

Unit 5: Product Life Cycle Management

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5.1 Life cycle management: the approval is a beginning

An approval is a photograph of a product at one moment; manufacture then continues for decades, through new suppliers, bigger batches, better methods, new sites and tightening science. **Product life cycle management**, in the regulatory sense, is the discipline of keeping the registered product and the real product identical, by classifying every change, filing it by the correct route, and reporting what the law requires on schedule. ICH has given the discipline its modern frame in **ICH Q12**, which adds lifecycle instruments (established conditions, and post approval change management protocols that agree in advance how a change will be judged) to the older filing categories this unit teaches. The unit's geography is the United States system, whose category names the syllabus adopts, with the European variations system as the standing comparison: in the EU, changes are filed as Type IA (minor, do and tell, notified within twelve months or immediately for the IA immediate notification subclass), Type IB (minor, tell, wait and do, thirty days) and Type II (major, prior approval). The American ladder follows.

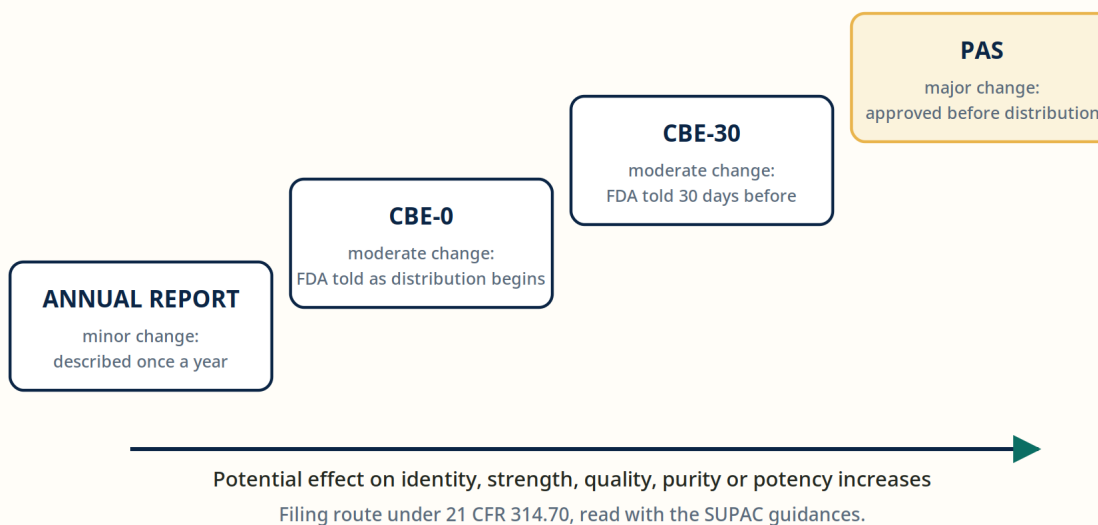
5.2 The United States reporting categories: PAS, CBE-30, CBE-0, annual report

United States law (21 CFR 314.70) sorts post approval changes to an approved application by their **potential to affect the drug's identity, strength, quality, purity or potency**, and the filing route follows the sort:

Route	Name and rule	Timing
PAS	Prior Approval Supplement: a major change, substantial potential to affect the product	FDA approval before the changed product is distributed
CBE-30	Changes Being Effectuated in 30 days: a moderate change	FDA must receive the supplement at least 30 days before distribution
CBE-0	Changes Being Effectuated: a moderate change FDA has designated for immediate effect	FDA receives the supplement at the time distribution begins
Annual report	A minor change, minimal potential to affect the product	Described in the annual report , no supplement

The classification is the examinable skill. Major changes (PAS) include a new manufacturing site for most products, a change in the drug substance synthesis, a formulation change outside accepted ranges, a new indication (filed as an efficacy supplement). Moderate changes of the CBE family include many specification, method and process adjustments within defined bounds. Minor changes, an editorial labelling correction, a like for like equipment replacement, ride in the annual report. Two disciplines surround the ladder: the change is first judged under **SUPAC** (next section) where a guidance applies, and the supplement or report is itself a piece of regulatory writing of Unit 2's kind, a mini dossier arguing, with data, that the changed product remains the approved product. Misclassification is a compliance failure in both directions: filing a major change as minor is a violation, and wasting prior approval on a minor change burns review resources the system cannot spare.

