

PharmacoLearn

MPH104T Regulatory Affair, M.Pharm Semester 1

Unit 1: Documentation in Pharmaceutical Industry and Generic Drug Product Development

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Regulatory Affair, subject code MPH104T, is a core Semester 1 subject of M.Pharm Pharmaceuticals. It carries 4 credits and 60 hours of theory, taught at 4 hours per week, for 100 marks. Every medicine that reaches a patient has passed through a regulatory system: someone outside the company has examined the evidence for its quality, safety and efficacy and has given a legal permission to sell it. This subject teaches how that permission is obtained and kept. It begins with the documents a pharmaceutical company must maintain and with the development of generic drugs under the United States system built by the Hatch-Waxman Act, then moves to what approval demands for an API, a biologic and a novel therapy, and how a foreign manufacturer registers in the US. The third unit covers the chemistry, manufacturing and controls (CMC) story, post approval duties, the Common Technical Document, the ICH guidelines and the requirements of the EU, UK, Australia and the rest of the world. The last two units follow a new drug backwards into development: the non clinical work and the global dossiers (IND, IMPD, investigator brochure) that open the door to human testing, and finally the clinical trial itself, with its protocol, ethics committee, informed consent, privacy protection and safety monitoring. A student who completes this subject should be able to explain which application a product needs, what evidence each part of the dossier must carry, and what a company must keep doing after approval to stay on the market.

1.1 Documentation in the pharmaceutical industry

Documentation is the written memory of a pharmaceutical company, and in a regulated industry it is also legal evidence. Regulators work on a simple principle: if an activity is not documented, it is treated as not done. Batch records prove that a batch was made exactly as approved; specifications and test records prove it met its quality limits; distribution records prove where every pack went, which is what makes a recall possible.

Good documentation practice asks that records are:

- **Attributable:** every entry shows who did the work and who checked it, with signatures and dates.
- **Legible and permanent:** entries are made in ink or in a controlled electronic system, and corrections are made by a single line strike-through with initials and date, never by overwriting or correction fluid, so the original entry stays readable.
- **Contemporaneous:** records are written at the time the activity happens, not reconstructed later.
- **Original and accurate:** the record is the original observation or a certified copy, and it matches what actually happened.
- **Controlled:** documents carry a title, a unique number, a version or revision number and effective dates; obsolete versions are withdrawn so that only the current approved version can be used.

The main document families are specifications and test procedures, standard operating procedures (SOPs), the master formula record and the batch records made from it, validation documents, and the records of distribution, complaints and recalls. Three of these are named in the syllabus and are covered in the next sections: the master formula record, the Drug Master File and distribution records.

1.2 Master formula record and batch records

The **master formula record (MFR)**, also called the master production record or master batch record, is the approved master document that states exactly how one batch of a product is to be made. It is prepared and approved by the production and quality functions before any batch is manufactured, and every batch of that product must follow it.

Contents of a master formula record:

- Name of the product, its dosage form and strength, and the batch size.
- The complete formula: every ingredient with its pharmacopoeial grade, quantity per unit and quantity per batch, including permitted overages and the reason for them.
- A step by step manufacturing procedure, in the order operations are performed, with equipment to be used and the in-process controls and limits at each stage (for example mixing time, drying temperature and loss on drying limit, blend uniformity).
- Theoretical yield and the permitted yield range, packaging instructions and packaging materials.
- Labelling requirements, storage conditions and the shelf life of the product.
- Safety precautions and the signatures of the persons who prepared, checked and approved the document.

For each actual batch, a **batch manufacturing record (BMR)** is issued as a controlled copy of the MFR. Operators record what was really done against each step: actual quantities weighed, actual times and temperatures, in-process results, deviations and their justification, and the actual yield. The completed BMR, together with the batch packaging record and the analytical reports, is reviewed by quality assurance before the batch is released. The MFR is the instruction; the BMR is the evidence that the instruction was followed for that batch. Confusing the two, or making batches from an uncontrolled copy of the formula, is a serious compliance failure because a wrong version can put a wrong formula into production.

1.3 Drug Master File (DMF)

A **Drug Master File (DMF)** is a submission to a regulatory authority, most fully developed in the US FDA system, that holds confidential, detailed information about a facility, a process or a material used in making a drug. The classic example is the API manufacturer: the maker of the active substance files its complete chemistry and manufacturing details in a DMF, so that each finished dose manufacturer who buys that API can refer to the DMF in its own application instead of receiving, and disclosing, the API maker's trade secrets.

