Coming to America – Successfully Tackling the FDA Landscape

Often the regulatory guidelines in other parts of the world differ significantly. However, by engaging experienced consultants or through interactions with the FDA, sponsors learn what will be needed to register their drug product in the US

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The FDA is tasked with regulating the safety and effectiveness of drugs, biologics, and devices under the *Federal Food, Drug and Cosmetic Act* (FFD&CA) and the *Public Health Service Act* (PHSA). Center for Drug Evaluation and Research is the lead centre for the regulation of human drugs (over the counter drugs and prescription drugs) both investigational and licenced.

The Center for Biologics Evaluation and Research regulates an array of diverse and complex biological products, both investigational and licenced, including: allergenics, blood and blood components, gene therapies, human tissues and cellular products, vaccines, xenotransplantation products, as well as therapeutic proteins, such as insulins. Amino acid polymers composed of 40 or fewer amino acids are outside the scope of the term 'protein' (1). Biological products are mostly produced in a living system, such as plants, animal cells, or microorganisms, whereas small molecule drug products are typically manufactured through chemical synthesis.

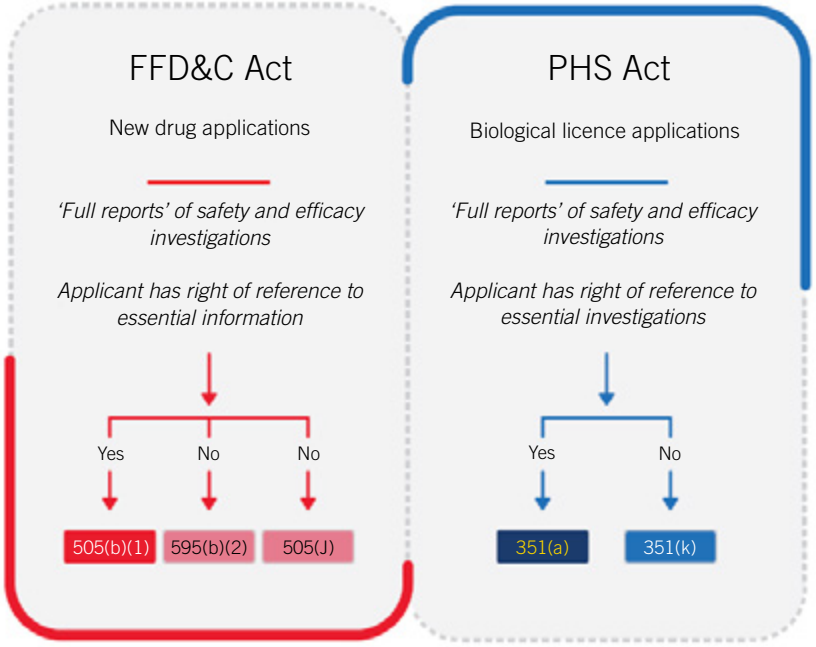

Figure 1: US drug/biologic approval pathways. This diagram is based on information from the FFD&CA and PHSA

Many pharmaceutical/biopharmaceutical companies are successfully developing and marketing drug products in their own countries such as China, Japan, South Korea, Taiwan, and India, among others, and there is widespread interest in Asian pharma/biopharma companies to learn how drugs are regulated in the US and what it will take to bring those products to the US market. This article will detail US regulatory pathways for drugs and biologics, as well as FDA expectations for chemistry, manufacturing, and controls (CMC), nonclinical and clinical development.

