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DSUR vs. PSUR/PBRER: A Pharmacovigilance Comparison

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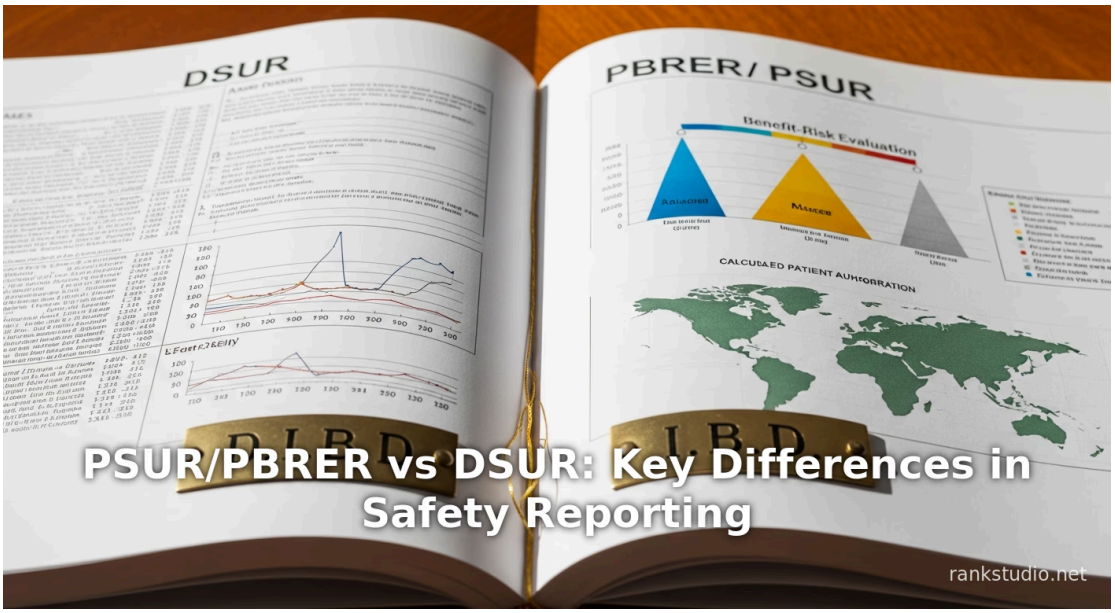

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Executive Summary

This report provides an in-depth analysis of periodic pharmacovigilance reporting—specifically, the **Periodic Safety Update Report (PSUR)** or its ICH-aligned successor **Periodic Benefit-Risk Evaluation Report (PBRER)**, versus the **Development Safety Update Report (DSUR)**. Both PSUR/PBRER and DSUR are cornerstone documents in drug safety surveillance, but they apply to different stages of a product's lifecycle and have distinct owners, contents, timing, and governance. In brief:

- **Ownership:** PSURs/PBRERs are prepared and submitted by the **marketing authorization holder (MAH)** of an approved product (www.ema.europa.eu) (istitlaa.ncc.gov.sa). In contrast, a DSUR is prepared by the **sponsor** of the clinical trial(s) for an investigational drug (www.scribd.com). The sponsor (or MAH) may delegate preparation (e.g. to a CRO), but legal responsibility remains.

- **Scope (What's inside):** PSURs/PBRERs provide a **cumulative benefit-risk evaluation** of a marketed medicinal product, integrating all new safety data (clinical, nonclinical, literature) since the last report, along with an updated analysis of benefits and risks (www.prometrika.com) (istitlaa.ncc.gov.sa). DSURs provide an **annual safety update** for drugs *under development*, covering all clinical trial data, cumulative patient exposure, safety findings (from trials, observational studies, literature, etc.), and any relevant regulatory or labeling changes (www.researchgate.net) (www.scribd.com). DSURs essentially subsume all safety update requirements (e.g. IND annual reports in the US and Annual Safety Reports in the EU) into one harmonized document (www.researchgate.net) (www.prometrika.com).
- **Formats and Content:** Both report types follow ICH-defined structures. A PBRER (ICH E2C(R2)) emphasizes an *integrated benefit-risk assessment*, including sections on cumulative patient exposure, important safety findings (clinical trials, literature, off-label use), and an overall summary assessment (www.prometrika.com) (istitlaa.ncc.gov.sa). A DSUR (ICH E2F) includes sections such as *Worldwide Marketing Status (if any), Actions taken in reporting period, Changes to Reference Safety Information (RSI), Inventory of Clinical Trials, Cumulative Subject Exposure, Line Listings of Serious Adverse Events, and New Safety Findings from Trials* (www.scribd.com) (www.scribd.com). The DSUR's organization is broadly similar to a postmarketing PSUR but with additional fields and appendices to reflect the developmental context (www.researchgate.net).
- **Timeline:** PSURs/PBRERs are submitted according to regulatory-defined schedules (e.g. every 6 months initially, then annually, etc., often governed by national/EU pharmacovigilance legislation) and with fixed deadlines (typically 70–90 days after the Data Lock Point) (www.ema.europa.eu) (istitlaa.ncc.gov.sa). In the EU, a **periodic safety reporting schedule** (the EURD List) specifies PSUR/PBRER intervals based on approval dates (the "birth date" concept) (www.ema.europa.eu) (www.ema.europa.eu). In the US, post-marketing safety is covered by quarterly Adverse Experience reports (first 3 years) and annual reports thereafter – however, companies may submit a PBRER in lieu of FDA's native formats (PADER/PAER) with appropriate waivers (www.prometrika.com) (www.fda.gov). DSURs are submitted **annually**: they are anchored on the sponsor's first clinical trial authorization (the Development International Birth Date, DIBD) (www.prometrika.com) (www.scribd.com). (For example, in the US an IND annual report is due within ~60 days of the IND anniversary; similarly, EMA requires an Annual Safety Report/DSUR each year from trial initiation (www.hpra.ie) (www.scribd.com).)
- **Governance and Oversight:** Both reports are mandated or strongly encouraged by international guidelines and regional laws. PSURs/PBRERs are legally required for approved drugs (e.g. under EU pharmacovigilance legislation) and are reviewed by authorities (EMA's PRAC/CHMP or national agencies) to determine needed risk management actions (www.ema.europa.eu) (www.ema.europa.eu). DSURs, while introduced by ICH guidance, effectively harmonize existing national requirements (IND annual, EU ASR) and are expected by regulators worldwide (Europe, US, Japan, etc.) (www.ema.europa.eu) (www.researchgate.net). Quality systems within sponsor organizations ensure preparation (often led by pharmacovigilance teams with medical review), and submission is done via electronic platforms (eCTD, repositories) per agency rules (www.scribd.com) (www.ema.europa.eu). Both report types are linked to the Risk Management Plan (RMP) and may inform regulatory decisions (label changes, additional studies).This report explores these aspects in depth, with regulatory references, practical considerations, comparative analyses, and case examples. We also discuss implementation challenges, global perspectives, and future directions.

1. Introduction and Background

The ongoing evaluation of a drug's safety throughout its lifecycle is a core function of pharmacovigilance. **Aggregate safety reports** – those that summarize data collected over defined periods – are fundamental to this process. The two principal categories of such reports are:

- **Periodic reports for marketed products:** Traditionally called **Periodic Safety Update Reports (PSURs)**, now standardized under the ICH as **Periodic Benefit-Risk Evaluation Reports (PBRERs)**. These are prepared *after a product has been authorized (post-marketing)* to aggregate all new safety information and reassess its benefit-risk profile (www.ema.europa.eu) (istitlaa.ncc.gov.sa).
- **Annual reports for investigational products:** Known as **Development Safety Update Reports (DSURs)**, these cover the clinical development phase (pre-approval) and provide regulators with an annual safety overview during trials (www.ema.europa.eu) (www.scribd.com). DSURs replaced earlier country-specific reports (e.g. the US IND annual report, the EU Clinical Trial Annual Safety Report) under the ICH E2F guideline (www.ema.europa.eu) (www.researchgate.net).

Why such reports? The rationale is to ensure continuous monitoring: clinical trials have limited size and duration, so once a drug is used more widely (or continues to be investigated), additional safety signals may emerge. Regulators require aggregate evaluations to detect trends, verify the risk-benefit balance, and decide if labeling updates or further action are needed (www.ema.europa.eu) (www.scribd.com). The idea is that systematic, periodic reporting (rather than only one-off studies or spontaneous cases) provides a fuller picture of drug safety.