Key features of the DMF system:

- A DMF is **not approved or disapproved** by itself. It is only reviewed when an application (IND, NDA or ANDA) refers to it, and it is reviewed as part of that application.
- The applicant asks the DMF holder for a **letter of authorisation (LOA)**, which the applicant includes in its application. The LOA permits the agency to review the DMF in support of that application. Without an LOA the agency will not look at the DMF for that applicant.
- The DMF holder must keep the file current, reporting changes and filing an annual update listing, and must inform every authorised applicant of changes that could affect their products.
- Deficiencies found in the DMF during review are communicated to the DMF holder, not to the applicant, because the contents are confidential to the holder. The applicant is only told that the DMF is not adequate to support the application until the holder corrects it.

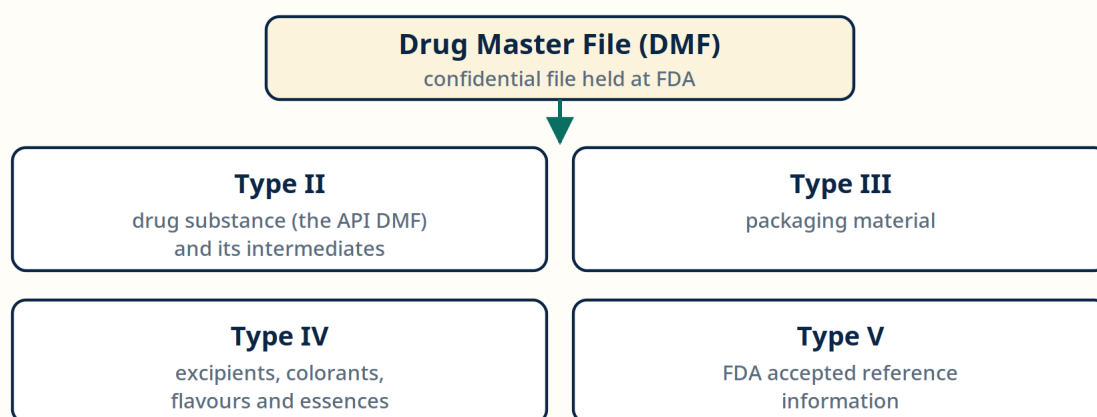
Types of DMF in the US system:

Type	Subject of the file	Status
Type I	Manufacturing site, facilities and operating procedures	No longer accepted; replaced by site information in applications and establishment registration
Type II	Drug substance, drug substance intermediate, and material used in their preparation	The most commonly used type (the API DMF)
Type III	Packaging material	In use
Type IV	Excipient, colorant, flavour, essence or material used in their preparation	In use
Type V	FDA accepted reference information (for example certain facility or clinical study related information)	In use, only after the agency agrees to accept it

In Europe the same need is met by the **Active Substance Master File (ASMF)** procedure, and a **Certificate of Suitability (CEP)** from the EDQM can be used instead where a pharmacopoeial monograph exists for the substance; these are the European counterparts students should be able to name alongside the US DMF.

How a DMF supports an application
 API manufacturer prepares DMF -> files it with FDA, receives DMF number
 Finished dose applicant -> obtains letter of authorisation from holder
 Applicant submits ANDA or NDA -> refers to the DMF by number
 FDA reviewers -> review the DMF only for that application
 Deficiency in the DMF -> told to the holder, holder corrects the DMF

Drug Master File: Types in the US System



Type I (facilities) is no longer accepted.

A DMF is reviewed only when an application refers to it under a letter of authorisation.

Figure: Drug Master File types in the US system: the file is held confidentially at FDA and is reviewed only when an application refers to it under a letter of authorisation.

1.4 Distribution records and recall readiness

Distribution records are the records that link finished batches to the customers who received them: the consignee name and address, the product, batch number, quantity and date of dispatch, and the transport details. Good manufacturing practice requires distribution records to be complete enough, and kept long enough, that the complete history of a batch can be traced forward to every customer and backward to its raw materials.

Their regulatory importance is practical rather than theoretical:

- **Recalls:** if a defect is discovered, distribution records decide how fast and how completely the affected batches can be recovered from the market. A recall exercise (mock recall) is used to test whether the records can trace 100 percent of a batch within the required time.
- **Complaint investigation:** a complaint about a pack can be traced to its batch, its BMR and its analytical results only through the distribution and batch numbering chain.
- **Expiry and stock rotation control:** distribution records support first expiry first out handling and the detection of expired or diverted stock in the chain.