The Post Approval Reporting Ladder



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Figure: The United States reporting ladder of 21 CFR 314.70: the greater a change's potential effect on the product, the earlier the agency must be told, from annual record to prior approval.

5.3 SUPAC: the scale up and post approval changes guidances

SUPAC (Scale Up and Post Approval Changes) is the series of FDA guidances that operationalises section 5.2 for the commonest changes, giving each change type **levels** with the tests and filing route each level attracts. The family a student should be able to name: **SUPAC-IR** for immediate release solid oral dosage forms, **SUPAC-MR** for modified release solid orals, and **SUPAC-SS** for nonsterile semisolid dosage forms, with companion guidance for manufacturing equipment addenda and for changes to an approved NDA or ANDA in the chemistry, manufacturing and controls documentation. Within a SUPAC guidance, a change is sorted (for example Level 1, Level 2, Level 3 in SUPAC-IR) across the dimensions the guidance calls components and composition, site, batch size (scale), equipment and process; each level then prescribes the evidence (commonly comparative dissolution, sometimes stability, in the higher levels bioequivalence) and the filing (annual report, CBE, or PAS). SUPAC's teaching point is regulatory writing's deepest one: the agency has published, in advance, the questions it will ask about a change and the data it will accept as answers, so the competent regulatory professional reads the guidance before making the change, not after.

5.4 The annual report and post marketing reporting

Beside the supplements stands the periodic traffic of an approved application. The **annual report** (21 CFR 314.81), due within sixty days of the anniversary of the approval, reports the year's minor changes (section 5.2), the distribution data, the labelling in use, the status of post marketing commitments and studies, and a summary of significant new information bearing on the product's safety and efficacy. The wider **post marketing reporting requirements** run continuously, not annually: **adverse experience reporting**, periodic and expedited, under the pharmacovigilance rules; **field alert reports**, required within three working days when a distributed drug product shows significant problems (bacterial contamination, a labelling mix up, a failure to meet specifications) that could affect its safety or efficacy; and biological product deviation reports for licensed biologics on the parallel track. The common thread is that approval converts the company's knowledge duties into standing legal duties: from the day of approval, what the company learns about its product, it largely owes the agency, on a clock.

5.5 Post approval labeling changes

Labelling is part of the registered product, and changing it after approval follows its own graded logic, which this syllabus item isolates. Safety driven strengthening of labelling is deliberately made fast: a company that acquires new safety information may strengthen warnings, contraindications or adverse reaction statements by a **changes being effected supplement** and implement on filing, rather than waiting through prior approval while an out of date label circulates; the agency then reviews and may negotiate different wording. Other labelling changes sort by the ladder of section 5.2: editorial and minor changes in the annual report, substantive changes to indications, dosage or claims by prior approval supplement (an efficacy supplement, with the clinical dossier of Unit 2 behind it). The discipline connecting this section to Unit 1's print pack specifications is completeness: a labelling change is not made when the supplement is filed but when every printed component, leaflet, carton, label and electronic copy, has been converted to the new text and the old stock destroyed, and the batch records of Unit 1 are how that conversion is proven.