Table 1 below summarizes the key differences between PSUR/PBRER and DSUR at a glance. The subsequent sections explain each aspect in detail.

Feature	PSUR/PBRER (Postmarketing)	DSUR (Pre-approval/Clinical)
Purpose	Periodic *benefit-risk evaluation* of a marketed product, summarizing new safety information since approval. Intended to confirm/update the product's risk-benefit balance (www.ema.europa.eu) (istitlaa.ncc.gov.sa).	Annual *safety update* for an investigational drug, summarizing all trial data and subject exposure since last report. Ensures continued monitoring during development (www.researchgate.net) (www.scribd.com).
Owner & Submitter	Marketing Authorization Holder (MAH) – the company holding the approved product license (www.ema.europa.eu) (istitlaa.ncc.gov.sa).	Clinical trial Sponsor – the entity initiating/financing the trials (often a pharma company) (www.scribd.com).
Applicable Stage	After marketing authorization (post-approval). May start with launch (initial 6-monthly or annual reports) and continue yearly (or per local schedule) thereafter (www.ema.europa.eu).	Throughout the clinical development phase – from first trial approval in any country, annually until trials end. Covers Phase I–III studies (www.scribd.com) (www.hpra.ie).

Feature	PSUR/PBRER (Postmarketing)	DSUR (Pre-approval/Clinical)
Regulatory Basis (Key Guidelines)	ICH E2C(R1)/E2C(R2) Guideline (PBRER) (www.ema.europa.eu). EU: Statutory requirements (Regulation 1235/2010, GVP Module VII) dictate PSUR/PBRER schedules. FDA: PBRER may be submitted in place of US periodic reports (with waiver) (www.fda.gov). Other regions (e.g. India, Japan) have similar requirements.	ICH E2F Guideline (DSUR) (www.ema.europa.eu). In practice, replaces US IND annual report (21 CFR 312.33) and EU Annual Safety Report under the Clinical Trial Directive/Regulation (www.ema.europa.eu) (www.hpra.ie). Countries (US, EU, Japan, etc.) encourage or allow submission of a DSUR to satisfy these national obligations.
Frequency & Timeline	As mandated – often *every 6 months for the first 2 years*, then annually (or per the EU-wide EURD list) (www.ema.europa.eu) (istitlaa.ncc.gov.sa). Deadlines are typically set (e.g. 70 days after DLP for ≤12-month intervals, 90 days for longer) (www.ema.europa.eu) (istitlaa.ncc.gov.sa). Ad-hoc PSURs are requested by authorities if needed. FDA requires quarterly reporting for new NDA/BLAs (first 3 years) and annual thereafter (www.prometrika.com), but allows converting these to a PBRER schedule.	Annually (once every 12 months) after trial initiation (www.scribd.com) (www.hpra.ie). The “annual period” usually begins at the sponsor’s first worldwide trial authorization (the Development International Birth Date, DIBD) (www.prometrika.com). The data lock point is often aligned to this date or chosen close by (with regulatory approval of any alignment) (www.prometrika.com). ICH E2F calls for submission no later than 60 calendar days after the data lock point; FDA expects IND annual reports within 60 days of the IND anniversary.
Regulatory Oversight	Reviewed by regulators (e.g. EMA/PRAC or FDA) to identify new signals or need for action (label changes, etc.) (www.ema.europa.eu) (www.prometrika.com). PSUR/PBRER compliance is legally enforced (EMA requires electronic submissions to its PSUR repository (www.ema.europa.eu)). Non-compliance can lead to regulatory sanctions.	Submitted to clinical trial authorities (e.g. FDA for INDs; EU national Competent Authorities and Ethics Committees) annually. In EU, the DSUR (often termed Annual Safety Report) is required by Clinical Trial Regulation (www.hpra.ie). Failure to report can breach trial regulations. DSUR content informs investigators and ethics committees, ensuring patient safety oversight (www.researchgate.net).
Key Content Focus	**Aggregate safety & benefit-risk:** All major safety data from the market (including clinical trials *post*-approval, spontaneous ICSRs, literature, other sources) plus updated benefit analyses (www.prometrika.com) (istitlaa.ncc.gov.sa). Emphasis on trends and benefit-risk balance.	**Clinical trial safety:** Cumulative subject exposure (trial enrollment and patient-years on study), summaries of serious adverse events from trials (line listings and summaries), any trial-specific safety findings, and changes to Reference Safety Information (e.g. Investigator's Brochure) (www.scribd.com) (www.scribd.com). Still includes nonclinical/literature if relevant. Safety data from marketed use *can* be included if product is concurrently marketed (www.scribd.com).
Format & Sections	Structured by ICH (R2) template. Its 20 sections include: 1) Introduction, 2) Worldwide Marketing Approval Status, 3) Actions Taken for Safety Reasons, 4) Changes to Reference Safety Information, 5) Estimated Exposure and Use Patterns, 6) Data in Summary Tabulations, 7) Significant Findings from Clinical Trials, 15–16) Signal Overview and Signal and Risk Evaluation, 17) Benefit Evaluation, 18) Integrated Benefit-Risk Analysis, 19) Conclusions and Actions (istitlaa.ncc.gov.sa) (www.prometrika.com). (The exact section numbering is defined in ICH E2C(R2)).	Sections per ICH E2F: 1) Introduction (identifying sponsor, product, reporting period, etc.); 2) Worldwide Marketing Approval Status (if authorized anywhere); 3) Actions taken for safety reasons (e.g. holds, risk management changes); 4) Changes to RSI (e.g. IB updates); 5) Inventory of ongoing/completed trials; 6) Estimated Cumulative Exposure (trials and, if applicable, marketing); 7) Tabulations/line listings of serious adverse events; 8) Significant findings from trials (by Phase), long-term follow-up, off-label use, combination therapies; 9) Noninterventional studies; 10) Other clinical trial/study safety information, with further sections through 20) Conclusions (www.scribd.com). (See Table 2, below, for a side-by-side outline of some sections.)

Feature	PSUR/PBRER (Postmarketing)	DSUR (Pre-approval/Clinical)
Relationship	When a drug moves from development to market, reporting shifts to PSUR/PBRER. In some cases, data from the last DSUR feed into the first PSUR/PBRER. Regulators allow some synchronization: e.g. aligning DSUR data lock points to the first marketing authorization date to streamline dual reporting (www.prometrika.com).	Conversely, if safety issues emerge late in development or immediately post-approval, both reports might cover overlapping data (coexisting DSUR and PSUR/PBRER). Sponsors coordinate to avoid duplication, leveraging the "modular approach" recommended by ICH/GVP (common content reused across DSUR, PSUR, RMP) (istitlaa.ncc.gov.sa).

Tables 1 and 2 below further illustrate key comparisons and typical content outlines. Subsequent sections unpack these aspects, drawing on regulatory guidelines, industry practices, and expert analyses.

2. Historical Evolution of Periodic Safety Reporting

Periodic aggregate reporting in pharmacovigilance has evolved over decades under the auspices of international harmonization (CIOMS, ICH) and regional regulations.

- **PSUR Development:** In 1996 ICH published the original E2C guideline (Step 4, 1996) establishing the Periodic Safety Update Report (PSUR) as a harmonized format for postmarketing safety reports. That guideline defined basic structure and timing (www.prometrika.com). The EU adopted it in directives (e.g., Directive 2001/83/EC, later Regulation 1235/2010) making PSUR submission mandatory for authorized products (www.ema.europa.eu). Over time, the approach to PSURs became more benefit-focused. ICH E2C was revised to E2C(R2), effective in 2012, renaming it **Periodic Benefit-Risk Evaluation Report (PBRER)** to emphasize analysis of both risks and benefits (www.prometrika.com). EU GVP Module VII (2013, revised 2020) updated guidance accordingly (www.ema.europa.eu). By 2016, global regulators had converged on PBRER as the preferred format (www.prometrika.com).
- **DSUR Development:** In parallel, the need for harmonized annual safety reporting in clinical trials was recognized. Prior to ICH E2F, each region had its own system: the US required an IND Annual Report, the EU a Clinical Trial Annual Safety Report, Japan others, etc. In August 2010 ICH finalized guideline E2F (Step 4) introducing the **Development Safety Update Report (DSUR)** as a common standard for investigational products (www.ema.europa.eu). This meant, for example, that the FDA and EMA would accept a single DSUR in place of their own national annual reports (www.ema.europa.eu) (www.researchgate.net). ISSUES around DSUR implementation (e.g. IRB use, incomplete harmonization) were discussed by experts (www.researchgate.net). In August 2011 FDA issued final guidance adopting ICH E2F (FDA E2F guidance) (www.scribd.com), (www.scribd.com).