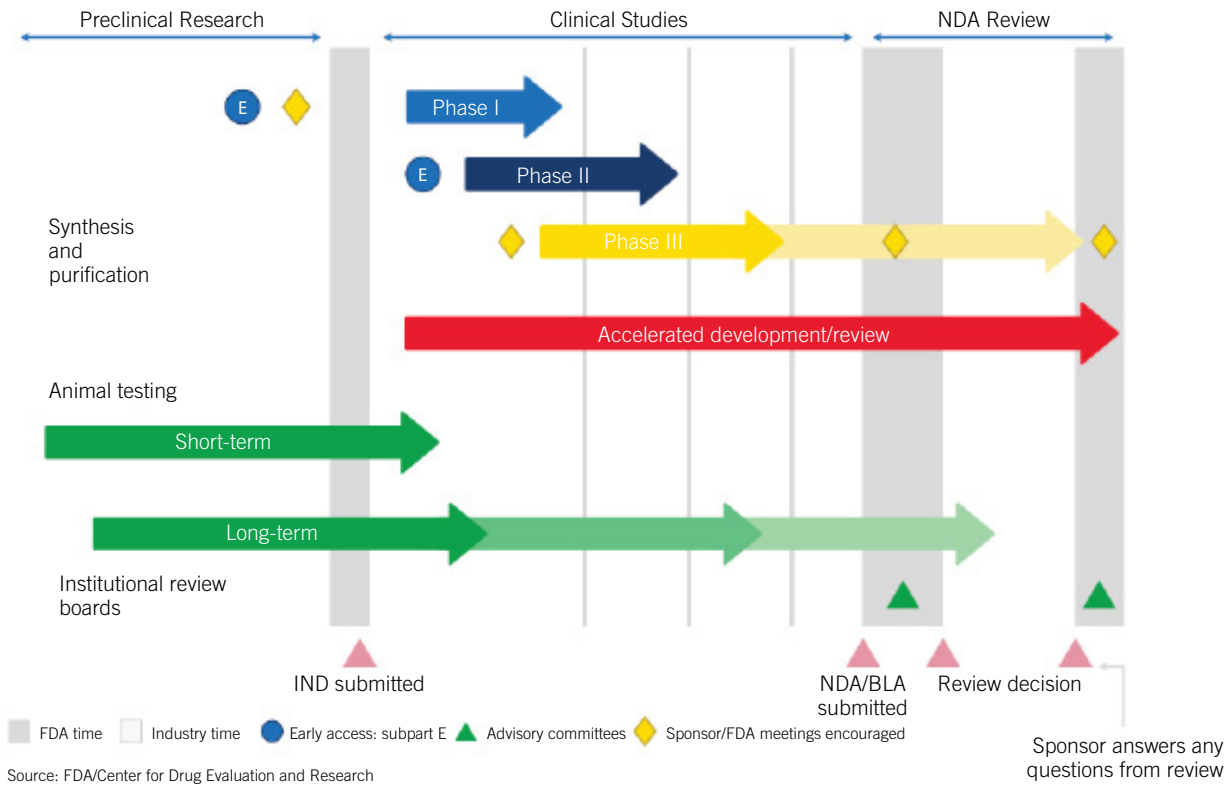

Figure 2: Stages of product development. Source: FDA.gov

US Regulatory Pathways

The major regulatory pathways for drug approval in the US are outlined in **Figure 1**, page 53.

If a sponsor is developing a new novel drug, meaning that the active ingredient has never been approved by the FDA, then the developmental pathway to follow will be 505(b) (1). Under this pathway, all investigations supporting safety and effectiveness, both clinical and nonclinical, are conducted by or on behalf of the sponsor.

Drugs approved under the 505(b) pathway must contain full safety and efficacy investigation reports for the proposed drug product. However, some of the information can come from non-applicant studies, meaning those from published literature, or in the FDA's safety and/or efficacy findings for a reference-listed drug once the FDA-granted exclusivity period for the innovator drug has expired and there is no infringement of any granted patents (2).

Once the FDA-approved drugs come off patent, pharma companies can develop copies of that drug, called generics, under the 505(j) pathway. A generic drug product has to be comparable to an innovator drug product in dosage form, strength, route of administration, quality, performance characteristics, and intended use (2). The applications for generic drugs are termed 'abbreviated' because they are generally not required to include nonclinical (animal) and clinical (human) safety and efficacy data. However, the applicants of generic drugs do need to clinically demonstrate through a bioequivalence study, or studies, in healthy volunteers that their drug performs the same as the innovator drug. In order to garner drug approval, the generic version has to deliver the same amount of active ingredients into a subject's bloodstream in the same amount of time as the innovator drug.

