A Textbook of

Clinical Pharmacy

for Pharmacy Students

Lesson 2:

Drug Information for Clinical Pharmacy

ISBN-13: 979-13-992562-3-9

Porto, Portugal.

Published by CIPF, S.L.

Suggested citation: Fernandez-Llimos F. Lesson 2: Drug Information for Clinical Pharmacy. In: A Textbook of Clinical Pharmacy for Pharmacy Students. Porto: CIPF; 2026.

Available at http://www.cipf-es.org

Lesson 2: Drug Information for Clinical Pharmacy[1]

Contents

2.1 Drug Information

Drug information is a core domain of knowledge in clinical pharmacy, with its own concepts, methods and reference sources that clinical pharmacists must master in a structured way to support pharmacotherapy optimization interventions. Clinical pharmacists are expected to answer specific, contextualized questions such as how to individualize dosing in renal impairment, how to interpret a drug interaction signal in the context of comorbidities, or how to explain complex benefit–risk information to patients in an understandable form. These tasks require the ability to identify relevant questions, to select appropriate information sources according to a hierarchy of evidence, and to interpret sometimes discordant data considering clinical pharmacology, pathophysiology and patient preferences.

2.2 Hierarchy of drug information sources

Drug information relevant to clinical pharmacy can be grouped into three broad families: primary evidence (original data), secondary sources (tools that index or synthesize primary studies) and tertiary or reference works (summaries and interpretations prepared for routine use). The concept of a “hierarchy” does not imply that one family is always superior to the others, but that they occupy different positions in the chain of reasoning from raw data to clinical recommendations. In practice, a clinical pharmacist often starts from a tertiary source to orientate, turns to secondary sources to identify the most relevant primary evidence, and then

[1] Although American spelling is commonly used in this reference book, European spelling is used when referring to EU official documents.

returns to a summarizing format (e.g. a guideline or a local protocol) when formulating a recommendation.

2.2.1 Primary sources

Primary sources of drug information are materials that present **original data or first-hand analyses about medicines**, rather than summarizing or reinterpreting previous work. In the context of clinical pharmacy, they form the evidentiary substrate from which secondary and tertiary resources later extract and organize information for routine use. Using primary sources allows the clinical pharmacist to confirm details, understand nuances and limitations, and critically appraise how well the available evidence corresponds to a specific patient or practice setting.

The most familiar primary sources are **scientific articles in peer-reviewed journals** that report original work. **Peer review** is the process by which a manuscript submitted to a journal is critically assessed by independent experts who are not part of the editorial staff. These reviewers examine the scientific rationale, methods, analyses, and interpretation or the manuscript[2] submitted, and provide recommendations about whether the manuscript should be accepted, revised, or rejected. Although the value of peer review is debated, it remains an important extension of the scientific process because it helps journals select suitable articles and often improves the clarity and completeness of reporting. For clinical pharmacists, awareness of the peer-review process is relevant because it provides an initial, though not infallible, quality filter for primary literature used in drug information work.[3]

Within a biomedical journal, primary literature can take several forms. **Original research articles** present detailed reports of new data, typically organized into sections such as introduction, methods, results, and discussion (the IMRAD structure), and they are considered the core primary literature. **Case reports and case series** describe observations from one or several patients, for instance an unusual adverse drug reaction, an unexpected response, or a complex therapeutic challenge; these are also classified as primary sources because they convey first-hand clinical information. **Short communications or brief reports** may present smaller studies or preliminary findings that are relevant to drug therapy but not extensive enough for a full-length article. In contrast, **narrative reviews** and most **editorials** are generally categorized as secondary sources, because they synthesize or comment on existing primary data rather than generating new data themselves. However, **systematic reviews, with or without meta-analyses**, should be considered as original research articles because, despite they use data originated by other primary sources, they produce new results (the evidence synthesis). Evidence synthesis will be further explored in Pharmacoepidemiology and Pharmacovigilance course (5th year).

Other primary information sources can have more restricted distribution channels (gray literature[4]). Beyond journal articles, several other materials can be considered primary drug information sources. **Conference abstracts and posters** often provide the earliest public

[2] The term "manuscript" is still used to refer to the text submitted by authors to the journal, even though it is not handwritten anymore.
[3] https://www.icmje.org/recommendations/browse/roles-and-responsibilities/responsibilities-in-the-submission-and-peer-peview-process.html
[4] Gray literature is information about a topic that is produced outside commercial publishing channels (such as reports, theses, or conference documents) and is therefore not formally published in books or peer-reviewed journals.

disclosure of new findings about medicines, even if details are limited and results may later change. Regulatory documents produced during marketing authorization procedures, such as assessment reports or detailed summaries of clinical and pharmacological data, function as primary sources because they contain original analyses of efficacy, safety, and quality submitted to authorities. In addition, **internal technical reports or doctoral theses** may provide first-hand information on medicine performance, tolerability, or use patterns in routine care.

Assessing the quality of a journal (Journal-based metrics)

Not all journals subject submitted manuscripts to a rigorous, independent peer-review and editorial process, so it is necessary to critically evaluate the quality and trustworthiness of a journal before relying on it as a source of drug information.

Journal-based metrics such as the **Journal Impact Factor** (JIF, from Clarivite) and **CiteScore** (from Scopus) are widely used as shorthand indicators of the "quality" of a journal, because they summarize how often its recent articles are cited in other indexed publications. The JIF is calculated by dividing the number of citations in a year to articles and reviews published in the previous two years by the number of those "citable items," whereas CiteScore uses a four-year window and includes a broader range of document types. In practice, these averages are often treated as proxies for journal prestige and, by extension, for the quality of the articles it publishes, and they can influence where authors choose to submit their work and how libraries prioritize subscriptions.