The **"Lifecycle" approach** to safety reporting now integrates these: DSURs cover pre-approval, PBRERs post-approval, and together they form an uninterrupted safety monitoring scheme. Many sponsors thus maintain both processes during the transition from trials to marketing. The regulatory framework (ICH plus local laws) is graphically summarized in Figure 1 (below).

(Figure 1: Lifecycle Safety Reports – DSURs during clinical development, transitioning to PSURs/PBRERs after marketing approval. Data lock points (DLPs) are anchored on the first trial start vs first authorization date respectively.)

3. Regulatory Frameworks and Guiding Principles

ICH Guidelines: Both report types are specified by ICH:

- **ICH E2C(R2) "PBRER"** (International Council for Harmonisation, Topic E2C, R2 revision). Defines the *recommended format and content of periodic reports on benefit/risk*, for marketed products (including those "under further study") (www.ema.europa.eu) (www.prometrika.com). This is a *"Step 5"* (finalized) guideline that global regulators have adopted. It emphasizes an integrated benefit-risk evaluation overall. E2C(R2) recommends one PBRER per active substance (with exceptions for fixed combinations, line extensions, etc.) (www.ema.europa.eu). PBRER is considered a common global standard, so that regulators and MAHs worldwide can use the same document.
- **ICH E2F "DSUR"** (Topic E2F). Defines the format of the annual **Development Safety Update Report** (www.ema.europa.eu). It is likewise a *Step 4* harmonized guideline. E2F explicitly states that a DSUR "submitted annually… would meet national and regional requirements currently met by the U.S. IND Annual Report and the EU Annual Safety Report" (www.ema.europa.eu). The intent is that DSUR replaces disparate local reports, and may be used in the US, EU, and other ICH regions. The ICH DSUR guideline details sections to include and encourages one report per *development program*.

Regional Requirements: ICH provides the template, but each region may impose its own rules on timing/frequency:

- **European Union:** The EU pharmaceutical legislation (Regulation (EC) No 726/2004 and Implementing Reg 1235/2010) requires "periodic safety update reports" for all authorized medicines (www.ema.europa.eu). Since 2012 these have followed the ICH PBRER format (EU GVP Module VII rev.1). The EU uses a list called the *Periodic Safety Update Reports (PSUR)'s – Schedule (EURD List)* to set submission dates for each product. The first EU PSUR is often due 6 months after approval (if not waived), then every 6 months for 2 years, then annually for 2 more years, and then every 3 years for well-known products (www.ema.europa.eu) (www.ema.europa.eu) (EU-specific scheme). Submissions are mandatory via EMA's **PSUR Repository** (electronic system) for all centrally- and nationally-authorized products (www.ema.europa.eu) (www.ema.europa.eu).

For investigational products, the EU Clinical Trial Directive (2001/20/EC) and now Regulation (EU) 536/2014 require an **Annual Safety Report (ASR)** for each clinical trial. In practice, sponsors and regulators interpret this as fulfilling ICH DSUR requirements. For example, Ireland's HPRA guidance explicitly says the annual safety report should be in DSUR format and is required every year from trial start until the trial ends (www.hpra.ie). After 2022, the EU Clinical Trial Regulation harmonized these rules across member states.

- **United States:** Legally, the US regulations (21 CFR) include requirements for postmarketing safety (21 CFR 314.80-314.82) and IND annual reports (21 CFR 312.33). The FDA has issued guidance on substituting PBRER for the native formats. Specifically, FDA will accept the ICH PBRER in lieu of the US *Periodic Adverse Drug Experience Report* (PADER) and *Postmarketing Adverse Experience Report* (PAER) (www.fda.gov). For NDAs/BLAs, FDA traditionally required Adverse Experience reporting *quarterly* for the first 3 years and *annually* thereafter. When a sponsor opts to use PBRER, FDA often still expects that reports cover all relevant quarters and years (for example, submitting missing quarterly reports if a PBRER isn't filed quarterly) (www.prometrika.com). On the investigational side, 21 CFR 312.33 mandates an IND annual report due ~60 days after each IND anniversary. The E2F/DSUR paradigm is used informally, but FDA's guidance clarifies that DSUR content can satisfy the IND annual report requirement (www.ema.europa.eu). Firms often attach the required IND appendix to the DSUR when submitting to FDA.
- **Other Regions:** Many countries have adopted or referenced the ICH guidelines. For example, **India's** CDSCO requires PSUR submissions for new drugs (typically twice-yearly for 2 years, then annually) and DSURs for ongoing clinical trials (similar to ICH guidance). **Japan's** PMDA aligns with E2C/E2F. The **World Health Organization (WHO)** and international pharmacopeia encourage adherence to ICH standards for global consistency. However, local differences exist (cycle durations, acceptability of PBRER, etc.), so MAHs must tailor submissions per region's rules.

In summary, the ICH E2C(R2) and E2F guidelines provide a harmonized framework, but local regulations govern the exact obligations (timing, format, qualifiers). Sponsors must navigate this regulatory "governance" landscape carefully to remain compliant in each market.

4. The PSUR/PBRER in Detail

4.1 Purpose and Scope

A Periodic Safety Update Report (PSUR), now more properly called a Periodic Benefit-Risk Evaluation Report (PBRER), is a pharmacovigilance document **intended to provide an ongoing evaluation of the benefit-risk balance** of a medicinal product after authorization (www.ema.europa.eu) (istitlaa.ncc.gov.sa). It is submitted by the Marketing Authorization Holder (MAH) to regulatory authorities at specified intervals post-launch (www.ema.europa.eu) (istitlaa.ncc.gov.sa). The key objectives of the PSUR/PBRER are:

- **Aggregate new safety information:** Summarize adverse events from spontaneous databases, ongoing clinical trials, observational studies, and pertinent literature that occurred during the reporting period.
- **Evaluate risk trends:** Identify any new potential or confirmed risks (signals) by comparing observed data to expectations (e.g. from clinical trials or prior PSURs).
- **Review benefit:** Discuss whether the therapeutic benefits (based on efficacy data) continue to outweigh the risks, possibly incorporating new efficacy or use data.
- **Recommend action:** Advise if safety measures (label changes, risk minimization, additional studies) are needed, or if no action is necessary.

Importantly, the PBRER emphasizes **benefit-risk** analysis. It includes, by design, a dedicated section for *Benefit-Risk Evaluation* (www.scribd.com) (www.prometrika.com). Whereas older PSURs focused primarily on listing adverse reactions, the R2 revision stresses integrated assessment of both sides of the equation. For an approved product, this periodic reassessment ensures that any shifts in safety profile are promptly communicated and managed.

4.2 Ownership and Responsibility

Who prepares and submits the PSUR/PBRER? As the EMA explicitly states, “Marketing authorisation holders (MAHs) are legally required to submit PSURs” (www.ema.europa.eu). The MAH – the company (or companies) holding the drug’s marketing license in a region – is ultimately responsible for the contents and timing of the PSUR/PBRER (istitlaa.ncc.gov.sa). In practice, this task is typically handled by the pharmacovigilance department or Regulatory Affairs within the MAH organization, possibly with CRO support. Multi-national (co-)marketing situations require coordination: usually one MAH will prepare the report, or multiple MAHs for the same active substance may submit one combined PBRER if agreed (under ICH, one report per active substance is encouraged) (www.scribd.com). The allocation of “data lock point” (DLP) and due dates often follows a chosen *“reference member state”* or an International Birth Date (IBD) agreed among authorities.

Collateral Roles: While the MAH signs off on the report, other stakeholders contribute. Safety databases provide aggregate data. Medical experts review clinical findings. Quality/unitown oversight ensures compliance. Regulatory affairs teams might interface with authorities. Nonetheless, the MAH as the product’s legal owner is cited by name (“Marketing Authorisation Holder”) throughout guidance (www.ema.europa.eu) (istitlaa.ncc.gov.sa).

