

Unit 2: Regulatory Requirements for Product Approval

Free notes at pharmacolearn.fyi

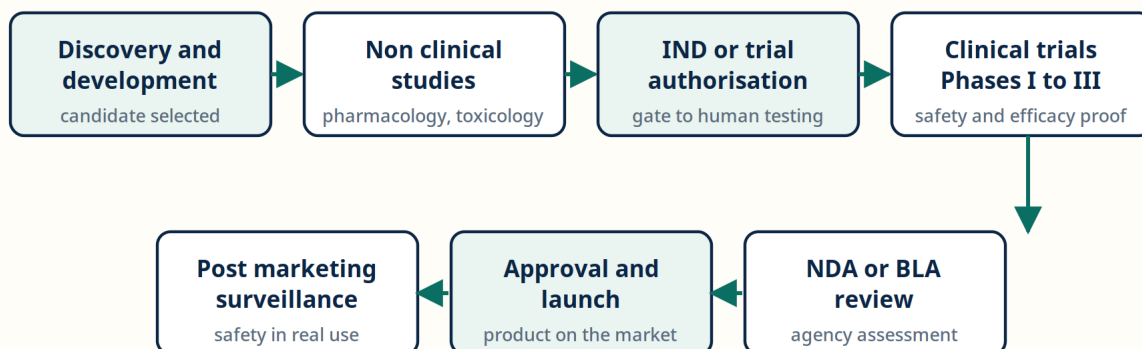
2.1 The principle of premarket approval

Modern drug law rests on one idea: a new drug may not be marketed until the regulator has approved it as safe and effective for its labelled use, and made by a process that reliably gives the approved quality. Approval requirements therefore always fall into three evidence blocks, and every application in every country is built from them:

- **Quality:** identity, strength, purity and stability of the substance and product, and a controlled manufacturing process (the CMC block of Unit 3).
- **Safety:** non clinical toxicology and the clinical safety record (Units 4 and 5).
- **Efficacy:** substantial evidence from adequate and well controlled clinical investigations that the drug does what its labelling claims.

What changes between product types is how much of each block the applicant must generate itself. That is the subject of this unit: the API underneath the product, ordinary small molecule products through the NDA and ANDA, biologics, and novel therapies, then the practical question of how a product made outside the United States is registered there.

Drug Development and Approval Pathway



Every stage is gated: the evidence of one stage opens the next.

Figure: The development and approval pathway: each stage is gated by the evidence of the stage before it.

2.2 Approval requirements for the API

The active pharmaceutical ingredient (API) is not approved as a stand alone product in the US system; it is approved as part of each finished product application that uses it. Its regulatory requirements are therefore documentary and quality based:

- **Full characterisation and specification:** identity, assay, impurities (including mutagenic impurity assessment under ICH M7 principles), residual solvents (ICH Q3C), elemental impurities (ICH Q3D), polymorphic form and particle size where these affect the product.

- **Manufacturing description and control:** the synthetic route, starting materials and their controls, critical steps and intermediates, in process controls, and process validation expectations, all carried in the DMF or its regional equivalent (Unit 1.3) or in Module 3 of the application itself.
- **Stability and retest:** stability data under ICH Q1 conditions supporting a retest period or shelf life for the substance, with a defined container closure system.
- **GMP compliance of the API site:** the site is subject to inspection against GMP expectations for APIs (ICH Q7 is the reference standard), including for foreign sites supplying the US.

2.3 Approval requirements for biologics

Biologics are products made from living systems: monoclonal antibodies, recombinant proteins, vaccines, blood products and similar. In the US they are licensed through a **Biologics Licence Application (BLA)** under the Public Health Service Act rather than an ordinary NDA, and the reviewing centre is the biologics centre of FDA. Their special requirements follow from their nature:

- The product is defined by its process: a living production system cannot be copied exactly, so characterisation, comparability after process changes, and control of the cell substrate and adventitious agents (viral safety) carry far more weight than for a small molecule.
- Immunogenicity must be studied, because the patient's immune system can react to a biological product.
- A **biosimilar** is the biologic counterpart of a generic: it must be shown to be highly similar to a reference biologic, with no clinically meaningful differences in safety, purity and potency, through a stepwise programme of analytical comparison, animal work where needed, and clinical studies targeted at the remaining uncertainty. The abbreviated biosimilar pathway was created by the Biologics Price Competition and Innovation Act of 2009, and the further status of **interchangeable** biosimilar carries additional switching evidence expectations.

