

Unit 1: Documentation in Pharmaceutical Industry

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Documentation and Regulatory Writing, subject code MRA102T, is the second core subject of M.Pharm Regulatory Affairs, Semester 1. It carries 4 credits and 60 hours of theory, taught at 4 hours per week, for 100 marks. Where MRA101T taught the good practices that govern the work, this subject teaches the paper the work leaves behind: the documents of the pharmaceutical industry, the dossier that carries them to a regulator, and the audits, inspections and lifecycle filings that test and maintain them for the whole life of a product. The course is designed to impart fundamental knowledge on documentation and general principles involved in regulatory writing and submission to agencies. Its objectives run in the order of the units: to know the various documents pertaining to drugs in the pharmaceutical industry; to understand the basics of regulatory compilation; to create and assemble the submission as per the requirements of agencies; and to follow up the submissions and post approval document requirements. Unit 1 works through the industry's own documents, from the exploratory brief that opens a development project to the certificate that releases a batch. Unit 2 builds the dossier and sends it, in paper, in electronic CTD, in the regional variants and through India's SUGAM portal. Unit 3 turns to audits, the industry's own checking instrument, and Unit 4 to inspections, the regulator's. Unit 5 closes the loop with product life cycle management: the supplements and reports that keep an approval lawful as the product changes, and the enforcement that follows when the documents do not match the facts. A student who masters this subject can write, compile, audit and defend the written record of a medicine from first brief to final annual report.

1.1 Documentation: the evidence system of the industry

Every other subject of this branch runs on documents, and Unit 1 is where the documents themselves are studied. A pharmaceutical **document** is not paperwork in the dismissive sense: it is the evidence that a medicine was designed, made, tested and released as the registration promised, and the industry's working rule, met already in MRA101T, is that if it is not recorded, it was not done. Documentation divides by function. **Product development documents** (the exploratory brief, plan and report of section 1.2) show why the product is what it is. **Master documents** (the master formula record of section 1.3) state how it must always be made. **Execution records** (batch records, sections 1.4 to 1.6) show how this batch actually was made. **Output documents** (the certificate of analysis, distribution records, sections 1.7 and 1.8) state what the batch proved to be and where it went. **Standing reference documents** (the site master file, section 1.9) describe the site itself, and **confidential reference files** (the drug master file, section 1.10) let a supplier place its secrets with the regulator and no one else.

Behind all of them sits **good documentation practice**: entries made at the time of the activity, legible, indelible, attributable to a named person, and corrected by single line strike through with initials and date so the original remains readable. The modern statement of these expectations is the **ALCOA** set (attributable, legible, contemporaneous, original, accurate), extended as ALCOA plus by completeness, consistency, endurance and availability. Regulatory writing, the second half of this subject's title, is the craft of producing such documents for a regulator's reading: precise about what was done and found, economical, consistent in terminology, and honest about limitations, because every sentence of a submission may one day be read back to its author in an inspection or a court.

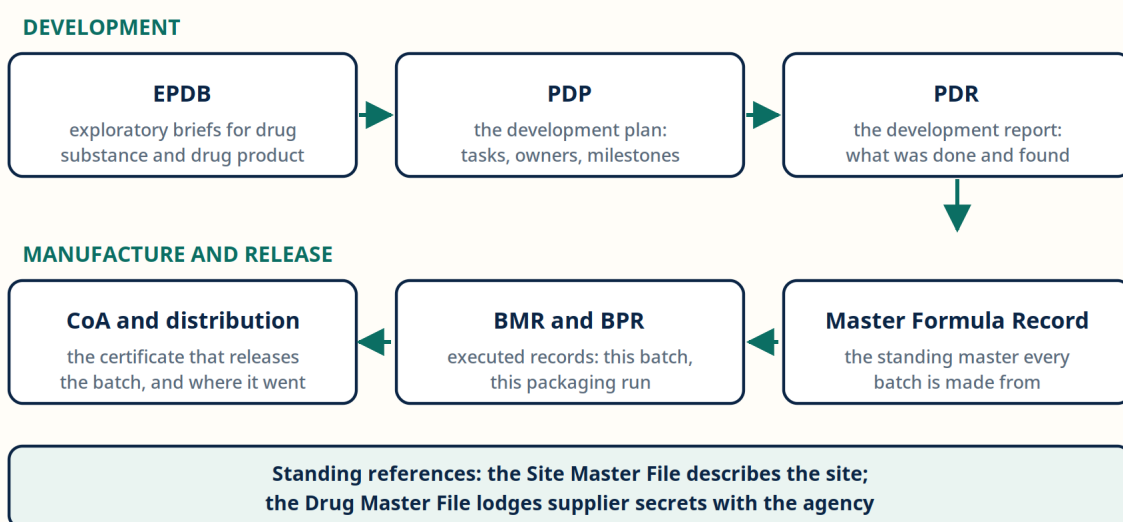
1.2 The development chain: EPDB, PDP and PDR