4.3 Content and Structure

The **structure** of the PBRER is precisely outlined in ICH E2C(R2) and incorporated into EU GVP Module VII (istitlaa.ncc.gov.sa). Broadly, the report includes the following (section numbers follow the 20-section ICH E2C(R2) table of contents (ICH E2C(R2))):

- **Section 1: Introduction (Scope, objectives)** – Defines the report’s scope: product name, active substance, MAH, therapeutic indication(s), the reporting period dates, and reference sources (label, risk information) (istitlaa.ncc.gov.sa). It may list which clinical studies are included.
- **Section 2: Worldwide Marketing Approval Status** – Summarizes where the product is approved, major dosage forms, indications, and any regulatory updates around the DLP. (This is more relevant if the product gained approvals in new countries during the interval.)
- **Section 3: Actions Taken in the Reporting Interval for Safety Reasons** – Lists any regulatory actions (safety communication, or modifications to the risk management plan) taken by the MAH or authorities due to safety concerns.
- **Section 4: Changes to Reference Safety Information** – Describes changes to the reference product information used for the report (typically the company core safety information) since the last report.

- **Section 5: Estimated Exposure and Use Patterns** – Presents cumulative clinical-trial exposure and interval and cumulative postmarketing exposure (e.g. patient-years estimated from sales data, if available).
- **Section 6: Data in Summary Tabulations** – Provides cumulative and interval summary tabulations of serious adverse events from clinical trials and of adverse reactions from postmarketing sources. (ICH emphasizes focusing on *cumulative summary tabulations* rather than exhaustive line listings of every case (istitlaa.ncc.gov.sa); detailed case reports are not included systematically).
- **Section 7: Summaries of Significant Findings from Clinical Trials during the Reporting Interval** – Summarizes any new trial results or analyses that have safety or efficacy implications.
- **Sections 8–14:** Findings from non-interventional studies, information from other clinical trials and sources, non-clinical data, literature (publications evaluated during the period relevant to safety), other periodic reports, lack of efficacy in controlled clinical trials, and late-breaking information.
- **Sections 15–16: Overview of Signals; Signal and Risk Evaluation** – Reconciles new, ongoing and closed signals with the identified and potential risks, including a summary of important risks.
- **Section 17: Benefit Evaluation** – Summarizes important baseline efficacy and effectiveness information and any new benefit information.
- **Section 18: Integrated Benefit-Risk Analysis for Authorized Indications** – A narrative analysis of whether the benefit-risk balance has changed. This is the distinctive feature of PBRER: it should integrate all safety findings in the context of the product's evolving benefit information (www.prometrika.com).
- **Sections 19–20:** Conclusions and actions, followed by appendices.

(Note: The exact section numbering and headings can vary between PSUR (ICH R1) and PBRER (R2) versions. The above is a high-level outline.)

PSUR/PBRERs are expected to focus on **scientific analysis and summaries**, not simply aggregating raw data. As Saudi Arabia's GVP guidance (mirroring Europe's) notes: "detailed listings of individual cases shall not be included systematically. The PSUR/PBRER should focus on summary information, scientific safety assessment and integrated benefit-risk evaluation" (istitlaa.ncc.gov.sa). In practice, the main body text should highlight trends, while detailed case listings, if any, may be appended or omitted except where needed to illustrate a point.

Content Sources

Data feeding the PSUR/PBRER comes from multiple sources:

- **Spontaneous Reporting Databases**: All relevant Individual Case Safety Reports (ICSRs) from global sources.
- **Clinical Studies**: Ongoing post-marketing commitments or Phase IV studies, and sometimes relevant Phase III that completes.
- **Published Literature**: Peer-reviewed articles or case series about the product.
- **Epidemiological Data**: If available, registries or usage studies can inform patient counts/exposures.
- **Regulatory Communications**: Since last report, any serious safety updates (e.g. Dear Doctor letters) are summarized.

- **Other Regions' Safety Reports**: If the product is approved in a region not covered, the MAH may also include that data.

The MAH compiles these data and performs **signal detection**/analysis (often with a Medical Officer) to identify any new issues. Each important safety issue must be discussed in the context of benefit. For example, if a new adverse event pattern emerges, the MAH will evaluate whether it significantly alters the risk profile given how effective the drug is for its indication.

4.4 Timelines and Scheduling

General Rule: The submission timing of PSURs/PBRERs is driven by two factors: (a) the *data lock point (DLP)* (the cutoff date for data included) and (b) regulatory deadlines (how long after the DLP the report is due). The deadlines are **legally binding** (in regions like the EU) and published in timelines schedules.

- **Data Lock Point (DLP):** This is a retrospective date (day 0) marking the end of the reporting period. For example, if a product's PSUR cycle is 6 months, and the first cycle ended June 30, 2024 (DLP), the data included would be all up to and including that date. The next report would cover data from 1 July 2024 onward. The DLP typically aligns to an arbitrary cycle date (e.g. every 6 months from initial authorization). The DLP essentially defines the interval of data.

Sponsors often **synchronize DLPs** across countries for efficiency. In fact, ICH and regulators allow companies to align DSUR and PBRER DLPs under certain conditions (www.prometrika.com). For example, if a sponsor initially started reporting DSURs on an IND anniversary (say, 1 March each year), they may seek regulatory agreement to shift to a DLP that matches the product's first marketing date (the International Birth Date, IBD). This avoids having one year with 15 months data vs 6 months data in different reports. However, such changes typically require discussion with authorities (sometimes via waiver requests in the FDA) (www.prometrika.com).

- **Submission Deadlines:** Once the DLP is set, the MAH has a fixed number of days to submit the PSUR/PBRER. According to EU rules (reflected in EMA guidance), the report is due **within 70 calendar days** after the DLP if the reporting interval was ≤12 months, and **within 90 days** if the interval was >12 months (www.ema.europa.eu) (istitlaa.ncc.gov.sa). For leeway, EMA provides a submission window: reports can be unlocked in the PSUR Repository up to 3 months before the due date and no later than the official deadline (www.ema.europa.eu). Ad hoc PSUR requests (to cover specific safety concerns) are also typically due within 90 days unless stated otherwise.

For example, as EMA FAQ clarifies: for a 12-month PSUR, submission must be no later than 70 days after the end of that year (www.ema.europa.eu). In practice, companies target earlier (often 60–65 days) to allow for review. If the product has been up for several years, reports may shift to 36-month intervals, but deadlines after an interval >1 year are set at 90 days (www.ema.europa.eu).

- **Starting and Changing Cycles:** Special rules apply for new approvals. EMA notes that if a product was authorized after the current DLP, the MAH need not submit a PSUR until the next scheduled DLP (www.ema.europa.eu). If a product's approval comes before a DLP, then reporting obligation kicks in

immediately. For a new EU Marketing Authorisation (centralised), a separate EURD entry is created. The first PSUR/PBRER deadline is often based on the European Birth Date (EBD) or the product's IBD, aligned per agreed strategy (www.ema.europa.eu). After that, updates to the frequency (captured in the MA license and on the EURD List) take effect six months after the update's publication (www.ema.europa.eu).

- **US Quarters/Years:** In the USA, the FDA's long-standing schedule (per 21 CFR) is: submit adverse experience reports **quarterly** for the first 3 years post-approval, then **annually** thereafter. If a sponsor submits a PBRER instead, FDA typically expects that any missing quarterly reports (for quarters not covered by the PBRER) be filed as supplemental reports (www.prometrika.com). For example, the FDA guidance on PBRERs explains that if a product is on a 6-month PBRER cycle but originally required quarterly reports, the sponsor should either file quarterly reports in the missing quarters or obtain a PSUR waiver (www.fda.gov). Therefore, integrating PBRER into the US compliance framework often involves additional logistics.
- **DSUR Schedules:** By contrast, DSURs have a simpler timing: one per year. The start date is the sponsor's first authorization to conduct an interventional clinical trial in any country (the DIBD) (www.prometrika.com). The DSUR then covers the 12-month "developmental safety reporting period" from that date (± small shifts for administrative convenience). For example, if the first IND was authorized on 15 April 2022, the first DSUR might cover 15 Apr 2022 – 14 Apr 2023 (DLP on 14 Apr 2023), with submission due around mid-June 2023. The FDA guidance on DSUR implies that the IND annual report requirement (60 days post-anniversary) would align with this schedule (www.scribd.com). EU law (for trials under Directive/CTReg) also expects annual reports from trial start (www.hpra.ie), which regulators accept in DSUR format. Marketing approval alone does not end DSUR reporting: if clinical development continues, DSURs continue for as long as national or regional rules require, while PSUR/PBRER reporting runs in parallel (www.scribd.com) (www.prometrika.com).