2.4 Approval requirements for novel therapies

Novel therapies include cell therapies, gene therapies, tissue engineered products and first in class products built on new platforms. Their regulatory handling extends the biologics model rather than replacing it:

- Products are reviewed by specialist offices (in FDA, the office responsible for therapeutic products including cell and gene therapy within the biologics centre), and early, frequent agency interaction is expected because standard templates fit poorly.
- Long term follow up of patients is a characteristic requirement for gene therapy products, because integrating vectors and genome edits can show effects only after years.
- Expedited programmes exist to speed development of products for serious conditions with unmet need (fast track, breakthrough therapy, regenerative medicine advanced therapy designation, priority review and accelerated approval in the US; PRIME and conditional marketing authorisation in the EU). These change the intensity and timing of review, not the underlying duty to show quality, safety and efficacy; accelerated or conditional approvals carry confirmatory study obligations after marketing.
- Orphan drug designation for rare diseases brings fee relief, protocol assistance and a period of market exclusivity, and is frequently the entry route for novel therapy developers.

2.5 Obtaining an NDA

An NDA is obtained by assembling the full evidence in CTD format (Unit 3) and carrying it through review:

Obtaining an NDA (US), outline
Complete non clinical programme (Unit 4)
-> IND in force, clinical Phases I to III completed (Unit 5)
-> pre-NDA meeting with FDA: agree contents and open issues
-> compile and submit NDA in eCTD with user fee
-> filing review: accepted for review or refuse to file
-> discipline reviews, site inspections, advisory committee if needed
-> action: approval letter or complete response letter
-> labelling agreement and post marketing commitments

The applicant's practical burden is the evidence itself: three blocks of Unit 2.1, all generated by the sponsor, plus manufacturing sites ready for pre-approval inspection and labelling that matches the proven claims word for word.

2.6 Obtaining an ANDA for a generic drug

The ANDA applicant must show that its product is the **pharmaceutical equivalent** and **bioequivalent** of the reference listed drug:

- Same active ingredient, dosage form, route of administration and strength as the reference product.
- The same conditions of use and, with permitted exceptions, the same labelling.
- Bioequivalence demonstrated as in Unit 1.9, with comparative dissolution supporting the formulation.
- Quality data for its own product and process, with the API covered by a DMF reference or full data.
- A patent certification for every Orange Book patent and respect for any unexpired exclusivity (Unit 1.6).

Because the evidence pattern is fixed, generic development is an exercise in matching: match the reference product's form and performance, prove it with dissolution and one or two BE studies, and keep the quality block complete and inspection ready.

2.7 US registration for foreign drugs: ways and means

A drug made outside the United States enters the US system through the same product applications, plus a layer of establishment and import controls:

- **Product approval first:** the foreign product needs its own approved NDA or ANDA like any US product. Approval examines the foreign data on the same standards; foreign clinical studies not under an IND are acceptable when conducted to GCP and when the agency can validate the data, including by inspection.
- **Establishment registration and drug listing:** every foreign establishment that manufactures, processes, packs or labels a drug for the US market must register with FDA and list its products, and must renew the registration and listing as required. Registration is an administrative listing, not an approval.
- **US agent:** a foreign establishment must name a United States agent as its official contact point for FDA communications.
- **Inspection:** foreign sites are inspected by FDA on the same GMP expectations as domestic sites, increasingly on an unannounced or short notice basis; refusal of inspection is itself a ground to treat products as adulterated and block entry.
- **Import controls:** shipments can be sampled, examined and detained at the border; firms and products with a history of problems can be placed on import alert and detained without physical examination until compliance is shown.
- **DMF and site files:** the API and site information for foreign suppliers travels through DMFs (Unit 1.3), so the confidentiality and authorisation mechanics of the DMF system are part of the foreign registration route.

Registering a Foreign Drug in the US

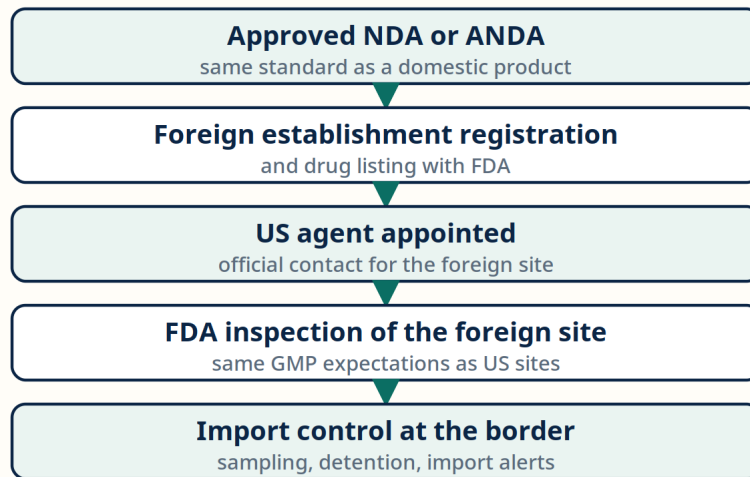


Figure: Registering a foreign drug in the US: the product application plus the establishment, agent, inspection and import control layers.