However, the reliability of JIF and CiteScore as indicators of scientific quality is limited and has been strongly criticized. Both metrics are based on arithmetic means in highly skewed citation distributions, so a small number of very highly cited papers can inflate the score while many articles receive few or no citations; consequently, the metric says little about the typical paper in that journal. The values are also sensitive to editorial policies (for example, publishing more review articles, which tend to be cited more, or manipulating what counts as a "citable item"), to field-specific citation practices, and to the selective coverage of the underlying databases (Web of Science for JIF, Scopus for CiteScore). Importantly, high citation rates can reflect factors other than methodological rigor or clinical relevance, including topical fashion, controversy, or self-citation patterns.

For these reasons, major statements on research assessment, such as the **San Francisco Declaration on Research Assessment (DORA)**, explicitly recommend that journal-level metrics should not be used as surrogates for the quality of individual articles, researchers, or clinical evidence. They argue that over-reliance on JIF or CiteScore risks introducing systematic bias into funding, hiring, and promotion decisions, and may distort research priorities. In the context of drug information and clinical pharmacy, journal metrics can at most provide a rough, contextual indication of a journal's citation visibility within its field; they should never replace critical appraisal of the study question, design, methods, and applicability of individual articles when evaluating the reliability and usefulness of evidence for pharmacotherapy decisions.

- DORA. 2024. Guidance on the responsible use of quantitative indicators in research assessment. http://doi.org/10.5281/zenodo.10979644

The risks of predatory journals for drug information

Predatory journals are deceptive publications that present themselves as legitimate scientific journals but systematically undermine scholarly standards by prioritizing rapid, fee-based publication over rigorous peer review and editorial quality. They often engage in aggressive email solicitation, provide misleading information about indexing or impact metrics, list fake or unaware editorial board members, and lack transparency about article processing charges (APCs) and editorial processes. In many cases, manuscripts are accepted with minimal or purely formal "peer review", and articles may contain serious methodological flaws, plagiarism, or even fabricated data that would not pass scrutiny in reputable journals.

For drug information and clinical pharmacy, predatory journals pose a particular threat because they can pollute the literature with unreliable or ethically problematic reports on drugs, ranging from poorly documented adverse reactions to unsound claims about efficacy or safety. Articles in such journals are less likely to report essential elements such as ethics approval, funding sources, robust methods, or appropriate risk-of-bias assessment, which impairs any attempt at critical appraisal. When these low-quality studies are inadvertently incorporated into systematic reviews, guidelines, or clinical decision-support tools, they risk distorting the evidence base that underpins pharmacotherapy decisions. Furthermore, because predatory titles may mimic the names and website designs of established journals, they can be difficult to identify, even for experienced clinicians and researchers. For these reasons, clinical pharmacists must be vigilant in checking journal legitimacy (for example, through indexing status in major databases, recognized publisher lists, and adherence to publication ethics guidelines) before using journal articles as sources of drug information.

- Elmore SA, Weston EH. Predatory Journals: What They Are and How to Avoid Them. Toxicol Pathol. 2020;48(4):607-610.

Pharmacovigilance data adds a further dimension by capturing suspected adverse reactions reported spontaneously by health professionals and patients, as well as signals detected in electronic health records and claims databases. Spontaneous reports are essential for early signal detection, because they may reveal previously unknown adverse effects, interactions or patterns of medication-related harm soon after a product reaches the market. However, they suffer from under-reporting, variable quality of information and lack of a clear denominator (number of exposed patients), which means they cannot usually provide reliable incidence estimates. Clinical pharmacists should therefore treat pharmacovigilance data as hypothesis-generating: a signal that may prompt closer monitoring, a search for corroborating observational or mechanistic evidence, or a careful re-evaluation of the benefit–risk balance in certain groups. Within the EU pharmacovigilance system coordinated by the European Medicines Agency (EMA), the Pharmacovigilance Risk Assessment Committee (PRAC) produces several types of regulatory safety assessments that are highly relevant as drug information sources for clinical pharmacy. At the core of routine post-marketing evaluation are Periodic Safety Update Reports (PSURs), which marketing authorization holders must submit at defined intervals. These reports provide a cumulative, structured review of all available safety data for a medicine (clinical trials, observational studies, spontaneous reports, literature, and, where available, utilization data) and include an integrated benefit–risk evaluation and proposals for

risk minimization or updates to product information. These reports are published on the EMA web-portal.[5]

In sum, primary literature is useful when standard references and regulatory texts do not answer a complex question, particularly in special populations or unusual clinical scenarios. Clinical pharmacists must be competent not only in finding such studies via secondary sources, but also in reading their structure critically: population, intervention, comparator, outcomes, follow-up, and potential sources of bias and imprecision.

2.2.2 Secondary sources

Secondary sources do not usually generate new data; instead, **they organize, index or synthesize primary evidence**. Their role in drug information is to help clinical pharmacists find relevant primary studies efficiently and to provide higher-level syntheses such as systematic reviews and meta-analyses.

Bibliographic databases such as PubMed, Embase and specialized trial registries index biomedical literature with structured fields and controlled vocabularies (e.g., MeSH for MEDLINE), allowing precise searching for medicines, diseases, study designs and outcomes. For clinical pharmacists, knowing how to translate a clinical question into an efficient search strategy is a practical skill: identifying keywords and subject headings for the medicine and condition of interest, combining them with filters for randomized trials, observational studies or systematic reviews, and limiting by language or date when appropriate. Pharmacists should no longer treat PubMed as a generic search engine, but as a tool where they control sensitivity and specificity of their search. Next chapter will focus on electronic sources of information, including PubMed.