1.5 Generic drugs: innovator products and generic products

A **generic drug** is a copy of an already marketed innovator (brand name, reference) product. It contains the same active substance, in the same strength and dosage form, for the same route of administration, and it must be shown to be **bioequivalent** to the reference product (Unit 1.9), meaning it delivers the active substance to the site of action at the same rate and to the same extent. Because safety and efficacy were already established for the innovator product, the generic applicant does not repeat the clinical development programme; the bridge to the innovator's data is bioequivalence.

Feature	Innovator (brand) product	Generic product
Active substance	New, discovered and developed by the applicant	Same as the reference product
Development evidence	Full non clinical and clinical programme	Pharmaceutical quality data plus bioequivalence
US application	NDA (New Drug Application)	ANDA (Abbreviated New Drug Application)
Patent and data position	Protected by patents and regulatory exclusivity	Can be filed only as the Hatch-Waxman rules permit (Section 1.6)
Labelling	Sets the reference labelling	Must be essentially the same as the reference product labelling
Price position	Higher, recovers research cost during exclusivity	Lower, competes mainly on price after entry

1.6 The Hatch-Waxman Act and its amendments

The **Drug Price Competition and Patent Term Restoration Act of 1984**, universally called the **Hatch-Waxman Act** after its sponsors, is the law that created the modern US generic industry. Before 1984 a generic maker effectively had to repeat clinical trials, so few generics were filed. The Act balanced two goals: reward innovation, and let safe generic copies compete as soon as legitimate protection ends.

Main provisions:

- **The ANDA pathway:** a generic can be approved through an Abbreviated New Drug Application under section 505(j) of the Food, Drug and Cosmetic Act, relying on the agency's earlier finding of safety and efficacy for the reference listed drug, with bioequivalence as the scientific bridge.
- **Patent term restoration:** to compensate for the time a patented drug spends in development and review, part of the patent term lost can be restored, up to a maximum of five years of extension, and so that the remaining effective patent life after approval does not exceed fourteen years.

- **Regulatory exclusivities:** a new chemical entity receives five years of exclusivity during which an ANDA generally cannot be submitted for the first four years and cannot be approved before five years; changes to an approved drug that needed new clinical investigations receive three years of exclusivity for the protected change; orphan drugs and paediatric studies carry their own exclusivity provisions.
- **Patent listing and certification:** innovators list their drug patents in the FDA **Orange Book** (the register of approved drug products with therapeutic equivalence evaluations). Every ANDA applicant must certify for each listed patent one of four positions, the **paragraph certifications**:
- **Paragraph I:** no patent information has been filed for the drug.
- **Paragraph II:** the patent has already expired.
- **Paragraph III:** the applicant will wait; approval is sought only after the patent expires.
- **Paragraph IV:** the patent is invalid, unenforceable, or will not be infringed by the generic product.
- **Paragraph IV litigation and the 30 month stay:** a Paragraph IV certification is legally treated as an act of infringement, so the patent owner can sue. If the owner sues within the prescribed window after notice, approval of the ANDA is stayed for up to 30 months while the case runs, unless the court decides sooner.
- **180 day first generic exclusivity:** the first applicant to file a substantially complete ANDA with a Paragraph IV certification receives 180 days of generic marketing exclusivity, during which the agency generally cannot approve later ANDAs for the same drug. Later amendments (notably the Medicare Modernization Act of 2003) added forfeiture events so this exclusivity cannot be used to block the market indefinitely, and tightened the rules to one 30 month stay per ANDA.

Amendments and related later laws students should recognise by name include the 2003 Medicare Modernization Act changes to Hatch-Waxman, the generic drug user fee programme (GDUFA) that funds ANDA review through industry fees, and the biosimilar pathway created by the Biologics Price Competition and Innovation Act of 2009, which is the Hatch-Waxman style framework adapted to biologics (Unit 2).

1.7 The Code of Federal Regulations (CFR)

The **Code of Federal Regulations (CFR)** is the codification of the rules issued by US federal agencies. Drug regulation sits in **Title 21, Food and Drugs**. A regulation in the CFR has the force of law, unlike a guidance document, which states the agency's current thinking and is not binding. Knowing the important parts of Title 21 is basic regulatory literacy:

Part of 21 CFR	Subject
Part 11	Electronic records and electronic signatures
Parts 210 and 211	Current good manufacturing practice for drug products
Part 312	Investigational New Drug (IND) application
Part 314	Applications for FDA approval to market a new drug (NDA and ANDA rules)
Part 320	Bioavailability and bioequivalence requirements
Part 601	Biologics licence applications

The CFR matters in day to day work because application contents, GMP duties, labelling rules and post approval reporting duties are all specified there; an answer in an examination or in a regulatory job that cites the governing part of the CFR is a stronger answer than a general statement.