Biological products, just as drugs, are used for the treatment, prevention, or cure of diseases in humans. While chemically synthesised small molecular weight drugs have a well-defined structure and can be thoroughly characterised, biological products are generally derived from living material (human, animal, plant or microorganism), complex in structure, and, therefore, usually not fully characterised. Since biologic products are a subset of drugs; they both are regulated under provisions of the FFD&CA, but only biologic products are licenced under section 351 of the PHSA (2).

The stages of product development and when to engage with the FDA to obtain input for the applicable stage of development are presented in **Figure 2** and **Figure 3**.

It is highly recommended that sponsors meet with the FDA to obtain concurrence for the various stages of development, namely CMC,

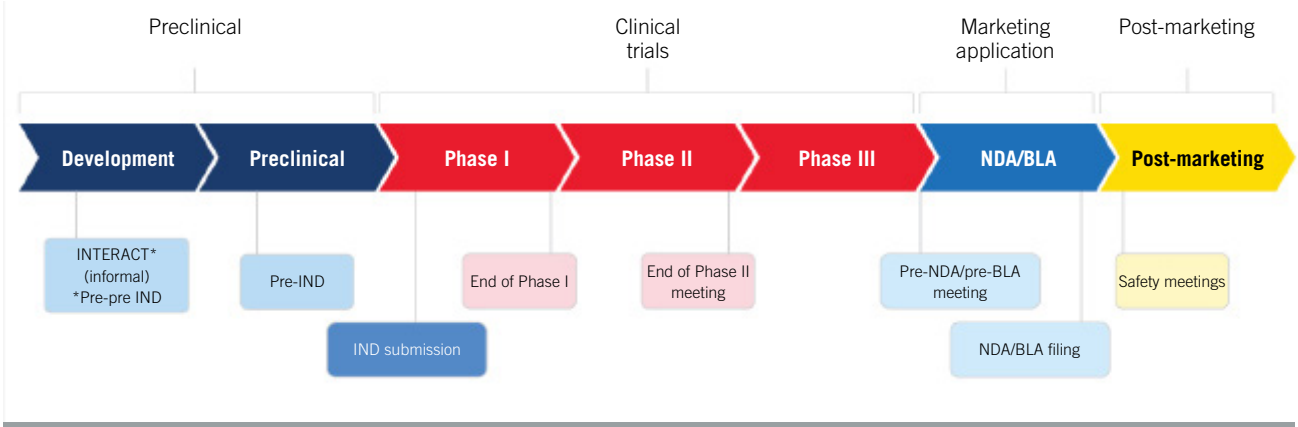

Figure 3: Opportunities for interactions with FDA during product development. Source: FDA.gov

nonclinical, and clinical to avoid doing unnecessary analytical, nonclinical, and clinical studies to save time and money in the overall product development programme. Please note that the INTERACT meeting is only available for advanced therapy products, such as cell and gene therapy products.

FDA CMC Expectations

CMC is an integral part of any pharmaceutical product development for both drugs and biologics. Federal Code of Regulations 21 CFR 312.23(a)(7)(i) includes the graded nature of CMC information needed as product development progresses. The manufacture of the quality drug product is a must if the sponsor wants to have the drug product approved for the US market, and compliance with GMPs is required (3). The FDA and ICH have issued many guidance documents that outline the regulatory agencies' expectations for CMC development. The FDA generally expects to see the following information in the drug substance section of the investigational new drug (IND) application (4-6).