Development begins with a brief, not a batch. The **Exploratory Product Development Brief (EPDB)** is the short document that opens a product development project, and the syllabus's first examinable point is that it is written **twice, once for the drug substance and once for the drug product**, because the two raise different questions. The drug substance EPDB sets out the molecule or active ingredient to be developed: its identity and source (synthetic route, fermentation or extraction), the target quality profile of the substance, known chemistry and stability risks, likely impurity and polymorph questions, scale and equipment needs, and the markets whose pharmacopoeias it must satisfy. The drug product EPDB sets out the medicine to be built around it: the proposed dosage form, strength and pack, the target product profile in clinical terms (indication, population, dosing), the intended markets and their format expectations, the competitive frame, and the development risks the project must retire first. An EPDB is a decision document: management reads it to give or refuse the go ahead, so it is short, factual and explicit about uncertainty, the first exercise in regulatory writing a student meets.

Given the go ahead, the **Product Development Plan (PDP)** converts the brief into a programme. Where the EPDB asks whether and why, the PDP states what, who, when and at what cost: the development tasks (preformulation, formulation development, analytical method development and validation, stability programme, scale up and technology transfer), their sequence and milestones, the responsible functions, the materials and equipment required, and the documentation each task must produce. The plan is a controlled document in its own right, revised as results arrive, and the timetable it sets is what later registration timelines are built on.

The **Product Development Report (PDR)** closes the chain by recording what was actually done and found. Written in the logic of ICH Q8 pharmaceutical development, it assembles the quality target product profile, the critical quality attributes of the product, the risk assessments that selected the formulation and process, the experiments (often designed statistically) that explored them, the design space if one is claimed, and the control strategy that manufacturing will inherit. The PDR is the ancestor of Module 3 of the dossier in Unit 2 and of the master formula record that follows here: development explains, in the PDR, exactly what production will be ordered to repeat, in the MFR.

The Document Chain: Brief to Batch



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Figure: The document chain of Unit 1: the exploratory briefs open the project, the plan programmes it, the report records it, and the master record converts it into standing instructions that each batch record then executes and evidences.

How a number travels through the documentation system

Development finding (PDR): this blend needs 30 minutes of mixing

-> Standing instruction (MFR): mix for 30 minutes, record start and stop

-> Execution evidence (BMR): mixed 10:05 to 10:35, operator signed

-> Test evidence (CoA): blend uniformity within specification

-> Release and shipment (distribution record): batch to named consignee

1.3 The Master Formula Record: the standing order

The **Master Formula Record (MFR)**, called the master production record in the United States system (the master production and control records of 21 CFR 211 Subpart J, met in MRA101T), is the approved master document from which every batch of a product is made. It is written once, by development and production together, approved by quality, and changed only through change control. A complete MFR states: the product name, strength and dosage form; the **master formula**, the quantity of every ingredient for the standard batch size, including any calculated overages and their justification; the **master process**, step by step manufacturing and in-process control instructions with equipment, parameters and limits; the packaging instructions or a reference to them; the in-process and finished product specifications the batch must meet; and the yield limits within which the batch is expected to fall. Two disciplines make the MFR work. It describes exactly one batch size and one process, so that no operator ever scales or improvises on the floor; and every batch record issued for manufacture is a faithful copy of it, generated under control, so that a deviation can always be read as a departure from a known master. The MFR is the point where regulatory writing becomes manufacturing law inside the company.