Governance Considerations: Both DSURs and PBRERs require rigorous project management to meet timelines. Typically, a "Period Safety Report" team assembles data soon after the DLP, drafts content, circulates internally for medical/regulatory review, and finalizes well before the due date. For PBRERs, any delay can have legal consequences, so MAHs often track "submission windows" via the EURD list or local PV requirements. Late or missing PSURs can result in regulatory injunctions or fines. Similarly, DSUR delays can jeopardize trial authorizations or inspections.

In summary, **timing** of safety reports is tightly controlled by law and guidance. The PSUR/PBRER schedule, defined by product «birth dates» and intervals, ensures continuous monitoring of marketed medicines (www.ema.europa.eu) (www.ema.europa.eu). The DSUR schedule, annual and based on trial start, ensures no gap during drug development (www.scribd.com) (www.hpra.ie). Aligning these timelines (so the DSUR and the first PSUR coincide) is often a goal for efficiency (www.prometrika.com).

4.5 Governance and Submission Processes

Responsibilities: As noted, the MAH (or delegated sponsor) must organize the PSUR/PBRER process. This involves cross-functional oversight: medical, safety, regulatory, and legal teams collaborate. Many companies establish an annual schedule and assign internal “leaders” for each report, especially for globally distributed products with multiple affiliates. Firms often appoint a “Lead Member State” in the EU to coordinate the single assessment procedure for PSURs of centrally authorized products (EU Regulation 1235/2010).

Quality Control: Good Pharmacovigilance Practices (GVP) **Module I (Organization and Responsibilities)** and Module VII outline that PSURs/PBRERs must be prepared under a quality system (with documented procedures), checked for accuracy, and approved by qualified persons (e.g. QPPV in EU) (istitlaa.ncc.gov.sa). Internal audits or inspections may review PSUR/PBRER files for compliance.

Submission: PBRERs or PSURs are submitted electronically:

- In the **EU**, the **PSUR Repository** (via EMA’s eSubmission Gateway or Web Client) has been mandatory since 2016 (www.ema.europa.eu). Both centralized and national PSURs go through this single portal. PSURs are presented as a new eCTD sequence in the respective eCTD lifecycle of the concerned product, and the legally binding submission deadline is the one published in the EURD list. The repository assigns the procedure number and tracks the assessment by the appointed EMA administrator / Rapporteur. Responses to questions (RSI = request for supplementary information) also flow through this system.
- In the **US**, PBRERs/DSURs (for INDs/NDA) are submitted via FDA’s Electronic Submissions Gateway in eCTD format (or in the FDA-preferred E2B XML case report format for expedited reports, but for aggregate it’s eCTD). The FDA requires adherence to *FDA’s eCTD standards*, and DSURs intended for FDA should contain the IND annual report appendix as mandated (FDA expects Form FDA 1571 to accompany each IND annual report (FDA)).
- In **other regions**, increasingly electronic submissions (e.g. eCTV/NeCTAR in Japan, SEMP in India, etc.) are used. Where not yet electronic, paper CTD submissions may still occur, but this is phasing out. The actual guidance documents (EU GVP Module VII, US FDA guidances) provide specific (often modest) differences in format, but generally an eCTD PBRER has the same content worldwide, adapted per local regulations.

Assessment: National and regional regulators review PSUR/PBRERs systematically. For EU centralized products, a Rapporteur (from a member state) performs a PSUR assessment under the Pharmacovigilance Risk Assessment Committee (PRAC) framework (www.ema.europa.eu). The result is a PRAC assessment and possibly a CHMP recommendation. For national products, one or more Member States may review the PSUR (often via the Mutual Recognition or EU Single Assessment procedures). If questions arise, regulators may issue a formal request for information (RSI) to the MAH, to which the MAH must respond (usually within 30-60 days). The RSI process is managed through the PSUR Repository as well (www.ema.europa.eu).

In the US, FDA’s CBER/CDER reviews PSURs/PBRERs on file, and may issue an Information Request or new label recommendation. However, if the sponsor uses PBRER upstream of NDA submission (rare), it guides ongoing safety dialogue with FDA. By statute, FDA also reviews IND annual reports (now DSURs) to see if

trials should continue as is.

Cross-report Coordination: The **modular approach** advocated (see EMA GVP VII, VII.B.5) means that information common to multiple documents (such as DSUR, RMP, PSUR) should be prepared once and reused. For example, the Company Core Data Sheet (CCDS) and Investigator Brochure (IB) often serve as Reference Safety Information for PSURs and DSURs respectively (www.prometrika.com). Sponsors might maintain a global data sheet so that all documents draw from a single vetted safety profile. This reduces duplication and ensures consistency across reports (istitlaa.ncc.gov.sa).

Recordkeeping: Copies of all submitted PSURs, and responses to regulator queries, must be kept. In the EU, submissions through the central repository are archived by EMA. Sponsors also keep records of their internal review (sign-offs by responsible persons). During inspections, regulatory authorities may request the "PSUR file" or "DSUR file" to verify compliance and content control.

4.6 Real-World Example: COVID-19 Vaccine PSURs

The COVID-19 pandemic illustrated accelerated pharmacovigilance processes. For COVID-19 vaccines, regulators established *monthly* safety reporting in the first year (an extreme case of accelerated periodic reporting) (www.ema.europa.eu). In the EU, special guidance mandated very frequent PSURs for these vaccines, reflecting the critical need for real-time benefit-risk data under emergency rollout. This case shows that the PSUR system can be adapted in extraordinary situations. However, for most products the standard schedules noted above apply.

(Case Note: For example, Comirnaty (Pfizer's COVID-19 vaccine) had monthly PSUR submissions as specified by EMA, with very short submission deadlines to ensure rapid review. This regimen was an exception justified by public health urgency (www.ema.europa.eu).)

5. The DSUR in Detail

5.1 Purpose and Scope

The **Development Safety Update Report (DSUR)** is the annual safety report for investigational drugs. Its purpose is to provide regulators **with a comprehensive, periodic review of all safety information arising from a drug's clinical development** (www.researchgate.net) (www.scribd.com). Key points:

- **Scope:** DSUR covers data from all clinical trials in all participating regions (and any marketing if the drug is approved somewhere) for a given active substance, its fixed combinations, and all dosage forms/indications being studied (www.scribd.com). If the same investigational drug is studied under multiple INDs or CTAs, the sponsor should coordinate to produce one global DSUR (see below) (www.scribd.com).
- **Owner:** The **sponsor of the clinical trial(s)** is responsible. In ICH terms, the sponsor "takes responsibility for the preparation, content and submission of a DSUR" (www.scribd.com). This is typically the biotech/pharma company sponsoring development. If the sponsor is a consortium or there are co-

development partners, they should agree – ideally submitting a single DSUR. The sponsor may delegate drafting (e.g. to a CRO), but cannot delegate the responsibility for content or reporting.

A DSUR includes both safety and benefit-risk elements for development. It aims not only to analyze risks but also comment (briefly) on the emerging benefit (efficacy signals) of ongoing trials (www.researchgate.net). It is a **global annual safety summary**, providing one unified document instead of multiple local annual reports.

5.2 Content and Structure

ICH E2F provides a detailed outline of DSUR contents. Table 2 (below) compares high-level sections of a DSUR with those of a PBRER, highlighting parallels and unique elements. In summary, a DSUR typically contains:

1. **Administrative Information:** Sponsor name and contact, product(s) name, DOSAGE form, reporting period, DLP, etc. (Often unnumbered cover info, but included in Section I).
2. **Worldwide Marketing Approval Status (if any):** Since DSUR covers development, this is usually “none” until the drug is authorized. If the drug was (rarely) approved in one country while still in trials elsewhere, the DSUR should note that.
3. **Actions Taken for Safety Reasons:** Any clinical holds, suspensions, or risk management actions taken related to trials.
4. **Changes to Reference Safety Information (RSI):** Updates to the Investigator Brochure (IB) or protocol safety sections that occurred (similar to PSUR, but here IB is the RSI) (www.scribd.com).
5. **Inventory of Clinical Trials:** A table or list of all clinical studies ongoing or completed in the reporting period, including trial IDs, phase, indication, patient numbers (www.scribd.com).
6. **Estimated Cumulative Exposure:**

- **6.1 Cumulative Subject Exposure** (all trials in development program) – often expressed as subject-years by age group or region (www.scribd.com).
- **6.2 Patient Exposure from Marketing Experience:** If the drug is marketed anywhere, include marketing exposure (customer usage) up to DLP (may be limited if recently launched) (www.scribd.com).