Detailed description of physical, chemical, or biological characteristics and evidence supporting structure and identity of the active pharmaceutical ingredient(s) is very important. For biologics, please include primary, secondary, tertiary, etc., structures as warranted. The FDA expects to see the following in the IND:

1. Name and address of manufacturer or manufacturers (if more than one) should be provided
2. Description of the general method of preparation of the drug substance, including a list of the reagents, solvents, and any catalysts that may be used. A detailed flow diagram with in-process controls should be provided. Additional information may be needed to assess the safety of biotechnology-derived drugs or drugs extracted from human, animal, or plant sources. Please consult relevant FDA guidance for these types of products
3. The acceptance criteria and analytical methods used to ensure the identity, strength, quality, and purity of the drug substance, with a brief description of the test methods used (e.g., nuclear magnetic resonance, infrared, UV spectra to prove the identity, and high-performance liquid chromatograms to support the purity level and impurities, etc.) should be provided. It should be noted that the FDA expects sponsors to use of state-of-the-art equipment for analytical testing. Test results should be provided
4. Information to support stability of the drug substance during storage in the intended container closure and during the toxicological and clinical studies will be needed

For the manufacture of the drug product, the FDA expects to see the following information in the IND:

- Description of the formulation or routes of administration intended to be used in the clinical trial. For oral administration, suspensions, or solutions in addition to the more usual tablets, powders, and capsules can be considered. Sterility and pyrogenicity must be ensured for products intended for ophthalmic, inhalational (aqueous base), or parenteral administration. For biological products, freedom from viruses, mycoplasma, and foreign DNA, should be ensured. All excipients should be generally recognised as safe or part of a formulation that is already approved or licenced in the US for the same route of administration and amount, or they must be adequately qualified through appropriate animal studies
- A list of all components and composition used in manufacturing process, including alternative sources of inactive ingredients used in the manufacture of the drug product
- Summary of quantitative composition of the IND product and dosage form
- Brief general description of the manufacturing process (in the form of a flow diagram), complete with in-process controls and container closure, as well as packaging procedure
- Acceptance criteria and analytical methods used to ensure the identity, strength, quality, and purity of the drug product
- Drug product release specifications will need to be included. For injectable products, additional tests

include sterility and pyrogenicity, endotoxin levels, and particulate matter. Summary table of release testing for multiple batches should be included
- Stability test results for the drug product, especially planned clinical batch should be included in the IND

If a placebo arm is planned for the clinical study, then a brief general description of the composition, manufacture, and control of any placebo formulation should be included in the IND. The description of the placebo product can be similar to the description of the drug product as provided above.

The FDA also has a requirement for environmental assessment of the investigational drug product (7). This section is designed to assess the impact of the drug product on the environment. In most cases, the FDA grants an exclusion from such an assessment. However, a categorical exclusion will depend upon the size of the study population and drug manufactured for the study. In general, categorical exclusion is based on a number of factors (21CFR25.31): environmental compartment (soil, air, water) into which the drug product will be released; drug degradation and to what degree; and safety margin between expected environmental concentration and effect level.

It should be noted that the amount of data in the CMC section increases as the product development goes from a Phase I to a Phase III study and eventually filing of the drug application as an NDA/BLA, etc. The FDA has many guidance documents available for drugs and biologics for consultation on the FDA website, which is easily accessible online.

FDA Nonclinical Expectations

Before a drug can be tested in humans in the clinic, the FDA expects a litany of *in vitro* and *in vivo* nonclinical testing to be conducted (8). The types of nonclinical safety studies for a pharmaceutical/biopharmaceutical product usually include pharmacology studies, general toxicity studies, toxicokinetic and nonclinical pharmacokinetic studies, reproduction toxicity studies, genotoxicity studies, and carcinogenicity studies to assess the potential of drugs that are intended for a long duration of use. Other nonclinical studies may include studies to assess phototoxicity, immunotoxicity, juvenile animal toxicity, and abuse liability on a case-by-case basis. Information on preclinical studies for small molecules can be found in ICH M3 while that for biologics can be found in ICH S6.

Safety pharmacology and pharmacodynamic studies generally should be conducted before human exposure. The core battery of safety pharmacology studies includes the assessment of drug effects on cardiovascular, central nervous, and respiratory systems. The relevant guidance are ICH S7A and S7B. The primary pharmacodynamic studies (*in vivo* and/or *in vitro*) are generally conducted early in product development and are intended to investigate the mechanism of action and/or effects of a substance in relation to its desired therapeutic target.