1.4 The Batch Manufacturing Record and its calculations

The **Batch Manufacturing Record (BMR)**, or batch production record, is the executed copy of the MFR for one batch. Issued by quality or production control with a unique batch number before manufacture begins, it travels with the batch, and every instruction in it is answered, contemporaneously, by an entry: the actual quantity weighed, the equipment actually used, the times actually started and stopped, the in-process results actually obtained, each entry signed by the operator who did the work and checked by a second named person for the critical steps. The completed BMR, reviewed and approved by quality, is the primary evidence on which the batch is released, and the document an inspector reads first when a batch is questioned years later.

The syllabus names the BMR's **calculations** expressly, and they are the record's arithmetic spine:

The three calculations every BMR carries

1. Quantity adjustment for potency:

quantity to weigh = (batch size x label claim x 100) / assay percent
(so a substance assaying at 98.4 percent on as-is basis is weighed proportionally higher, and the arithmetic is shown, not buried)

2. Percentage yield at each stage and at the end:

percent yield = (actual quantity obtained / theoretical quantity) x 100
worked example: theoretical 50.0 kg, obtained 48.6 kg, yield 97.2 percent

3. Reconciliation of every controlled material (next section)

Each calculation is performed by one person and independently verified by a second, whose signature is part of the record; a BMR whose arithmetic is wrong is a defective record even when the batch is perfect, because the next reader cannot tell the two situations apart.

1.5 Batch reconciliation

Batch reconciliation is the accounting that closes a batch's material balance: for every controlled input, the quantity issued must equal the quantity used, plus the quantity returned, plus the quantity destroyed as

waste or samples, within defined limits. It is applied most strictly to the items where a gap hurts: printed packaging materials and labels (section 1.6), where accountability approaches 100 percent and any unexplained difference must be investigated before release, because a stray label is a future mislabelled pack; and to the bulk product itself, where the reconciliation of tablets or litres filled against bulk manufactured exposes loss, diversion or mix up. The yield of section 1.4 and the reconciliation of this section are the same instinct at two scales: a batch whose numbers do not add up is not yet a releasable batch, whatever its test results say. Reconciliation failures are investigated and recorded in the batch record itself, and the investigation, not merely the outcome, is what auditors and inspectors read.

1.6 Batch Packaging Records and print pack specifications

Packaging has its own record because packaging errors, above all wrong labels, are the industry's classic recall trigger. The **Batch Packaging Record (BPR)** is issued with the batch like the BMR and executed step by step: line clearance before start (the formal check, recorded, that the line is empty of the previous product and its materials), the labels and printed materials issued, counted and coded (batch number, manufacturing and expiry dates printed or embossed), the quantities packed by format, the samples taken for retention and checking, the reconciliation of all printed materials, and the destruction of unused coded materials. Attached to it are the **print pack specifications**: the controlled specification of everything printed that reaches the pack, the label and carton text, pack leaflet, colours and their tolerances, barcode and pharmacode, Braille where a market requires it, and the approved artwork version. Printed matter is treated as a controlled component, issued against the specification, counted like a drug, and never left on a line overnight: the discipline of this section is the reason a patient in any country can trust that the name on the box is the medicine inside it.

1.7 Distribution records

The record system does not end at the factory gate. **Distribution records** capture, for each batch, what was shipped, in what quantity, on what date, and to which consignee, in enough detail that the manufacturer can identify and reach every first recipient of every batch within hours. Their purpose is singular and serious: they are the working tool of the **recall** of Unit 5, and the measure of a recall's competence is whether the distribution records can answer, completely and quickly, the question "where did every unit of this batch go?" Distribution records also evidence the chain of custody that good distribution practice (MRA101T, Unit 4) requires: a shipment that cannot be traced is a shipment whose storage and handling cannot be vouched for, and in falsified medicine investigations the distribution record is frequently the document that separates genuine product from intrusion.