1.8 Drug product performance in vitro

In vitro performance is what the dosage form does in laboratory apparatus, above all in the dissolution test. For a generic product, dissolution testing has three regulatory jobs:

- **Quality control:** batch to batch consistency is shown by every batch meeting the dissolution specification.
- **Development evidence:** the generic formulation is compared with the reference product in **comparative dissolution profiling**, usually in media across the physiological pH range (typically pH 1.2, 4.5 and 6.8), and the profiles are compared, commonly with the similarity factor f_2 .
- **Bioequivalence support and waivers:** where the rules permit, strong in vitro data can support a **biowaiver**, approval without an in vivo study, the classic case being immediate release products of highly soluble, highly permeable drugs (BCS Class I) with rapid dissolution and similar profiles to the reference.

1.9 Bioavailability and bioequivalence assessment in vivo

Bioavailability (BA) is the rate and extent to which the active substance is absorbed and becomes available at the site of action; in practice it is measured from the blood concentration time curve. A **bioequivalence (BE)** study compares the test (generic) product with the reference product, most often in a single dose, two period, two sequence crossover study in healthy volunteers under fasting conditions, with a fed study added where food affects absorption or the reference labelling requires dosing with food.

The comparison is statistical. The key parameters are the area under the curve (AUC, extent) and the maximum concentration (C_{max} , rate). The products are accepted as bioequivalent when the 90 percent confidence interval for the ratio of the test to reference geometric means of AUC and C_{max} falls entirely within the acceptance range of 80.00 to 125.00 percent. Narrow therapeutic index drugs are handled with tightened or scaled approaches in several jurisdictions, because the ordinary range may allow clinically important differences.

A **BA/BE study is a clinical study in regulatory terms**: it needs ethics committee approval, informed consent, GCP compliance and analytical work in a validated bioanalytical laboratory, which is why companies often outsource it (Section 1.14).

1.10 The ANDA approval process

The ANDA route, step by step:

ANDA approval process (US)
Select reference listed drug from the Orange Book
-> develop formulation, file or refer to the API DMF
-> comparative dissolution and pilot BE work
-> pivotal BE study against the reference product
-> compile ANDA (CTD format: quality, BE, labelling modules)
-> patent certification for every Orange Book patent
-> FDA filing check, scientific review, facility inspection
-> deficiency letters and applicant responses, cycle as needed
-> approval letter; tentative approval if a patent or exclusivity still blocks marketing, final approval when it clears

Two outcomes students must distinguish: an **approval letter** allows marketing, while a **tentative approval** means the application is scientifically complete but cannot be finally approved yet because a patent or exclusivity period has not run out; the product cannot be sold until final approval. A **complete response letter** is the modern deficiency letter: it lists everything that prevents approval, and the clock restarts when the applicant resubmits.

ANDA Approval Process (US)

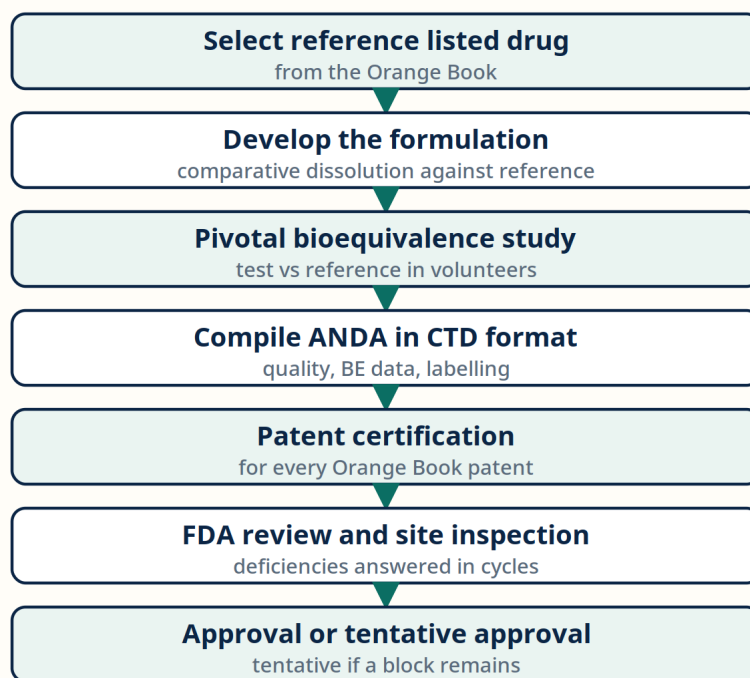


Figure: The ANDA approval process: bioequivalence and quality evidence in place of a new clinical programme, with the patent certification running alongside.