Before initiating clinical studies, *in vitro* metabolic and plasma protein binding studies in animals and humans and systemic exposure data in the species used for repeated-dose toxicity studies generally should be evaluated per ICH S3A. Absorption, distribution, metabolism, and excretion (ADME) study in test species should also be available before exposing large numbers of human subjects for long durations, such as in Phase III studies.

The duration, therapeutic indication, and scope of the proposed clinical trial(s) dictates the duration of the

Duration of indicated treatment	Rodent	Non-rodent
Up to 2 weeks	1 month	1 month
>2 weeks to 1 month	3 months	3 months
>1 month to 3 months	6 months	6 months
>3 months	6 months[a]	6 months[a,b]

a. There can be cases where a paediatric population is the primary population, and existing animal studies (toxicology or pharmacology) have identified potential developmental concerns for target organs. In these cases, long-term toxicity testing starting in juvenile animals can be appropriate in some circumstances (see section XII in **reference 12**).

b. The following are examples where nonrodent studies of up to 6 months' duration can also be appropriate for the US:
- When immunogenicity or intolerance confounds conduct of longer-term studies
- Repeated short-term drug exposure even if clinical trial duration exceeds 6 months, such as intermittent treatment of migraine, erectile dysfunction, or herpes simplex
- Drugs administered on a chronic basis to reduce the risk of recurrence of cancer
- Drugs for indications for which life expectancy is short

Table 1: Recommended duration of repeated-dose toxicity studies to support marketing. Source: FDA.gov

repeated-dose toxicity studies. In principle, the duration of the animal toxicity studies should be assessed in two mammalian species (rodent and non-rodent) and the duration should be equal to or exceed the duration of the human clinical trials up to the maximum recommended duration of the repeated dose toxicity studies (**Table 1**) (8).

Local tolerance studies by the intended therapeutic route are generally conducted as part of the general toxicity studies.

A gene mutation assay is generally considered sufficient to support all single-dose clinical development trials. A complete battery of tests for genotoxicity should be completed before initiation of Phase II trials. Generally, this is not needed for biologic products, and researchers should seek a waiver from the FDA.

A case-by-case determination should be made as to whether carcinogenicity studies are needed for the clinical indication based on product carcinogenic risk. If they are needed, they will need to be completed prior to marketing application. Generally, these are not needed for biologic products, and one can seek a waiver from FDA.

Reproduction toxicity studies should be conducted as is appropriate for the population that is to be exposed. Men can be included in Phase I and II trials before the conduct of the male fertility study since an evaluation of the male reproductive organs is performed in the repeated dose toxicity studies. In the US, assessment of embryo-foetal development can be deferred until before Phase III for women of childbearing potential using precautions to prevent pregnancy in clinical trials.

FDA Clinical Expectations

In order to protect subjects participating in first-in-human studies (FIH), the estimation of the first dose in humans is extremely important. All of the relevant nonclinical data needs to be assessed, including pharmacokinetics, pharmacodynamics, and pharmacological/toxicological profile. The no observed adverse effect level (NOAEL) in relevant animal species, which is assessed in the safety studies, provides this important information in estimating the starting dose in FIH studies.

General clinical development programmes include a single dose pharmacokinetic/pharmacodynamic (if applicable) study either in healthy volunteers or patient population depending upon the drug being studied, followed by a dose-escalation study to determine the effective/safe dose to study in the Phase II study. This is followed by two adequate and well-controlled trials, or one adequate and well-controlled trial plus confirmatory evidence, or reliance on the FDA's previous findings of effectiveness of an approved drug if legally permissible (8). The benefits of the drug will need to outweigh the adverse effects, under the conditions of use defined in labelling for the drug to be approved by the FDA.

For clinical trials, the FDA expects to see "substantial evidence" of effectiveness for both the quality and the quantity of the evidence. The clinical studies will need to be appropriately designed. The gold standard is a randomised, double-blind, well-controlled, statistically powered study that is placebo-controlled, if warranted, or has non-inferiority study design with an active comparator (if relevant). A large multicentre trial may also satisfy the legal requirement for substantial evidence of effectiveness. FDA regulations in 21 CFR 314.126(b) describe aspects of an adequate and well-controlled clinical investigation, including choice of control, methods of how patients are assigned to treatment, types of measures needed to minimise bias (e.g., blinding), efficacy endpoints, and statistical methods to analyse clinical investigation's results to assess the effectiveness of the drug (9-10).