1.8 The Certificate of Analysis: the batch's report card

The **Certificate of Analysis (CoA)** is the formal document that states a batch was tested and met its specification. Issued per batch of drug substance or drug product (and for materials supplied between companies, where the buyer's quality unit relies on it wholly or in part), a proper CoA carries: the product name and material code; the batch number and manufacturing and expiry dates; the name and address of the manufacturing site; the specification reference and version; each test performed with its limit and its actual result (results, not the bare word "complies", for the tests that carry numbers); the date of analysis; and the signature of the authorised quality person who certifies it. Two writing rules matter for examination answers. A CoA certifies a **batch**, not a product in general: a certificate borrowed across batches is a falsified document. And the certificate summarises the laboratory's records; it never replaces them, so a CoA that cannot be traced back to raw data in the issuing laboratory fails the data integrity standard of section 1.1. Between companies, the CoA is also a legal instrument: contracts and quality agreements state what it must contain, and regulators hold the receiving company responsible for verifying supplier

certificates rather than merely filing them.

1.9 The Site Master File: the site describes itself

The **Site Master File (SMF)** is a document prepared by the manufacturer that describes the site itself: its organisation, activities and quality system, in a standard format an inspector can read before arrival. Its structure follows the PIC/S guide (PE 008) used internationally: general information on the site and its licensed activities; quality management system; personnel and their qualifications; premises and equipment; documentation; production; quality control; distribution, complaints and recalls; and self inspections, with appendices of products, licences and certificates. The SMF is deliberately factual rather than argumentative: it is the site's official self description, kept current, supplied to regulators on request and used during licensing and inspection planning. Its regulatory writing lesson is discipline: because the SMF is read against the physical site during inspection, every sentence in it must be literally true on the day it is read, which is why it is version controlled like a dossier document and updated when anything it describes changes.

1.10 Drug Master Files: secrets lodged with the regulator

The **Drug Master File (DMF)** solves a commercial dilemma: a drug substance or excipient maker must let the regulator read its confidential manufacturing detail, but cannot hand that detail to every customer who buys its material. The DMF is a file submitted by the holder **directly to the agency**, which the customer's application then references by number under a **letter of authorization** from the holder: the agency reads everything, the customer reads nothing confidential, and the approval of the customer's product rests on data its maker never saw. The United States system classifies DMFs by subject:

DMF type	Subject
Type I	Manufacturing site, facilities, operating procedures and personnel
Type II	Drug substance, drug substance intermediate, and material used in their preparation, or drug product
Type III	Packaging material
Type IV	Excipient, colorant, flavor, essence, or material used in their preparation
Type V	FDA accepted reference information

Type II is the workhorse, the file behind most generic applications. Two standard notes complete the picture honestly: FDA no longer accepts new **Type I** DMFs (that site information is expected in the application itself), and a DMF is **never approved or disapproved on its own**: it is reviewed only in the context of an application that references it, and deficiencies are communicated to the holder, who amends the file, while the customer's application waits. The European system reaches the same end by the Active Substance Master File (ASMF) procedure, which splits the file into an open part the applicant sees and a closed part it does not, and India relies principally on the dossier itself and, for substances covered by the European Pharmacopoeia, the Certificate of Suitability (CEP). The DMF family, in whatever regional costume, is documentation's most elegant idea: confidentiality preserved, review uncompromised.

The Five Drug Master File Types

TYPE I	TYPE II	TYPE III	TYPE IV	TYPE V
Site, facilities, operating procedures and personnel	Drug substance and its intermediates, or drug product	Packaging material	Excipient, colorant, flavor, essence or material used	FDA accepted reference information
no new files accepted by FDA	the workhorse file	containers, closures, films	the additive file	the agreed catch all

The holder files with the agency; the customer references the number
under a letter of authorization, and never sees the confidential content

A DMF is reviewed only when an authorised application references it.

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Figure: The five DMF types by subject matter. Type II, the drug substance file, supports the largest number of applications; the file is reviewed only when an authorised application references it.

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