7. **Safety Data Presentations:**

- **Line Listings:** Tabulated lists of **serious adverse reactions** that occurred during the reporting period (www.scribd.com). (ICH E2F calls for interval line listings of serious adverse reactions, plus cumulative summary tabulations of serious adverse events.)
- **Tabulations:** Cumulative summary tabulations of serious adverse events across the development program (www.scribd.com). This typically includes totals by body system (System Organ Class) and important events, often per trial or per age group.

8. **Significant Findings from Clinical Trials:**

- 8.1 Completed trials (new data).
- 8.2 Ongoing trials (new interim safety data).

- 8.3 Long-term follow-up (e.g. of previously observed patients).
- 8.4 Other therapeutic use of the investigational drug (off-label or expanded access programs).
- 8.5 New safety data related to combination therapies. These sections discuss any inference or signal from the data, such as unusual events, trends, or risk factors.

9. **Safety Findings from Noninterventional Studies:** If any postmarketing observational studies or epidemiology were done alongside development, include here.
10. **Other Information:** Any other safety-related info (e.g. updates to risk management, toxicology, discussion of benefit).
11. **Benefit-Risk Appraisal:** While not always a separate heading, a concluding section should comment on benefit-risk for trials participants. E2F does mention “statements on the benefit-risk balance” (www.researchgate.net), although this is less formally structured than in the PBRER.

The DSUR is often structured very similarly to a PSUR in terms of numbering (in fact, ICH shows DSUR Table of Contents that mirrors PSUR, but tailored to development) (www.scribd.com) (www.scribd.com). The excerpts above from the E2F guideline and its content list reinforce the overlap. For example, the emphasis on listing worldwide status and changes to RSI in Sections 2–4 mirrors the PBRER, while sections 5–9 align closely (clinical trial inventory vs clinical trial summaries in PSUR, etc.) (www.scribd.com) (www.scribd.com).

Critically, the DSUR **“will essentially cover all requirements of the existing periodic reports required during clinical development in the US and EU”** (www.researchgate.net). It integrates IND annual report content (trial status, safety findings, study list, registry results) and EU ASR content (IB updates, exposure tables) into one. Because of this comprehensive scope, preparing a DSUR can be labor-intensive: all global trials must contribute data, safety reviews must be done per trial, and cumulative analyses performed. The sponsor ensures that all relevant data (even from CROs or partners) are included in the aggregate DSUR.

Multiple Sponsors / Single DSUR

In co-development scenarios (e.g. a drug licensed by multiple companies, or a collaborative consortium), the E2F guideline instructs: **“When more than one sponsor is involved in drug development… the parties should arrange to prepare a single DSUR, if possible.”** (www.scribd.com). This ensures consistency and avoids conflicting reports. If separate DSURs must be prepared (for different indications or geographies), the parties should clearly define boundaries (each DSUR specifying which trials it covers) (www.scribd.com).

5.3 Ownership and Responsibility (Sponsor)

By definition, a DSUR is prepared by the **sponsor of the clinical trial (or development program)**. The FDA/E2F guidance is explicit: “The sponsor* of a clinical trial is considered responsible for the preparation, content and submission of a DSUR” (www.scribd.com). In practice, the sponsor assigns the DSUR to the head of pharmacovigilance or clinical safety. The sponsor may delegate actual drafting to a CRO or affiliate PV unit, but the sponsor’s ultimate clinical safety officer or QPPV (EU) signs off on it.

Responsibility extends until the DSUR is submitted to all relevant authorities (IND Annual Report to FDA, ASR to EU CAs, etc.). Even after marketing approval, if clinical trials continue under the original IND/CTA, the sponsor still prepares DSURs (unless the IND is closed).

Marketing approval does not by itself end DSUR responsibilities: DSURs continue for as long as national or regional rules require. A final DSUR is designated when the annual-report obligation ends in the relevant country or region, and it should say so (www.scribd.com). Once approved, the Marketing Authorization Holder (who might be the same company or a different licensee) also has PSUR/PBRER duties, which may run in parallel with the DSUR while development continues.

5.4 Timelines and Synchronization

As noted, DSURs are **annual**. The DSUR timeframe begins on the date of sponsor's first authorization to conduct a clinical trial in any country (the DIBD) (www.prometrika.com). For example, if the first clinical trial authorization (IND in US or CTA in EU/Japan) was granted on 10 June 2023, then the first DSUR will cover 10 Jun 2023–9 Jun 2024. Subsequent DSURs cover successive 12-month periods.

ICH E2F calls for DSUR submission to the concerned authorities no later than 60 calendar days after the DSUR data lock point. The FDA requires IND annual reports within 60 days of the IND anniversary date. The EU CT directive required DSUR/ASR "within 60 days" historically, now replaced by similar CTR language. Sponsors should confirm each jurisdiction's deadline when setting the operational due date.

Aligning DSUR and PBRER schedules: When a drug nears approval, sponsors often try to coordinate the final DSUR and first PSUR. Regulatory guidance acknowledges this: "the next DSUR should be no longer than one year… [aligned] with DLPs of the PBRER… with approval from authorities" (www.prometrika.com). In practice, a company might shift the DSUR cycle to match the planned first PBRER date. For instance, if a drug is approved on 1 April 2024, the sponsor might take the DSUR that would have been due late June 2024 and align its data lock point with the first PBRER, while still preparing the DSUR and PSUR/PBRER as separate, complete reports. Under ICH E2F each report should be comprehensive and stand alone, even where relevant safety findings appear in both. Such synchronization often requires notifying the agencies (e.g. through an IND amendment or pre-consultation).

5.5 Global Perspectives

Different regions may have minor variations in DSUR practice:

- **Europe:** The EU Clinical Trial Regulation (536/2014) and previous Directive mandated annual safety reports. In many EU countries, the DSUR is explicitly required for any ongoing trial (www.hpra.ie). Regulators expect one DSUR for global data. Some NCAs have issued local guidance (e.g. Spain's AEMPS annual report form) but generally accept ICH DSUR format. In countries that were not EU e.g. the UK MHRA also follows similar practice.
- **United States:** While not codified, FDA strongly supports adopting ICH DSUR. FDA's E2F guidance (draft 2008, final August 2011) and its IND annual-report guidance state that FDA will accept the DSUR to meet the IND annual report requirement (FDA) (www.ema.europa.eu). Sponsors must still include required IND report elements (e.g. signed FDA forms) with the DSUR. Submission is done via CBER/CDER channels (as part of IND/IDE annual).

- **Japan:** Japan has implemented ICH E2F. Check applicable Japanese reporting requirements before treating an ICH-format DSUR as satisfying a local obligation.
- **Global Use:** In practice, multinational programs almost always use the ICH DSUR everywhere (no country insists on a different format). Some emerging regions (Brazil, China) may require an annual safety report, and increasingly accept ICH-style DSUR.

5.6 Case Example: Harmonizing DSURs and PBRERs

Example Scenario: A pharmaceutical company is developing “Drug X”. The first Phase I IND was approved in Canada on 1 January 2020 (this is the DIBD). The company submits a DSUR covering 2020, and then annually (2021, 2022, 2023). In parallel, Drug X obtained FDA Breakthrough status and was submitted for US approval, which is granted on 1 July 2023. The sponsor coordinates with regulators to align reporting: the DSUR continues on its annual cycle while development continues, and separate PSURs/PBRERs begin on the post-approval schedule set by each authority. Each report follows its own interval and deadline, and relevant safety findings may appear in both.

This case illustrates the **transition** from clinical-phase reporting (DSUR) to postmarketing reporting (PBRER) and the need for careful timing coordination.

6. PSUR/PBRER vs DSUR: A Comparative Analysis

While PSUR/PBRER and DSUR share a common goal (periodic safety evaluation), their contexts differ fundamentally:

- **Lifecycle Stage:** DSUR applies to **clinical development** (investigational use, including development that continues after approval), whereas PBRER applies **post-approval** (authorized products). Both may be due in parallel under national or regional rules.
- **Owner:** As noted, the DSUR is the **clinical sponsor’s** report, while the PSUR/PBRER is the **MAH’s** report. In many cases, after marketing approval the original sponsoring company may also be the MAH (so responsibilities shift internally). In some cases, different companies may hold development vs marketing rights, requiring transfer of safety reporting duties at approval.
- **Content Focus:** DSUR content focuses on **trial participants** (exposures and events in studies). PBRER content focuses on **real-world patients** (use in practice, plus possibly remaining trials). Accordingly:
- **Exposure Data:** DSUR exposure is measured in trial subjects and patient-weeks; PSUR exposure is measured in patient-years on therapy (often estimated from sales or prescriptions).
- **Safety Events:** DSUR must include all serious adverse events from trials (with case narratives if needed), whereas PSUR includes spontaneous reports and study data equally (with emphasis on aggregated tabulations).

