US REGULATORY PATHWAYS:

Bringing new drugs to the market in the US: an overview

To support its mission of protecting and advancing the public health, the US FDA has established several pathways for applicants to follow in order to bring new drugs to the market in the US. This continuing professional development supplement explains the available options which should enable selection of the appropriate regulatory pathway.

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The US FDA review of an application for a new medical product is a rigorous, multidisciplinary process that requires careful evaluation of the applicant’s development programme. After reviewing the application data, FDA officials determine whether the sponsor has adequately demonstrated the product’s quality, safety, and efficacy for its intended use in the target population.

Under US federal law, all medical products are intended for use in the diagnosis, cure, mitigation, treatment, or prevention of a disease. Although many aspects of the review and approval process for biologics are similar to the procedures outlined here, the scope of this article is limited to small molecules.

Types of applications

In the US, under section 505 of the Food, Drug, and Cosmetics (FD&C) Act, there are three types of new drug applications (NDAs) (see Table 1).

Requirements for NDAs

Safety, effectiveness and quality

The statutory requirements for NDA approval are described in 21 CFR 314.105 and approval is dependent on the applicant providing data that supports: 1) the product is safe and effective for the indication being studied, 2) the chemistry and manufacturing data and controls are sufficient to support the identity, strength, quality, purity and stability of the drug product, and 3) the labelling is appropriate to support safe use of the product. In addition, the reasons for not approving an NDA outlined in 21 CFR 314.125 must not apply.

According to 21 CFR 314.105, the FDA is required to exercise scientific judgement in the determination of the quantity and type of scientific data required to support approval of an NDA. This requirement is emphasised in FDA guidance documents, which state that an approval of a new drug can only occur when an applicant can demonstrate a positive benefit–risk assessment for the drug.

Further details regarding the FDA’s benefit-risk assessment process are outlined in the implementation plan published by the FDA as part of the PDUFA VI reauthorisation.1 FDA’s requirements for approval are based on “substantial evidence” to support the applicant’s claim of effectiveness of the drug. Substantial evidence is based on the submission of “adequate and well-controlled” clinical trials, which are described in 21 CFR 314.126.

It is important to understand how the FDA will view adequate and well-controlled studies within the context of a specific drug product. Within the limits imposed by the congressional scheme, the FDA has been flexible, broadly interpreting the requirements to the extent possible whenever compelling data on a specific drug were available. For example, although the FDA generally requires two adequate and well-controlled studies to support regular approval, at times, one study may be accepted. This could be the case when the study is well conducted, provides highly persuasive clinical and statistical results, and the conduct of a second study would be difficult to justify on ethical grounds. To support a single adequate and well-controlled study demonstrating effectiveness of a new use, in some cases, the agency has relied on relevant information from other adequate and well-controlled studies of a certain drug (eg, studies of different doses, different dosage forms, or different populations). In general, NDA approval based on one pivotal study is more likely for drugs that target a serious or life-threatening disease for which there is either no therapy, or the current therapies are inadequate. In addition to data in support of safety and effectiveness, an applicant is also required to provide comprehensive chemistry, manufacturing and controls (CMC) information. Specifically, 21 CFR 314.50, outlines the types of data the FDA requires the applicant to include in an NDA that are related to the identity, strength, quality and purity, and bioavailability of the drug substance and drug product. The CMC data supports the applicant’s commitment that the drug can be manufactured with the appropriate regulatory pathway.

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Table 1: Types of applications

<table>
<thead>
<tr>
<th>Application Type</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>505(b)(1) NDA</td>
<td>Typically used for novel drugs that have not previously been approved. This route requires the applicant to conduct all studies needed to demonstrate the quality, safety, and efficacy of the drug.</td>
</tr>
<tr>
<td>505(b)(2) NDA</td>
<td>Allows an applicant to use existing data from studies not conducted by or for the applicant, and for which the applicant does not have right of reference, to meet some or all of the safety and efficacy requirements. This means that a 505(b)(2) drug product may be developed in a way that is quicker, cheaper, and less risky, than a 505(b)(1) product.</td>
</tr>
<tr>
<td>505(j) application</td>
<td>Also called ANDAs, used for generic products and requires an applicant to demonstrate “bioequivalence” to the corresponding branded product, rather than replicating efficacy and safety studies.</td>
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Types of applications

In the US, under section 505 of the Food, Drug, and Cosmetics (FD&C) Act, there are three types of new drug applications (NDAs): 505(b)(1) NDA, 505(b)(2) NDA, and 505(j) application. The 505(b)(1) NDA is the route used for novel drugs that have not previously been approved. This route requires the applicant to conduct all studies needed to demonstrate the quality, safety, and efficacy of the drug. The 505(b)(2) NDA allows an applicant to use existing data from studies not conducted by or for the applicant, and for which the applicant does not have right of reference, to meet some or all of the safety and efficacy requirements. This means that a 505(b)(2) drug product may be developed in a way that is quicker, cheaper, and less risky, than a 505(b)(1) product. The 505(j) application, also called ANDA, is used for generic products and requires an applicant to demonstrate “bioequivalence” to the corresponding branded product, rather than replicating efficacy and safety studies.

Requirements for NDAs

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consistent, that the product is adequately controlled, and that all manufacturing processes are conducted according to current Good Manufacturing Practices (cGMPs).

### Labelling information

As described in 21 CFR 201, prescription drug labelling must contain a summary of the essential scientific information necessary to allow for the safe and effective use of the drug. The labelling must be informative, accurate, and not promotional in tone, or false or misleading. It must also be updated any time new information becomes available that renders the labelling inaccurate, false or misleading. The contents of full labelling are outlined in 21 CFR 201.56. Some sections may not be applicable, (for example, drug abuse and dependence), but an applicant is expected to provide data to support all relevant sections of labelling for an NDA at the time of submission. An applicant should also justify the omission of any section of labelling mentioned in the labelling regulations. In addition, FDA regulations state that the data in the label should be based on actual human experience whenever possible, and that reliance on animal data is only appropriate in certain identified labelling sections, or in special circumstances where human data cannot be collected.