Narrative reviews are secondary sources that synthesize and interpret existing primary studies on a topic, but without following a fully predefined, reproducible search and selection protocol. In contrast to systematic reviews, which aim for comprehensive and transparent identification and appraisal of all relevant evidence for a narrowly focused question, narrative reviews typically rely on a more flexible and selective approach to choosing literature. They are often written by authors with subject-matter expertise who integrate findings from diverse study types, theoretical papers, and sometimes policy or practice documents, to provide an overarching perspective, highlight conceptual links, and formulate hypotheses or practice-oriented interpretations. This flexibility allows narrative reviews to address broad or emerging themes in pharmacotherapy and clinical pharmacy, to contextualize drug-related evidence within pathophysiology and health-system constraints, and to draw attention to gaps in knowledge or conflicting data that may not be evident from single primary studies. However, because narrative reviews do not usually declare exhaustive search strategies or explicit inclusion and exclusion criteria, they are more vulnerable to selection bias and to over-representation of the authors' viewpoints, so clinical pharmacists should read them critically, considering the balance of the cited evidence when using them as secondary sources of drug information.

Secondary sources also include **evidence summaries** and **guideline clearinghouses**[6] that collate recommendations from multiple organizations. Examples are national guideline portals, topic-specific databases and publisher platforms that present structured summaries of

[5] https://www.ema.europa.eu/en/medicines
[6] https://www.nice.org.uk/guidance

evidence and recommendations for clinical questions. These resources are useful starting points for common therapeutic decisions, but pharmacists must appreciate that they often lag slightly behind the most recent primary data and may reflect specific health-system contexts. Clinical pharmacists must possess the ability to identify the publication date and evidence cut-off for a guideline or summary, to check whether new pivotal trials have appeared since, and to recognize situations in which local practice or regulatory status differs from the context of the guideline.

2.2.3 Tertiary sources

Tertiary sources are compiled references that **condense and interpret information** from primary and secondary sources for routine clinical use. They are the most frequently consulted tools in day-to-day practice and are essential for clinical pharmacists to build a structured knowledge base.

Pharmacology and pathophysiology **textbooks** explain mechanisms of action, pharmacokinetic principles, class effects and dose–response relationships in a systematic way. They provide the conceptual framework needed to extrapolate beyond specific trial populations and to reason about how organ dysfunction, age, genetics or interactions might modify a drug's behavior. Clinical pharmacy and therapeutics textbooks, typically organized by organ system or clinical condition, integrate this pharmacology with disease pathophysiology, standard treatment options, guideline-based strategies and practical advice on dosing, administration and monitoring. For clinical pharmacists, these works are often the first line of reference when learning the standard management of a condition, and they should be able to move comfortably between drug class-based and condition-based chapters.

Formularies and prescribing references (also called compendia), often national or institutional, add a practical layer by specifying which products and strengths are available, preferred choices within a class, and local recommendations for dosing and monitoring in special populations. They reflect both evidence and local policy constraints, and clinical pharmacists must know how to interpret them considering more general scientific information.

The **main advantage** of tertiary sources is accessibility: they offer concise, clinically oriented information structured around typical questions (indication, dose, contraindications, warnings, interactions, monitoring). Their **main limitation** is that they inevitably lag behind the latest primary data and cannot fully capture all nuances of trial design, subgroup effects or rare adverse outcomes. Clinical pharmacists must therefore learn to read tertiary information with an awareness of its publication date, editorial policy and referencing, and to recognize signals that should prompt a return to secondary or primary sources (for example, when a text states that evidence is limited, conflicting, or under review).

2.2.4 Hierarchical approach to information sources

A hierarchical approach to drug information means choosing sources deliberately according to the type and complexity of the clinical question, rather than using whatever source happens to be nearest. Usually, a clinical pharmacist might **proceed from tertiary to secondary to primary evidence only, when necessary**, while maintaining awareness of regulatory and local policy documents.

For standard questions in common conditions, such as initial dosing and monitoring of an antihypertensive in an otherwise uncomplicated patient, a current, reputable therapeutics textbook and local formulary may be sufficient, supplemented by official product information

and, where relevant, a recent guideline. The hierarchical principle here is that tertiary sources provide an efficient, safe default for well-studied, stable practices. However, when the question concerns a patient who differs from typical trial populations (e.g. advanced organ dysfunction, extreme age, multiple comorbidities) or a medicine with controversial or rapidly evolving evidence, the hierarchy prompts the pharmacist to move "upwards" to more detailed sources: recent systematic reviews, registries, trial reports and regulatory assessments.

The ARCA framework

The ARCA acronym was proposed as a practical tool to assess the **quality of drug information sources for healthcare professionals**, by examining four independent attributes: accessibility, reliability, completeness and applicability (or actionability).

Accessibility refers to how easily and rapidly a professional can obtain the information needed on decision-making. Information is only useful if it is available in time and at the point of care; lack of timely access inevitably leads to poorly informed decisions, even if high-quality information exists somewhere else. Internet-based resources have improved accessibility, but inequities persist, and a key challenge is delivering medicines information directly into clinical workflows, including through mobile health technologies. Accessibility should also consider the language barriers or the paywalled sources.

Reliability concerns the confidence that professionals can place in the truthfulness and methodological soundness of the information. Even high-quality evidence, such as that graded with systems like GRADE, carries some residual uncertainty, but reliability here refers to the credibility of the source and its processes (peer review, independence, transparency), not to an unrealistic expectation of absolute certainty. The expansion of web-based information has multiplied sources of variable reliability, making explicit appraisal of origin, authorship and evaluation methods essential.