- **Benefit Info:** DSUR may briefly note efficacy findings from trials to contextualize risk; PBRER explicitly includes efficacy information only to the extent needed for benefit-risk evaluation (and only for approved uses) (www.scribd.com).
- **Timing:** DSURs are uniformly annual; PSUR frequency is variable (initially more frequent, then extended, as per regulations). Because of this, the volume of data per report may differ: some PSURs can cover multiple years (if on a 3-year cycle) requiring more historical context. DSURs rarely exceed one year of data.
- **Sources of Data:**
- DSUR: primarily *internal clinical trial data* (though often pooled from multiple countries) (www.scribd.com). It may include pharmacokinetic or pharmacodynamic updates if new.
- PBRER: a broader set including *postmarketing surveillance, smaller local studies, expanded access data, etc.* Development trials (completed prior to approval) may also be included as background, but emphasis is on what's new since last marketing.
- Both may consider literature, but PBRER tends to rely more on published case reports from practice, whereas DSUR would mention publications of trial results.
- **Regulatory Triggers:** A DSUR is generally submitted because it's the scheduled annual report. A PSUR/PBRER is also scheduled, but regulators can request *ad hoc* PSURs for specific issues (e.g., immediately after a signal is detected elsewhere) – these are not part of DSUR practice. Conversely, there is no concept of an "ad hoc DSUR" – safety concerns in trials are usually addressed via protocol amendments, IND safety reports (e.g. 15-day reports) or amendments, not unscheduled annual reports.
- **Overlap Management:** If a product is under development and marketing simultaneously (e.g., if a country approves a drug while trials continue), two mechanisms may run in parallel. In that situation, the sponsor/MAH should clearly define what content goes into the DSUR vs the PSUR. The MAH should still include relevant clinical-trial findings in the PBRER even when those findings also appear in the DSUR, since each report must stand alone (though ICH guidance suggests unique DSUR sections that specifically address marketed exposure if applicable) (www.scribd.com).

The table below encapsulates these differences:

Aspect	PSUR/PBRER (Postmarketing)	DSUR (Development)
Applicability	Authorized product. Postmarketing surveillance.	Investigational product. Ongoing clinical research.
Responsible Party	Marketing Authorization Holder (MAH)	Clinical Sponsor (of the trial program)
Typical Timing	Scheduled per regulatory cycle (e.g. 6-mo, 12-mo, etc.)	Annually (every 12 months from first trial start)
Reporting Window (DLP)	Ends on a defined marketing-based date (e.g. marketing application anniversary or fixed CN)	Ends on a developer's chosen annual date (often sponsor's IND anniversary or IBD)

Aspect	PSUR/PBRER (Postmarketing)	DSUR (Development)
Deadline after DLP	70 days (EU, intervals up to 12 months) or 90 days (longer intervals); the EURD list date is binding	No later than 60 calendar days (ICH E2F); IND annual report within 60 days of the IND anniversary
Subject Exposure Metric	Patient-years of drug exposure (postlaunch)	Subject-years in clinical trials (by dose, route, etc.)
Safety Data Sources	Spontaneous AEs, literature, postmarketing studies, and relevant clinical-trial data, including trials in unapproved indications or populations	All clinical trial data (phases I–III), including adverse events, fit-for-purpose safety studies, etc.
Line Listings	Usually not exhaustively included in text (focus on summaries) (istitlaa.ncc.gov.sa)	Provided for serious/fatal events in trials (detailed as needed) (www.scribd.com)
Benefit Discussion	Formal benefit-risk section (integrated analysis) (www.prometrika.com)	Typically a brief benefit comment or risk/benefit statement (www.researchgate.net) (development benefit is provisional)
Regulatory Use	Basis for updating labelling, RMP, or issuing safety communications; reviewed by PRAC/EMA or FDA	Basis for assessing trial safety oversight; informs IRBs, ethics committees, and IND continuation
Global Harmonization	ICH E2C(R2) standard; variations in local deadlines (e.g. EU vs US)	ICH E2F global standard; replaces IND annual/EU ASR

(Table 2: Key differences in focus and structure between PSUR/PBRER and DSUR reports.)

6. Implementation Issues and Perspectives

Data Collection and Technology: Modern pharmacovigilance relies on electronic safety databases (e.g. Argus, ArisGlobal) to compile ICSRs from worldwide sources. For PSUR/PBRER, these systems can generate aggregate tables for adverse events (periodic tabulations). Similarly, clinical trial management systems hold subject exposure and trial data. Effective DSUR preparation requires careful integration of the clinical trial database (often via data transfers between CROs) with safety databases. XML standards (ICH E2B(R3)) are used to structure data. Sponsors may use specialized PV software to build line listings and safety narratives. Document management tools (Veeva, MasterControl) help manage draft review cycles. ECTD publishing tools package the final report for submission.

Governance and Oversight: Within a company, there must be clear SOPs for PSUR/PBRER and DSUR production. Typically, a steering committee or senior safety physician approves the final report (often called “Sign-Off”). Quality assurance (QA) may audit a sample of reports for compliance with regulations (as part of periodic PV system inspections). On the regulatory side, agencies conduct good pharmacovigilance practice (GVP) inspections that include checking PSUR/PBRER submission history, containment of data, and responsiveness to queries . For example, the EU Network and FDA may verify that all PSURs were filed by deadline, that the report content is consistent with the product information, and that new signals were appropriately addressed.

Challenges: Common issues include aligning data from global trials for a single DSUR, managing multiple languages (PSURs in the EU require translations once assessment is done (www.ema.europa.eu)), and stitching together data from disparate systems. Timing constraints can be tight, especially for complex global products or those on irregular schedules. For small companies or academic sponsors, preparing a DSUR can be particularly resource-intensive as it may require contracting specialists.

Future Directions: There is a movement toward more structured, data-driven aggregate reports. EMA now asks MAHs to manage PSUR procedures in its IRIS platform, while initial PSURs and responses to requests for supplementary information are still submitted to the PSUR Repository. Concepts like “theory of change” for safety (evidence synthesis beyond tabulations) are emerging. Advanced analytics and real-world evidence could eventually feed into how sections like benefit-risk are done. But the core concept of PSUR/PBRER and DSUR is likely to remain central in pharmacovigilance.

7. Case Studies and Practical Examples

Case Study 1 (illustrative scenario): Harmonizing Global Reporting Consider a hypothetical large pharmaceutical firm with a worldwide portfolio that adopted ICH formats to streamline reporting. For a new oncology drug, they maintained a single DSUR covering all countries’ trials (FDA INDs, EU CTAs, Japanese CTN, etc.). They set the DSUR DLP to March 1st each year (matching their IND anniversary). When the drug gains EU approval while trials continue, the firm keeps the DSUR on its annual cycle and starts separate PSURs/PBRERs on the EU schedule, aligning data lock points where authorities agree. Each report remains complete and stand-alone, which avoids gaps in either reporting stream.

Case Study 2 (illustrative scenario): Data Sharing vs. Duplication Consider a hypothetical biotech company that holds global trials but licenses US commercialization to a partner. During development, the biotech prepared all DSURs. Upon US approval, the partner took over PSURs in the US, while the original company continued to be MAH in Japan/EU. They agreed that the partner’s PSUR would incorporate any critical late-breaking clinical trial data from the biotech (since additional Phase III data were still under analysis). Conversely, the biotech’s DSUR used some safety data from the US trials submitted by the partner. They established a joint safety database access to minimize conflicts. A final DSUR would be designated only when the annual-report obligation actually ends in a jurisdiction, for example when development there stops.