1.11 The NDA approval process

The **New Drug Application (NDA)** is the full application for a new drug. Unlike the ANDA, it stands on the applicant's own complete evidence: pharmaceutical quality (CMC), non clinical pharmacology and toxicology, and adequate and well controlled clinical trials proving safety and effectiveness for the claimed use. The agency reviews each discipline separately (chemistry, pharmacology and toxicology, clinical, statistics, and others), inspects the manufacturing sites and the key clinical and bioanalytical sites, and takes the work to an advisory committee for novel or difficult questions when needed. The result is approval, a complete response letter, or, rarely now, a refusal to file at the very first check if the application is too incomplete to review. The NDA is covered again from the applicant's side in Units 2 and 4; in this unit the point is the contrast: **the ANDA borrows the innovator's evidence and adds bioequivalence; the NDA creates all of the evidence itself.**

1.12 Scale up and post approval changes (SUPAC)

Between the BE batch and full commercial production the process is **scaled up**, and after approval the product keeps changing: sites move, suppliers change, equipment is replaced, batch sizes grow. Regulation handles this through change control graded by the size of the change. The FDA's **SUPAC** guidances (Scale Up and Post Approval Changes, issued by dosage form family) classify changes into levels:

- **Level 1 changes:** minor changes with no expected effect on quality or performance (for example a like for like equipment change within the same design). Handled in the annual report.
- **Level 2 changes:** moderate changes that could affect quality (for example a site change within the same campus, or a larger batch size increase within defined limits). Need a changes being effected supplement and supporting data such as comparative dissolution.

- **Level 3 changes:** major changes likely to affect performance (for example a change in the formulation's composition beyond set limits, or a move to a different manufacturing site). Need a prior approval supplement, often with fresh BE evidence.

The operating idea, which also appears in EU variation rules in Unit 3, is that **the size of the regulatory filing follows the size of the risk**; identical logic applies to the API process, equipment and packaging changes.

1.13 Post marketing surveillance

Approval is based on limited numbers of patients treated for limited times, so the safety picture of a drug is completed only after marketing. **Post marketing surveillance** is the organised collection and assessment of safety information on marketed products: spontaneous adverse event reports from health professionals and patients, periodic safety update reporting to the agency, signal detection from accumulated data, and regulatory actions that follow, from labelling changes and safety communications to restriction or withdrawal of the product. In the US, applicants must report serious and unexpected adverse events to FDA on an expedited basis and file periodic adverse experience reports; the details of clinical trial safety reporting are in Unit 5, and the two duties should not be confused: Unit 5 reporting protects trial subjects during development, post marketing surveillance protects patients after approval. Post marketing surveillance also includes the surveillance of product quality (defect reports, field alerts for batches that may fail specification), which links back to the distribution records of Section 1.4.

1.14 Outsourcing BA and BE studies to a CRO

A **contract research organisation (CRO)** performs work for a sponsor under contract. BA and BE studies are the most commonly outsourced regulatory studies in the generic industry because they need a clinical unit, healthy volunteer panels, a validated bioanalytical laboratory and statistical support, all used only for short periods.

Points that carry regulatory weight:

- The **sponsor remains responsible** for the study even when a CRO performs it. Outsourcing transfers tasks, never accountability; the sponsor must select and audit the CRO and monitor the work.
- The transfer of duties must be written: the contract and any regulatory transfer of obligations (in the US, the transfer of obligations under 21 CFR 312.52 for IND studies) define exactly which duties the CRO holds.
- Typical failure points found in inspections are bioanalytical data integrity, inadequate validation records and consent or ethics documentation gaps, so vendor qualification for a BE CRO concentrates on the bioanalytical laboratory and its data systems.
- In India, BA/BE studies are conducted at centres registered with the licensing authority and studies follow the New Drugs and Clinical Trials Rules, with ethics committee approval mandatory; the same sponsor responsibility principle applies.