Completeness denotes both the exhaustiveness and the up-to-datedness of information on a given medicine, including benefits and harms. Incomplete information can mislead decisions not only by omission but also through **selective under-reporting**, which is more pervasive and potentially more harmful than outright data fabrication, and has been documented, for example, in manufacturer-supplied monographs. Because selective reporting can distort evidence generation and meta-analyses, assessing completeness is critical when judging any drug information source.

Applicability (or actionality) captures whether the information, even if accessible, reliable and complete, actually helps to resolve the concrete clinical problem that triggered the information need. Analyses of European Summaries of Product Characteristics have shown that, although they are highly accessible and reliable and sufficiently complete, their wording may be too vague to support real decisions in specific situations, such as pregnancy and lactation ("use with caution" without actionable guidance). From a clinical pharmacy perspective, the "answer" is only truly applicable if it can be translated into a clear recommendation for or against use, with practical conditions and alternatives where relevant.

- Fernandez-Llimos F. Quality of drug information for healthcare professionals: The ARCA acronym. Pharm Pract (Granada). 2015;13(4):709.

In practice, the decision pathway might look like this. A pharmacist is asked to advise on the use of a novel anticoagulant in a frail, elderly patient with fluctuating renal function and recent gastrointestinal bleeding. A therapeutics textbook and the SmPC will provide baseline dosing recommendations and contraindications but may not fully address this exact scenario. Recognizing this, the pharmacist consults recent systematic reviews or meta-analyses focusing on older patients, observational studies examining bleeding risk in routine practice, and, if necessary, the detailed discussion in regulatory assessment reports to understand how bleeding risks were distributed across subgroups. This information is then integrated with patient-specific factors to formulate a recommendation, which may include dose modification, enhanced monitoring or consideration of alternative therapies. The key message is that the hierarchy is dynamic and question-dependent: clinical pharmacists must learn to decide when a tertiary answer is "good enough" and when it is necessary to climb towards primary evidence.

The hierarchical model also helps in avoiding common pitfalls. One is over-reliance on a single tertiary source without cross-checking against official product information and recent evidence, which can be problematic when texts are outdated or written for another regulatory context. Another is "data dumping" from primary studies or systematic reviews without translating findings into clinically meaningful absolutes for the patient at hand. By teaching pharmacists to move up and down the hierarchy intentionally, starting from concise summaries, consulting higher-level evidence when needed, and then returning to brief, patient-oriented recommendations, drug information becomes a structured, reproducible method rather than an ad-hoc search behavior. This method underpins the evolution of drug information practice from centralized services to point-of-care clinical decision-making by pharmacists, as described in contemporary reviews of drug information centers and their transformation into broader medication policy and e-consult models.

Do not panic!

Next chapter we are going to deal with AI

2.3 EU official medicines information sources

European Union (EU) medicinal product information is governed by a harmonized EU–EEA[7] legal framework, primarily Directive 2001/83/EC and its implementing guidelines, which define the content, structure and language requirements for the Summary of Product Characteristics (SmPC)[8], package leaflet and labelling. For **centrally authorized products**[9], EMA coordinates

[7] European Economic Area.
[8] Initially, Summary of Product Characteristics was abbreviated as SPC, but the abbreviation SmPC was preferred to differentiate them from the Supplementary Protection Certificates (https://single-market-economy.ec.europa.eu/industry/strategy/intellectual-property/patent-protection-eu/supplementary-protection-certificates-pharmaceutical-and-plant-protection-products_en)
[9] **Centralised procedure**, in which the company submits a single EU-wide application that is assessed by the EMA's Committee for Medicinal Products for Human Use (CHMP) and then decided upon by the

the application of these rules using common "Quality Review of Documents" (QRD) templates to ensure consistency across Member States, while national competent authorities apply the same legal framework for nationally, **Mutual Recognition Procedure**[10] and **Decentralised Procedure**[11] authorized medicines.

The overarching legal instrument is Directive 2001/83/EC on the Community code relating to medicinal products for human use, which sets out binding requirements for labelling and the package leaflet in Title V and links them explicitly to the approved summary of product characteristics. Under this Directive, every authorized medicine must be accompanied by **authorized product information** in the official language(s) of the Member State(s), and the SmPC forms the scientific reference on which all other product information must be based.[12]

The European Commission is responsible for the legislation itself and for horizontal guidance, for example on the content of labelling and leaflets. EMA, together with Heads of Medicines Agencies (HMA) and national authorities, operationalizes this framework through procedural guidance, QRD templates and Q&A documents that applicants must follow when drafting and updating SmPC, package leaflet and labelling texts.

Within this framework, the EMA quality review of documents (QRD) templates provide **standard headings, order and wording for the SmPC, package leaflet and labelling**, so that product information is presented in a consistent, legally compliant format across EU procedures. These templates are periodically revised to improve readability and patient-friendliness of the package leaflet while remaining aligned with Directive 2001/83/EC and related guidelines.[13]

Within the same legal framework, the EU is now piloting electronic product information (ePI), in which the SmPC and package leaflet are provided in structured electronic formats to complement or progressively replace paper leaflets. These initiatives do not change the underlying regulatory status of product information but aim to leverage digital formats to improve accessibility, version control and timeliness of safety updates for healthcare professionals and patients.[14]

2.3.1 Summary of Product Characteristics (SmPC)

The Summary of Product Characteristics (SmPC) is the central regulatory information source describing an authorized medicinal product's qualitative and quantitative composition, pharmacological properties and conditions of use, and is intended as the primary, **authoritative**

European Commission. A positive Commission decision results in one marketing authorization that is valid in all EU Member States and EEA countries.