5.6 FDA inspection and enforcement: the 483, the EIR and the warning letter

Unit 4's surveillance inspection ends in documents with a legal afterlife, and this section teaches the sequence. On the spot, objectionable conditions are recorded on **Form FDA 483**, handed to management at the close of inspection: a list of observations, not yet the agency's final judgement, to which the company should respond in writing, with root cause and CAPA of Unit 4, within **fifteen business days** if the response is to be considered before the agency decides its next step. The inspection is then written up by the investigator in the **Establishment Inspection Report (EIR)**, and the agency classifies the outcome: **NAI**, no action indicated; **VAI**, voluntary action indicated, objectionable conditions found but not warranting formal action; or **OAI**, official action indicated, where regulatory or administrative action will follow. The characteristic OAI instrument is the **warning letter**: a public letter identifying significant violations, requiring correction and a written response (customarily within fifteen working days) describing the corrective plan, and warning that failure may bring the harder remedies of the next section without further notice. Warning letters are published, and their commercial damage, in customer audits, tenders and investor reading, often exceeds their legal force: in the documents economy of this subject, they are the point where documentation failures become public facts.

5.7 Recalls, seizure and injunctions: the enforcement ladder's top

When product already distributed presents a risk, the instrument is the **recall**: the removal or correction of marketed product that violates the law, conducted by the firm, monitored and classified by the agency. FDA classifies recalls by health hazard, on the basis of a health hazard evaluation: **Class I**, a reasonable probability of serious adverse health consequences, including death; **Class II**, a probability of temporary or medically reversible consequences, or a remote probability of serious harm; **Class III**, exposure not likely to cause adverse health consequences. The recall's mechanics are documentation again: the strategy (depth of recall, to wholesale, retail or consumer level), the consignee notifications built from Unit 1's distribution records, the effectiveness checks that prove recipients acted, status reports, and termination when the agency is satisfied the product is recovered or corrected; a market withdrawal (a minor problem, no legal violation) and a stock recovery (product not yet distributed) are the neighbouring, lesser categories, and confusing them in an answer costs marks. Beyond recalls, the agency's statutory remedies escalate: **seizure**, a court action against the offending goods themselves (under section 304 of the Food, Drug, and Cosmetic Act), by which the product is condemned and removed; and **injunction**, a court order against the firm's conduct (under section 302), restraining further violation, in its developed form the **consent decree** under which major companies have operated for years under external oversight. The ladder as a whole, observation, report, warning, recall, seizure, injunction, is the enforcement grammar every earlier unit of this subject exists to keep a company off.

5.8 The ISO risk management standard

The unit closes with the standard its final phrase names. The **ISO risk management standard** is **ISO 31000**, Risk management: principles and guidelines, the generic international standard that frames risk management for any organisation: principles (risk management creates and protects value, is integrated, structured, customised, inclusive, dynamic and evidence based), a framework of leadership, integration, design, implementation, evaluation and improvement, and a process of communication and consultation, establishing context and criteria, **risk assessment** (identification, analysis, evaluation), risk treatment, monitoring and review, and recording and reporting. Beside the generic standard stands its pharmaceutical translations: **ICH Q9**, quality risk management, which applies the same cycle to product quality with tools from flowcharts to FMEA and HACCP, and **ISO 14971**, the sector standard for the application of risk management to **medical devices**, which Unit 3's ISO 13485 quality system expressly invokes. The closing lesson of the subject is that risk management is the grammar the whole course has been speaking: documentation that evidences control, audits and inspections that test it, changes classified by their risk to the product, and enforcement scaled to the risk that remains.

Frequently Asked Questions

Q: What is the difference between the Master Formula Record and the Batch Manufacturing

Record? The Master Formula Record is the standing master: the approved formula and process for a product, written once, from which every batch is made. The Batch Manufacturing Record is its executed copy for one batch: issued with a batch number, filled in contemporaneously as manufacture proceeds, carrying the batch's actual quantities, times, results, calculations and signatures, and reviewed by quality before the batch is released. One is the law, the other is the evidence that the law was obeyed on a particular day.

Q: What does a Batch Manufacturing Record calculate, and why are the calculations checked twice?

Three families of calculation: the quantity of each material to weigh, adjusted for its assay or potency; the percentage yield at each stage and for the batch, actual against theoretical; and the reconciliation of controlled materials, issued against used, returned and wasted. Each is performed by one person and independently verified by a second, because a wrongly calculated record cannot be distinguished afterwards from a wrongly made batch: the arithmetic is part of the evidence, so it is held to the same standard as the manufacture.