Figure 4: Comparison of expedited pathways. Source: FDA.gov

Primary and secondary clinical endpoints will need to be clearly prespecified and would need to be acceptable to the FDA. The FDA does have many guidance documents available to speak to the various therapeutic areas/diseases that can be consulted. They are all available by using the FDA's guidance search tool (10). In addition, discussion with appropriate review divisions early in clinical development can assist sponsors in identifying appropriate trial endpoints for a particular development programme.

In general, the FDA accepts clinical endpoints that reflect patient benefits (i.e., how patients feel, function, or survive) or validated surrogate endpoints that are reasonably likely to predict a clinical benefit. For drugs granted accelerated approval based on surrogate endpoint(s), the FDA requires post-approval trials to verify the predicted clinical benefit.

The statistical analysis will need to demonstrate a p-value of <0.05 (two sided) for concluding that the drug is effective in the chosen indication that was studied. For a serious disease where there is no available drug therapy, or in case of rare diseases where the sample size is often limited, a somewhat higher p-value – if prespecified and justified – may be acceptable to the FDA. Again, it is very important to meet with the FDA and obtain agreement on the study design including the planned statistical analyses.

There are a number of expedited pathways for drug approval for serious conditions and for drugs and biologics that have to meet specific criteria for each type of designation (see **Figure 4,** page 57) (11). They include Fast Track Designation, Breakthrough Therapy Designation, Accelerated Approval, Regenerative Medicine Advanced Therapy Designation, and Priority Review Designation. Benefits include intensive guidance for an efficient drug development programme, accelerated approval, priority review, and rolling submissions among others.

Summary

As the regulatory landscape for the development of drugs and biologics is continually being updated with advancements in technology and testing, as well as agencies gaining more experience, it is important for sponsors to consult the updated guidance documents and interact with the FDA during the drug development process to ensure that FDA expectations will be met when the drug/biologic applications are filed. It should be noted that an experienced regulatory partner can help sponsors navigate smoothly through FDA requirements as they develop drug products to seek US licensure for marketing.

References

1. *Visit: www.fda.gov/media/119272/download*
2. *Visit: www.fda.gov/drugs/development-approval-process-drugs/how-drugs-are-developed-and-approved*
3. *Visit: www.fda.gov/drugs/pharmaceutical-quality-resources/current-good-manufacturing-practice-cgmp-regulations*
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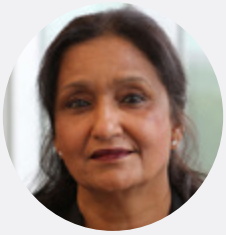
9. *Visit: www.fda.gov/media/129527/download*
10. *Visit: www.fda.gov/regulatory-information/search-fda-guidance-documents/demonstrating-substantial-evidence-effectiveness-human-drug-and-biological-products*
11. *Visit: https://www.fda.gov/files/drugs/published/Expedited-Programs-for-Serious-Conditions-Drugs-and-Biologics.pdf*



Dr Kamali Chance has more than 20 years of regulatory experience in developing country-specific and global regulatory strategies and clinical development plans to bring pharmaceutical and biotech products to market. As VP of Regulatory Affairs at **Linical Americas**, Dr Chance assists clients in preparing meeting requests and briefing packages to meet FDA requirements, including INTERACT meetings, pre-IND, EOP1, EOP2, and pre-NDA/pre-BLA meetings. She also accompanies clients as their US Agent and leads the discussions at FDA face-to-face meetings. Dr Chance received her PhD in Nutrition/Nutritional Biochemistry from the University of North Carolina in Greensboro, US, and her MPH from the University of North Carolina in Chapel Hill. She has Regulatory Affairs Certification from the Regulatory Affairs Professional Society.

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