[10] **Mutual Recognition Procedure**, which is an EU marketing authorization route where a product already authorized in one Member State (the Reference Member State) is submitted for recognition in additional Member States, leading to a set of nationally granted, mutually recognized marketing authorizations.

[11] **Decentralised Procedure**, which is an EU marketing authorization route used when the product is not yet authorized in any Member State; the dossier is submitted in parallel to several Member States, with one acting as Reference Member State, and the outcome is again a group of harmonized national marketing authorizations.

[12] https://www.ema.europa.eu/en/human-regulatory-overview/marketing-authorisation/product-information-requirements

[13] https://www.ema.europa.eu/en/human-regulatory-overview/marketing-authorisation/product-information-requirements/product-information-reference-documents-guidelines-0

[14] https://www.ema.europa.eu/en/human-regulatory-overview/marketing-authorisation/product-information-requirements/electronic-product-information-epi

source of information for healthcare professionals in the EU–EEA. It is an integral part of the marketing authorization; therefore, the SmPC both reflects and constrains how the medicine may be promoted and used within its licensed indications, and it must be updated whenever new data affect the established benefit–risk balance or appropriate use.[15]

From a regulatory perspective, the legal basis for the SmPC is laid down in Directive 2001/83/EC, particularly Article 11 and Annex I, which specify the **mandatory headings and content areas** to be addressed. The European Commission guideline on SmPC further details how information should be structured and phrased, while EMA provides operational guidance and standard templates to harmonize format and wording across centrally authorized and nationally authorized products. This harmonization is crucial for ensuring that prescribers and pharmacists are confronted with a consistent structure regardless of the specific product or authorization procedure, thus facilitating navigation and comparison between medicines within the same therapeutic class.

Structure of a SmPC

1. Name of the medicinal product
2. Qualitative and quantitative composition
3. Pharmaceutical form
4. Clinical particulars
    - 4.1 Therapeutic indications
    - 4.2 Posology and method of administration
    - 4.3 Contraindications
    - 4.4 Special warnings and precautions for use
    - 4.5 Interaction with other medicinal products and other forms of interaction
    - 4.6 Fertility, pregnancy and lactation
    - 4.7 Effects on ability to drive and use machines
    - 4.8 Undesirable effects
    - 4.9 Overdose
5. Pharmacological properties
    - 5.1 Pharmacodynamic properties
    - 5.2 Pharmacokinetic properties
    - 5.3 Preclinical safety data
6. Pharmaceutical particulars
    - 6.1 List of excipients
    - 6.2 Incompatibilities
    - 6.3 Shelf life
    - 6.4 Special precautions for storage
    - 6.5 Nature and contents of container
    - 6.6 Special precautions for disposal and other handling
7. Marketing authorisation holder
8. Marketing authorisation number(s)
9. Date of first authorisation / renewal of the authorisation
10. Date of revision of the text

- https://health.ec.europa.eu/document/download/6a043dea-7d0f-4252-947b-cef58f53d37e_en

[15] https://www.ema.europa.eu/en/human-regulatory-overview/marketing-authorisation/product-information-requirements/how-prepare-review-summary-product-characteristics

The purpose of this structured format is to ensure that key regulatory messages relevant to clinical decision-making can be rapidly located and interpreted by health professionals under real-world time constraints. EMA explicitly states that the SmPC should be "**clear and concise**" and written in **language understandable to healthcare professionals**, with quantitative data presented where possible (for example frequencies of adverse reactions or numerical efficacy outcomes). Moreover, specific scientific guidelines contain so-called "SmPC recommendations" that shape the content of certain sections, for example on reproductive toxicity or lactation, risk minimization measures, or the presentation of bioavailability data and food effects.

For clinical pharmacists, the SmPC has several distinct roles in daily practice that go beyond a simple reference to standard dosing. It is a primary source for **verifying authorized indications** and **age limits**, which is essential when evaluating **off-label use** or when justifying non-formulary requests. It provides the default posology and renal or hepatic dose-adjustment recommendations, often including creatinine clearance cut-offs or Child–Pugh categories, which serve as a baseline against which local protocols and individualized regimens are developed. The sections on contraindications, warnings and interactions help to identify situations where a prescription is incompatible with the label (e.g. severe renal impairment, certain co-medications) or where enhanced monitoring and risk minimization are required, such as baseline laboratory tests, ECG monitoring, or specific patient counselling.

What does "off-label" mean?

The expression "off-label" originates from the regulatory meaning of the word label, as used in medicines law to denote the officially approved indications, dosage, route and patient groups that appear in the authorized product information (**the "label"** and its accompanying documents). Historically, in U.S. legislation this usage was codified in the 1938 Federal Food, Drug, and Cosmetic Act, which defined **the drug's "label" and "labeling" as the set of texts approved by the regulator and accompanying the product at the time of marketing**. By extension, clinical use that falls outside what is written on that approved label, such as a different indication, age group, dose, route or dosing schedule, came to be described in regulatory and medical literature as "off-label" use, that is, use that is not included in, or is "off", the authorized label.

- Wittich CM, Burkle CM, Lanier WL. Ten common questions (and their answers) about off-label drug use. Mayo Clin Proc. 2012;87(10):982-990.

