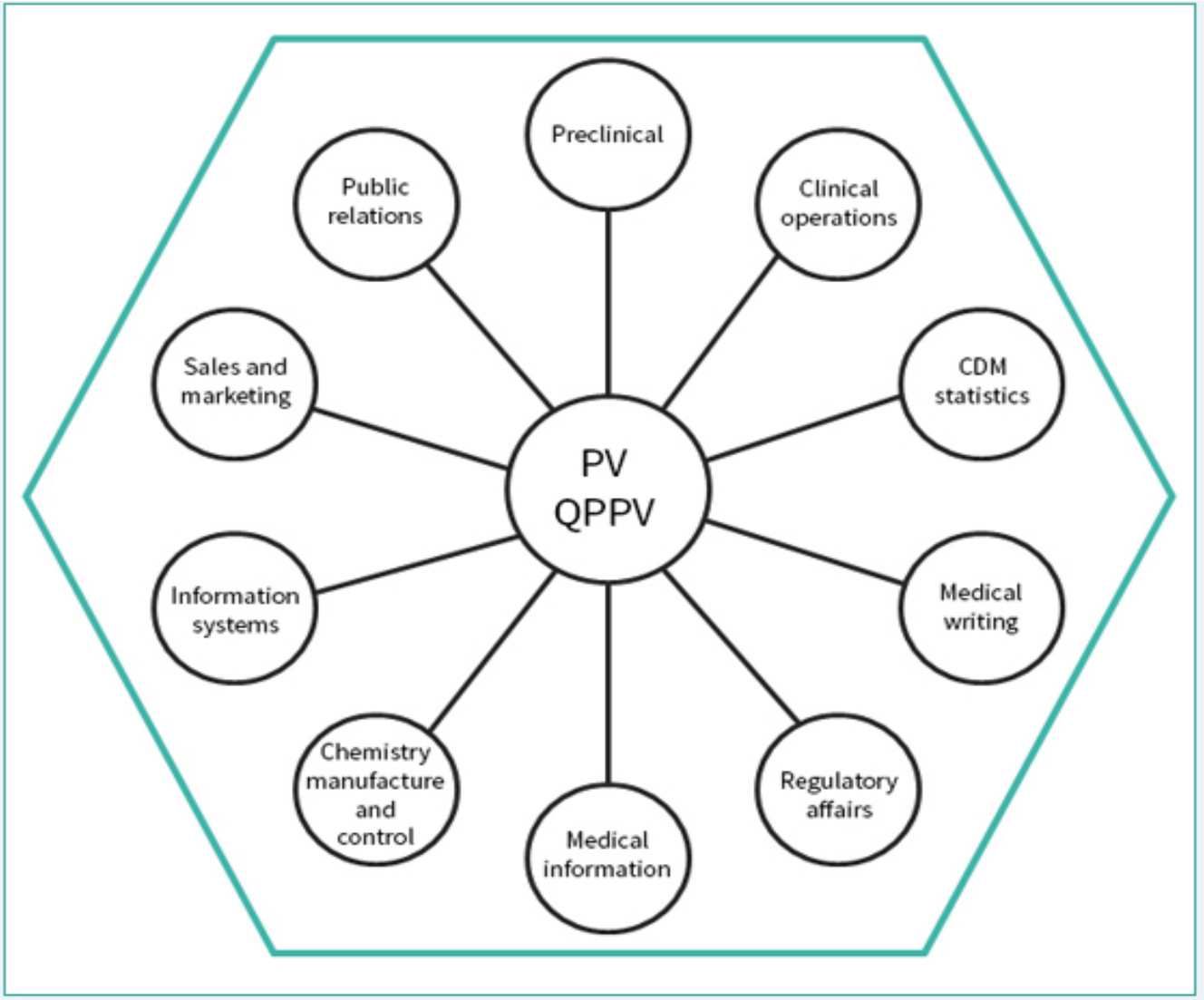
* Study/centre/patient
** 'Primary' SADR only

**TABLE 4 - EXAMPLES OF CUMULATIVE TABULATIONS OF SERIOUS ADVERSE EVENTS**

**CUMULATIVE SUMMARY TABULATION OF SERIOUS ADVERSE EVENTS (SAEs)**

| System Organ Class<br>Preferred Term | Total up to 31-Dec-07<br>[study drug] | Blinded | Active comparator | Placebo |
|---|---|---|---|---|
| **Investigations** | **18** | **4** | **7** | **2** |
| Alanine aminotransferase increased | 9 | 2 | 4 | 1 |
| Aspartate aminotransferase increased | 9 | 2 | 3 | 1 |
| **Nervous System Disorder** | **2** | **2** | **4** | **7** |
| Syncope | 2 | 2 | 4 | 7 |

# Departments Involved



# Conclusion

Periodic Safety Reports ensure that a product's benefits continue to outweigh its risks, and facilitate the weighing and monitoring of such events at predetermined time points.

As such, reports are clearly a vehicle to drive regulatory dialogue, however; determination of their contribution to the safe use of medicines as ancillary to existing Pharmacovigilance requirements still remains a challenge.

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# QUESTIONS

# THANK YOU!