Expert Commentary: Pharmacovigilance experts note that while the DSUR and PBRER frameworks are similar in spirit, in practice PSUR/PBRER tends to be a broader *risk management tool* (often reviewed in the context of RMPs and periodic safety meetings with regulators) whereas the DSUR is more of a *safety summary tool* for ongoing trial oversight (www.prometrika.com) (www.prometrika.com). Regulatory inspectors will compare PSUR/PBRER submissions against RMPs and question any discrepancies, so alignment with RMP is key. Industry professionals emphasize early planning: for example, scheduling the DSUR writing well before submission deadline to allow input from global investigators and data review committees, and similarly kicking off PSUR planning immediately after each DLP to coordinate pharmacovigilance and medical writing teams.

Statistical Aspects: While precise statistics (e.g. number of PSURs submitted per year globally) are proprietary, it is known that large MAHs submit hundreds of PSURs annually across regions. In signal management terms, one analysis (European response times) indicated that PSUR assessments by EMA typically take up to 134 days (going up to 2015, see EMA PSUR queries) (www.ema.europa.eu). For DSUR, compliance rates are high in regulated pharma companies, though no public dataset is available.

8. Future Directions

Looking ahead, several trends may shape aggregate safety reporting:

- **Global Harmonization:** Continued convergence of formats and electronic submissions worldwide. The FDA and EMA may further integrate PBRER usage (although U.S. still has no legal mandate). Emerging markets are adopting ICH formats, reducing fragmentation.
- **Digital Transformation:** Regulatory agencies and MAHs are moving toward structured data submissions (e.g. extracting case data from databases rather than attaching spreadsheets). Semantic tagging (e.g. ISO IDMP standards) may allow key tables (exposure, major adverse events) to be machine-readable in submissions. EMA's **IRIS platform** is now used to manage PSUR procedures, but it coexists with the PSUR Repository, which still receives initial PSURs and responses to requests for supplementary information.
- **Risk-Benefit Analytics:** The PBRER's focus on benefit-risk may lead to more formal quantitative methods (like PrOACT-URL frameworks or visual scales) becoming part of reports. Advanced data-mining could help highlight which new risks truly alter benefit-risk versus random fluctuations.
- **Integrated Reporting:** When development and marketing overlap, sponsors increasingly synchronize data lock points and share source data between reports. Under current ICH E2F guidance, however, the DSUR and PSUR/PBRER each remain comprehensive, stand-alone reports.
- **Regulatory Initiatives:** The EU's planned new pharmacovigilance legislation (e.g. revisions to GVP) and the FDA's ongoing Rulemakings (like the proposed MedWatch Annual Summary) could modify existing requirements. For example, FDA has proposed requiring an Annual Report for marketed products too, which may align more with PBRER principles.

In all cases, the core goal remains patient safety: as methodologies evolve, the principle that PSUR/PBRER and DSUR provide essential safety surveillance will not change.

9. Conclusion

PSUR/PBRER and DSUR are complementary pharmacovigilance deliverables covering a drug's lifecycle. The **PSUR/PBRER** is owned by the marketing authorization holder and synthesizes safety and benefit data for products in commerce, submitted on a schedule set by regulators. The **DSUR** is owned by the clinical trial sponsor and provides an annual safety update during development. Each report has a detailed structure (as defined by ICH E2C(R2) or E2F) and is mandated (or strongly encouraged) by international guidelines and national laws. Timelines and submission processes differ: PSUR/PBRER may be every 6 or 12 months (with

deadlines of 70–90 days post-data lock point) (www.ema.europa.eu) (istitlaa.ncc.gov.sa), whereas DSURs are annually submitted after each 12-month period (meeting IND/ASR requirements) (www.scribd.com) (www.hpra.ie).

Understanding who “owns” which report and what each contains is critical for compliance. In practice, sponsors often harmonize reporting – using DSUR data to feed into PSUR/PBRER and vice versa, where applicable (www.prometrika.com) (www.scribd.com). Both report types are evaluated by regulators to ensure emerging risks are detected and managed, thereby protecting public health.

This review has explored the history, contents, processes, and strategic considerations for PSUR/PBRER and DSUR. In an era of globalization, regulatory convergence, and technological change, they remain key instruments of the safety governance framework around medicinal products.

Table 1. *Summary Comparison of PSUR/PBRER and DSUR*

Characteristic	PSUR / PBRER (Marketing Phase)	DSUR (Clinical Development Phase)
Applicable to	Approved (marketed) products	Investigational products
Report Owner	Marketing Authorisation Holder (MAH) (www.ema.europa.eu)	Clinical Trial Sponsor (www.scribd.com)
Frequency	Usually 6- or 12-month cycles (per regulatory schedule, e.g. EURD list) (www.ema.europa.eu)	Annually (every 12 months from trial start) (www.scribd.com)
Data Lock Point (DLP)	Typically aligned with product’s approval “birth date” or scheduled interval ending	Aligned with sponsor’s first trial date (Development International Birth Date) (www.prometrika.com)
Submission Deadline	~70 days post-DLP (if interval ≤12 mo) or ~90 days (if >12 mo) (www.ema.europa.eu)	No later than 60 calendar days post-DLP (ICH E2F); IND annual report within 60 days of the IND anniversary
Main Content	Cumulative safety data from postmarketing use (ICSRs, literature, RWE), clinical trials data, and benefit-risk analysis (www.prometrika.com) (istitlaa.ncc.gov.sa)	Cumulative trial exposure, tabulated adverse events from trials, safety narrative from ongoing/completed studies (www.researchgate.net) (www.scribd.com)
Benefit Discussion	Formal benefit-risk evaluation section (www.prometrika.com)	Limited to trial context (evolving efficacy) (www.researchgate.net)
Reference Safety Info	Market label (SmPC/PI) at DLP (for RSI)	Investigator’s Brochure (IB) or trial documents
Regulatory Purpose	Update product label, risk management, inform regulators on emergent issues	Assess safety in trials, inform IRBs/ethics committees and regulators about trial continuation
Guidelines (ICH)	E2C(R2): PBRER (replaces ICH E2C R1 PSUR) (www.ema.europa.eu)	E2F: DSUR (common standard for IND annual reports) (www.ema.europa.eu)

Table 2. *Typical Sections in PBRER vs DSUR (Illustrative)*

Section	PBRER (Postmarketing)**	DSUR (Clinical Development)
Introduction	Intro & background; product details; safety info reference (Label)	Sponsor, product, reporting period; summary of indication & DLP
Marketing Status	Worldwide authorization status and dates	Investigational status (usually “N/A” if no marketing)
Safety Actions This Period	Updates to labelling, safety alerts, withdrawals, etc.	Safety-related trial actions (holds, protocol changes)
Changes to RSI	Label changes since last report	IB updates since last DSUR (reference safety info)
Trial Data	(If postmarketing trials continue, brief)	Detailed inventory and status of all trials (phase, numbers)
Exposure (Cumulative)	Patient-years of marketed use (estimates)	Subjects (and patient-time) from ongoing/completed trials (3.6.1) (www.scribd.com)
Exposure (Interval)	Exposure since last report (if multi-year gap)	Subjects enrolled in reporting period (for context)
Adverse Events	New safety signals or trends (published cases, spontaneous reports)	Tabulations of serious AEs in trials; line listings over interval
Significant Findings	New signals from all sources (trials, med lit)	New safety issues in completed trials / Ongoing trials updates
Nonclinical/Literature	Relevant new nonclinical findings or lit reviews	Any relevant new animal or in vitro data (rarely)
Benefit-Risk Evaluation	Integrated risk-benefit discussion (core section) (www.prometrika.com)	Brief mention of efficacy vs risk in trials (e.g. emerging trends) (www.researchgate.net)
Appendices	Detailed tables or case listings (as needed)	Append detailed tables (line listings, study listings, etc.)

Sources: ICH E2C(R2) guideline; ICH E2F guideline; EMA GVP Module VII (istitlaa.ncc.gov.sa); FDA guidances (www.fda.gov) (www.researchgate.net); expert literature (www.prometrika.com).

Acknowledgments

The content herein is based on publicly available guidelines and expert publications (www.ema.europa.eu) (www.prometrika.com) (www.scribd.com). The authors gratefully acknowledge EMA, FDA, ICH, and other regulatory resources for their comprehensive guidance documents, and industry experts for applied insights. All claims are supported by cited regulatory documents and authoritative sources.

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1. https://www.ema.europa.eu/en/human-regulatory-overview/post-authorisation/pharmacovigilance-post-authorisation/periodic-safety-update-reports-psurs
2. https://istitlaa.ncc.gov.sa/en/health/sfda/SFDAGVP/Pages/Article_007.aspx
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