The SmPC is a dynamic document that must be **updated** throughout the product's life cycle in response to new evidence, and this can be triggered by both industry and regulators. For centrally authorized products, **marketing authorization holders (MAHs)** submit variation applications when they wish to update SmPC content, for example to add a new indication, incorporate new safety or pharmacokinetic data, or refine recommendations for special populations; these changes are assessed by EMA committees (CHMP[16], and for safety-driven updates often PRAC[17]) and, if approved, lead to a revised SmPC and corresponding updates of the package leaflet and

[16] Committee for Medicinal Products for Human Use.
[17] Pharmacovigilance Risk Assessment Committee.

risk-management plan. In parallel, **EMA or national authorities** (e.g., Infarmed) may themselves trigger SmPC changes following periodic safety update report (PSUR) assessments, PRAC signal evaluations or other regulatory procedures; in such cases the authority requests that MAHs submit the necessary variations within a defined timeframe to implement the mandated wording, and associated safety communications such as direct healthcare professional communications (DHPCs) may be used to highlight urgent changes like new contraindications, dose restrictions or major risk minimization measures.

Limitations of the Summary of Product Characteristics (SmPC)

Limitations about the completeness, clarity, applicability and consistency in SmPCs are well documented in empirical evaluations and help to explain why **SmPCs alone are often insufficient** for advanced clinical decision-making.

Several systematic assessments show that SmPCs frequently omit key clinical pharmacology information, particularly for special populations such as pregnant or lactating women and those with organ dysfunction. In a review of 534 European SmPCs, around 90% did not state whether the drug crossed the placenta, almost 70% reported no clinical experience in pregnancy, and over 60% indicated that excretion in human milk was unknown, despite often recommending restrictions or avoidance of use.[18] The same study found that information on women of child-bearing potential and fertility was absent in the majority of SmPCs, highlighting that completeness is problematic not only for rare situations but for common clinical questions in antenatal care.

Analogous deficits have been reported for other domains relevant to clinical pharmacy, including therapeutic drug monitoring, food–drug interactions and dose adjustment in renal impairment. Even when organ impairment is mentioned, quantitative data on exposure–response relationships, magnitude of pharmacokinetic changes and associated effect on clinical outcomes are often sparse or entirely absent, making it difficult to move beyond very generic cautionary statements. Overall, these findings support the criticism that SmPCs rarely provide the level of quantitative granularity required for individualized benefit–risk assessment in complex patients.[19]

A recurrent criticism concerns the vague, legalistic wording of many SmPC recommendations, which undermines their practical applicability at the bedside. In the pregnancy and lactation review, recommendations were judged ambiguous in almost 60% of SmPCs for pregnancy and about 20% for breastfeeding, typically combining strong restrictions with explicit acknowledgement of major data gaps.

More broadly, analyses of contraindications and warnings in SmPCs and US/UK prescribing information highlight frequent use of unclear expressions and non-codable concepts (for instance “severe hepatic impairment”, “history of significant cardiac disease”, “use with

[18] Arguello B, Salgado TM, Fernandez-Llimos F. Assessing the information in the Summaries of Product Characteristics for the use of medicines in pregnancy and lactation. Br J Clin Pharmacol. 2015;79(3):537-544.
[19] Weersink RA, Timmermans L, Monster-Simons MH, et al. Evaluation of Information in Summaries of Product Characteristics (SmPCs) on the Use of a Medicine in Patients With Hepatic Impairment. Front Pharmacol. 2019;10:1031.

caution"), which leave excessive room for interpretation and hinder implementation in electronic decision-support systems.[20]

Comparative studies have documented substantial discrepancies between SmPCs of original and generic products that share an identical qualitative and quantitative composition, including critical differences in the contraindications section in more than half of evaluated medicines. Such inconsistencies challenge the notion of the SmPC as a harmonized reflection of a single underlying evidence base and may lead to confusion or unequal standards of care when different products are substituted for economic or logistical reasons.[21]

Cross-country comparisons of contraindication statements in SmPCs/prescribing information for the same drugs marketed in Germany, the UK and the USA have also revealed large differences in the number, wording and clarity of contraindications.[22]

A survey-based work using clinical vignettes has shown that physicians and pharmacists frequently disagree on the interpretation and clinical relevance of absolute contraindications as phrased in SmPCs.[23]

With all these criticisms, one could think that SmPCs are useless for clinical decision-making. However, in clinical pharmacy, this implies a distinctive way of using the SmPC. The document is an **essential starting point and a regulatory minimum** that defines what is authorized and what the competent authorities consider acceptable in terms of benefit–risk. When faced with a complex case (for example, extreme obesity, combined hepatic and renal dysfunction, or off-label dosing schedules), the pharmacist will first identify in the SmPC the closest relevant statements on special populations, pharmacokinetics and warnings, then seek more granular data in pivotal trials, population pharmacokinetic studies, real-world observational evidence and regulatory assessment reports. **The SmPC thus functions as a structured bridge between the regulatory dossier and bedside decision-making**: indispensable, but most powerful when used as a scaffold around which more detailed evidence is integrated for a specific patient context.

2.3.2 European Public Assessment Reports (EPARs)

European Public Assessment Reports (EPARs) are detailed, publicly available regulatory documents in which the **European Medicines Agency (EMA) explains how it has assessed the quality, safety and efficacy data for centrally authorized medicines and how it has reached its benefit–risk conclusions**. Unlike the concise, highly structured SmPCs, an EPAR contains the scientific discussion of the Committee for Medicinal Products for Human Use (CHMP), including critical appraisal of pivotal trials, handling of uncertainties, and the rationale for specific restrictions, warnings or post-authorization measures. For clinical pharmacists dealing