Q: What is a Drug Master File, and what are its five types? A Drug Master File is a confidential file a holder submits directly to the agency, so that an applicant can reference the holder's data in an application, under a letter of authorization, without ever seeing the confidential content. In the United States system the types are: Type I, manufacturing site, facilities, operating procedures and personnel (no longer accepted for new files); Type II, drug substance, its intermediates and materials, or drug product; Type III, packaging material; Type IV, excipient, colorant, flavor or similar material; and Type V, FDA accepted reference information. A DMF is never approved alone: it is reviewed only when an application references it.

Q: What is the difference between the CTD and the eCTD? The CTD (ICH M4) is an organisation of content: five modules, regional administrative information in Module 1, summaries in Module 2, and quality, nonclinical and clinical evidence in Modules 3, 4 and 5. The eCTD (ICH M2) is that same content in electronic form: a sequence of transmissions with a defined folder structure and an XML backbone that lists every document, its checksum and its lifecycle operation, so the current state of the application can be rebuilt from all its sequences. CTD says what goes where; eCTD says how it travels and changes.

Q: What is NeeS, and how does it differ from eCTD? NeeS, Non eCTD electronic Submissions, is a dossier supplied electronically in the CTD folder structure, as PDF documents navigated by hyperlinked tables of contents, but without the XML backbone. It therefore lacks the eCTD's automated lifecycle management and machine validation: it is a well organised set of documents rather than a database of them. It was Europe's transitional format and is still accepted for some procedures, while eCTD is mandatory for the major routes in the ICH regions.

Q: What is the SUGAM portal used for? SUGAM is the online portal of CDSCO, India's Central Drugs Standard Control Organization. Through it applicants register, file applications within CDSCO's remit (such as import registration and licences, clinical trial and bioequivalence permissions and related filings), upload the dossier documents, pay fees electronically, and then track the application, answering the authority's queries inside the same system. It gives the Indian dossier a tracked electronic lifecycle, as the Electronic Submissions Gateway does in the United States.

Q: What is the difference between an audit and an inspection? An audit is performed by or for the organisation (first party), by an interested partner such as a customer (second party), or by an independent certification body (third party); its force comes from the quality system or the contract. An inspection is performed by a regulatory authority using legal powers of entry, examination and copying; the site cannot decline it, and its outcomes are legal acts: licences, certificates, deficiency letters and enforcement. The floor technique is similar; the authority behind it is not.

Q: What is a pre-approval inspection, and what does it test? A pre-approval inspection is performed before a marketing application is approved, to verify that the facilities named in the dossier can do what the dossier promises. In the FDA model it tests three things: readiness for commercial manufacturing, conformance of actual practice to the application as filed, and the integrity of the data in the application, audited against raw records. A facility that fails cannot support an approval until the deficiencies are resolved, which is why compilation discipline and self inspection are, in effect, long term preparation for it.

Q: What is the difference between a correction, a corrective action and a preventive action in CAPA? A correction fixes the detected problem itself: the affected batch is quarantined, the wrong labels are destroyed. A corrective action removes the cause of a detected nonconformity so it cannot recur: the process, equipment, document or training that allowed it is changed. A preventive action removes the cause of a potential nonconformity, typically by extending the corrective lesson to other products, lines or sites where the same cause is present but has not yet produced a failure. CAPA closes only when the actions are verified to have been effective.

Q: What decides whether a post approval change is filed as a PAS, a CBE-30 or in the annual report? The change's potential to affect the drug product's identity, strength, quality, purity or potency, under 21 CFR 314.70 and the applicable SUPAC guidance. A major change with substantial potential effect is a Prior Approval Supplement, approved before distribution. A moderate change is a Changes Being Effected supplement, received by FDA at least thirty days before distribution (CBE-30), or at the time of distribution for designated changes (CBE-0). A minor change with minimal potential effect is simply described in the annual report. The classification is the skill: safety labelling, for example, is deliberately allowed the fast CBE route so that stronger warnings are not delayed.

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