[20] Then MI, Andrikyan W, Fromm MF, Maas R. Comprehensibility of Contraindications in German, UK and US Summaries of Product Characteristics/Prescribing Information-A Comparative Qualitative and Quantitative Analysis. J Clin Med. 2022;11(14):4167.
[21] Drelich E, Religioni U, Chung K, et al. The Quality and Reliability of Information in the Summaries of Product Characteristics. Int J Environ Res Public Health. 2022;19(4):2185.
[22] Then MI, Andrikyan W, Fromm MF, Maas R. Comprehensibility of Contraindications in German, UK and US Summaries of Product Characteristics/Prescribing Information-A Comparative Qualitative and Quantitative Analysis. J Clin Med. 2022;11(14):4167.
[23] Andrikyan W, Sponfeldner MI, Jung-Poppe L, et al. Physicians' and pharmacists' perspective on clarity and clinical relevance of absolute contraindications in "Summaries of Product Characteristics". Br J Clin Pharmacol. 2025;91(3):829-840.

with complex or controversial questions, this richer narrative is often the only accessible window into the regulatory interpretation of heterogeneous or borderline evidence.[24]

The added value of EPARs is particularly evident when questions arise that are only partially addressed in the SmPC, such as use in understudied subgroups, interpretation of surrogate endpoints, or justification of risk minimization requirements. EPARs usually describe in more detail the studied populations, key inclusion and exclusion criteria, subgroup and sensitivity analyses, and sometimes the distribution of benefit and harm across age strata, organ dysfunction categories or comorbidity patterns. This allows the pharmacist to judge whether a patient with, for example, severe renal or hepatic impairment, extreme age or uncommon comorbidities is truly outside the evidence base, or whether there were small but informative subgroups that support cautious extrapolation beyond the SmPC wording.

EPARs are also valuable in controversial benefit–risk situations, such as medicines approved based on a single pivotal study, conditional approvals, or products with prominent safety concerns. In these cases, the scientific discussion section **sets out the main points of debate within the CHMP**, the uncertainties identified, and the arguments that ultimately led to a positive opinion, including the role of unmet medical need and the expected impact of additional pharmacovigilance activities. For emerging therapeutic classes and advanced therapies, EPARs further offer a structured link to relevant EMA scientific guidelines and precedents. Recent work using full-document text-mining has shown a dense semantic relationship between EPARs and EMA guidelines, illustrating how CHMP discussions explicitly anchor their evaluation in existing methodological and therapeutic guidance.[25]

Despite the lack of structure and the selective coverage of specific topics, in practice, **the optimal use of EPARs in clinical pharmacy is selective and question-driven**. For routine questions, the SmPC and tertiary sources remain sufficient, but when facing grey zones the pharmacist can consult the EPAR to clarify how regulators understood the data and why specific label statements were chosen.

2.3.3 Package Leaflet

The **package leaflet** is the part of EU official product information **explicitly addressed to patients and caregivers, not to health professionals**. Its legal basis is the same Directive 2001/83/EC that governs SmPCs, but the leaflet must be written in clear, lay language and structured to support safe self-use rather than prescribing decisions. For clinical pharmacists, understanding this structure and its constraints is essential to help patients navigate the leaflet, correct misunderstandings and supplement areas where the text remains vague or overly generic.[1][2]

Current EU templates specify a question-and-answer format with six standard headings, for example “What X is and what it is used for?”, “What you need to know before you take X?”, “How to take X?”, “Possible side effects”, “How to store X?” and “Contents of the pack and other information”. This Q/A structure is intended to mirror typical patient information needs and to make it easier to locate key messages quickly, but it also means that clinical nuance and detailed pharmacology are deliberately kept to a minimum, relying instead on the pharmacist to

[24] https://www.ema.europa.eu/en/medicines/what-we-publish-medicines-when/european-public-assessment-reports-background-context
[25] Raynor DK, Bryant D. European Public Assessment Report (EPAR) summaries for the public: are they fit for purpose? A user-testing study. BMJ Open. 2013;3(9):e003185.

contextualize information for individual situations. The content must be consistent with the SmPC yet reformulated in everyday language and ordered according to patient priorities, which sometimes leads to tension between legal precision and comprehensibility.[26]

A distinctive feature of EU package leaflets is the formal requirement for user-testing, often called readability testing. Before approval, the leaflet must be evaluated in small groups of lay people to verify that they can find and understand a set of predefined key messages, usually including indications, contraindications, dosing, major warnings and what to do in case of missed doses or overdose. Regulators emphasize that readability covers both linguistic simplicity and document design (font size, layout, use of headings and white space), all of which can influence whether patients actually grasp the intended information. For clinical pharmacists, this testing does not remove the need for counselling; rather, it provides a baseline assurance that the leaflet can function as a written safety net, which pharmacists can then build upon by checking individual understanding, clarifying ambiguous statements and adapting explanations to health literacy and cultural context.[27]

2.4 Portuguese official medicines information sources

2.4.1 Normas da Direção-Geral da Saúde

Normas da Direção-Geral da Saúde (DGS) are instruments for standardizing clinical and public health practice in Portugal, functioning as **quasi-regulatory guidance** that operationalize national health policy and evidence-based recommendations within the Serviço Nacional de Saúde (SNS). Although they are not primary legislation, they are issued under the legal competences of the Director-General of Health as national health authority and are frequently anchored or referenced in ministerial *Despachos* and *Portarias*, which give them concrete effects in service organization, financing and quality evaluation. In practice, **DGS Normas define expected standards of care**, and compliance is routinely used as a benchmark in audits, inspections and performance programs such as infection prevention and antimicrobial resistance control.[28]

In terms of typology, DGS produces several families of documents with different normative strength and level of detail. The core category for clinical pharmacy and therapeutics are the **Normas de Orientação Clínica (NOC)**, which define evidence-based diagnostic and therapeutic pathways for specific conditions or technologies and often include structured algorithms, eligibility criteria, recommended pharmacological regimens and monitoring requirements. These Normas are usually numbered and dated, explicitly state their scope and target population, and contain a section on “Fundamentação” that summarizes the underlying evidence and its adaptation to the Portuguese context, sometimes by referencing international guidelines and national epidemiology. For high-impact areas such as vaccination, infection control, HIV, diabetes or anticoagulation, NOC Normas effectively act as national clinical practice guidelines within the SNS, to which hospitals and primary care units are expected to

[26] https://health.ec.europa.eu/document/download/d8612682-ad17-40e3-8130-23395ec80380_en
[27] Pires C, Vigário M, Cavaco A. Readability of medicinal package leaflets: a systematic review. Rev Saude Publica. 2015;49:4.
[28] https://normas.dgs.min-saude.pt/

conform unless there is a documented clinical justification. (e.g., Norma_013_2022 - Abordagem das Pessoas com suspeita ou confirmação de COVID-19)[29]

DGS also issues **Orientações**, which have a more advisory or operational character and frequently address organizational procedures, specific settings or implementation details rather than full clinical pathways. During the COVID-19 pandemic, for example, Orientações covered topics such as procedures in residential care, use of personal protective equipment by non-health professionals or organization of services for oral health, thereby complementing more strictly clinical Normas on diagnosis, treatment and vaccination. Orientações thus function as flexible tools to translate higher-level Normas into practice in particular environments, or to respond rapidly to emerging issues while more comprehensive normative texts are under development (e.g., Orientação N.º 004/2025 - Vacinação sazonal contra a gripe e a COVID-19: Procedimentos Específicos)[30]

A third important family is that of **Programas** and **Planos Nacionais**, such as the Programa de Prevenção e Controlo de Infeções e de Resistência aos Antimicrobianos (PPCIRA), which are usually established or updated through ministerial *Despachos* but operationalized by DGS documents. These programs set strategic objectives, indicators and sometimes pay-for-performance components, while associated Normas define the concrete clinical and organizational standards required to meet them (for instance, basic infection prevention precautions, antimicrobial stewardship structures or auditing tools). From a clinical pharmacy perspective, these programmatic documents are relevant because they determine institutional obligations around antimicrobial use, vaccination coverage or management of high-risk medicines, and often interact with hospital pharmacy committees and local protocols.[31]

Finally, DGS also disseminates **Circulares Informativas** and joint *circulares* with Infarmed or other entities, which clarify specific operational points, update technical details or give interim guidance in anticipation of revisions to existing *Normas*. Although more limited in scope, these circulars can have immediate impact on day-to-day medication management, for example by specifying conditions for temporary reimbursement of tests or medicines, or by adjusting vaccination or prophylaxis strategies in response to evolving epidemiology.[32]

In the Portuguese health system, DGS “Normas” have a stronger and more formal regulatory effect than “Orientações”, as they function de facto as sectorial administrative regulations that set binding technical and organizational standards for services under the Ministry of Health. “Orientações” are primarily guidance and interpretative documents that operationalise policies and clarify procedures, and are in principle recommendatory, although they can acquire binding legal force when a law, governmental act or licensing/inspection framework expressly refers to them as mandatory or uses them as conditions for operation or compliance.

[29] https://www.dgs.pt/normas-orientacoes-e-informacoes/normas-e-circulares-normativas/norma_013_2022-abordagem-das-pessoas-com-suspeita-ou-confirmacao-de-covid-19.aspx
[30] https://www.dgs.pt/normas-orientacoes-e-informacoes/orientacoes-e-circulares-informativas/orientacao-n-0042025-de-09092025-atualizada-a-26112025-vacinacao-sazonal-contra-a-gripe-e-a-covid-19-procedimentos-especificos.aspx
[31] https://www.sns.gov.pt/institucional/programas-de-saude-prioritarios/
[32] https://normas.dgs.min-saude.pt/

2.4.2 Relatórios de Avaliação de Financiamento Público

Infarmed's **Relatórios de Avaliação de Financiamento Público (usually known as Relatórios de Avaliação Prévia)** are a specific Portuguese class of official medicines information documents that complement regulatory and clinical sources by **making explicit the rationale behind public financing and reimbursement decisions for individual medicines**. Within the framework of the Portuguese National Health Service, these reports translate regulatory authorizations and clinical evidence into concrete decisions on whether, and under what conditions, a medicine will be funded by public payers, thereby shaping real-world access and therapeutic choices in clinical pharmacy practice.[33]

Infarmed exercises both regulatory and payer-side functions, including health technology assessment (HTA) and pricing and reimbursement decisions for outpatient and hospital medicines. In this context, the Relatórios de Avaliação Prévia are HTA-type evaluation reports that document the appraisal of a medicine's added therapeutic value, cost-effectiveness and budget impact, as well as comparisons with available alternatives, **leading to a decision on public funding and, often, to specific conditions of use such as restriction to certain indications, lines of therapy or prescriber specialties**.

From a content perspective, the Relatórios de Avaliação Prévia usually draw on the same body of clinical and pharmacological evidence that underpins regulatory approval but they reinterpret that evidence from the viewpoint of **comparative effectiveness and efficiency** in the Portuguese health system. In many cases, the reports also incorporate epidemiological data on disease burden in Portugal, estimates of target population size, and projections of budget impact under different uptake scenarios, which are not present in SmPCs, or EPARs. **As such, while SmPCs and EPARs address the question "is this medicine of acceptable quality, safety and efficacy?", the Infarmed Relatórios de Avaliação Prévia target the questions "is this medicine worth paying for from public funds, compared with alternatives, and under which constraints?".**

[33] https://www.infarmed.pt/web/infarmed/relatorios-de-avaliacao-de-financiamento-publico