The FDA requires that all relevant patent information for the new drug be submitted as part of the NDA. The requirements regarding submission of patent information are outlined in 21 CFR 314.50 and 314.53.

### Submission and review process

**Submission via electronic gateway**

As of 5 May 2017, applicants who submit an NDA or ANDA to the FDA for review and approval are required to do so electronically via the Electronic Submissions Gateway (ESG).\(^1\) The FDA has also implemented a number of data standards and electronic file requirements to ensure appropriate access to review the submitted information. Multiple guidance documents are available that outline the various requirements. The FDA may reject applications that do not adhere to the electronic submission formatting expectations.

**Timeline of the submission process**

Once an original NDA is submitted, FDA officials perform an initial filing review of the application. Based on this review, there are three possible outcomes:

1. If the application is complete and contains all of the safety and efficacy requirements. 505(b)(2) ANDAs (generic) require an applicant to demonstrate "bioequivalence" to the corresponding branded product, rather than replicating efficacy and safety studies. The proposed generic drug must be identical to the reference listed drug (RLD) with respect to the active ingredient, dosage strength, dosage form, and route of administration.

<table>
<thead>
<tr>
<th><strong>Application contains data from pre-clinical and clinical studies conducted by the applicant</strong></th>
<th>Full</th>
<th>Partial</th>
<th>Bioequivalence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pathway can be used for a new active moiety</strong></td>
<td>✓</td>
<td>✓</td>
<td>-</td>
</tr>
<tr>
<td><strong>Pathway can be used for new indication</strong></td>
<td>✓</td>
<td>✓</td>
<td>-</td>
</tr>
<tr>
<td><strong>Pathway can be used for new strength of an approved drug</strong></td>
<td>✓</td>
<td>✓</td>
<td>-</td>
</tr>
<tr>
<td><strong>Eligible for seven years’ exclusivity in case of orphan drug</strong></td>
<td>✓</td>
<td>✓</td>
<td>-</td>
</tr>
<tr>
<td><strong>Eligible for five years’ exclusivity for new chemical entity</strong></td>
<td>✓</td>
<td>Possible only in special cases</td>
<td>-</td>
</tr>
<tr>
<td><strong>Eligible for three years’ exclusivity for new indication</strong></td>
<td>✓</td>
<td>✓</td>
<td>-</td>
</tr>
<tr>
<td><strong>Eligible for six months’ exclusivity for paediatric indication</strong></td>
<td>✓</td>
<td>✓</td>
<td>-</td>
</tr>
<tr>
<td><strong>Eligible for 180 days’ exclusivity</strong></td>
<td>-</td>
<td>-</td>
<td>✓</td>
</tr>
</tbody>
</table>
A Day 74 letter should contain a list of the identified deficiencies and must be corrected by the applicant in a resubmission. If an RTF is not issued, FDA will issue a Day 74 letter that communicates any remaining filing issues, as well as the timeline for review. This includes the planned timing of the mid-cycle review meeting. The letter will communicate FDA’s preliminary plans on whether to hold an advisory committee (AC) meeting, and if the agency intends to conduct an expedited review. Once an application is accepted for review, the FDA Prescription Drug User Fee Act (PDUFA) goals are that standard new molecular entity (NME) reviews will be complete within ten months of the application being filed (12-month total review time from the receipt of the application). Applications that are accepted for priority review have a PDUFA goal review timeline of six months after the application is received (eight months total review time). The FDA holds a mid-cycle review meeting to assess the current status of the review process and determine whether the review process needs to be revised, at month 5 for standard reviews, and month 3 for priority reviews. A late cycle meeting is held two or three months before the PDUFA Action Date. This meeting serves as an opportunity to address any remaining issues and often a high-level discussion of labelling also occurs. For example, during the meeting potential AC issues might be discussed, along with any additional data or analyses that the applicant may need to provide. ACs are standing committees of experts, grouped broadly by therapeutic area, that are available to assist the FDA. AC meetings can be convened for any NME, in cases where there are major questions regarding an application, or in instances in which the FDA determines that there are significant public health issues involved in an application. The FDA will provide an early notification to the applicant in the Day 74 letter if the agency believes that an AC meeting will be necessary.

However, issues that warrant an AC may arise during the review, so applicants should be aware that the FDA could request a meeting during the review process. Applicants need to work closely with the regulatory project manager for preparation and efficient conduct of an AC meeting. If an AC is conducted, the applicant will be responsible for a detailed presentation of the application data that addresses the FDA’s concerns, and to answer questions from the committee regarding the issues. Following the late cycle meeting, final steps in the FDA review process (assuming a product will be approved) include finalising the label, risk evaluation and mitigation strategy (REMS) (if applicable), and any post-marketing commitments and/or post-marketing requirements. The FDA will then complete the review process and issue an approval for the product under review. During the review, the applicant can expect to receive a number of requests for information from FDA. These requests are generated as individual reviewers evaluate the data in the submission. They are intended to provide additional information or clarity for the reviewer. Requests can be as simple as confirmation of a data point, or as complex as requests for new statistical analyses or further justification of a particular point in the application. Requests generally include a timeline by which the FDA requests a response.

If the application is not approved due to one or more of the reasons listed in 21 CFR 314.125, a Complete Response Letter (CRL) will be sent to the applicant, outlining the reasons for the CRL and recommendations for corrective action. A graphic of the submission and approval process timeline is shown above (Figure 1). GCP and pre-approval inspections

As part of the approval process, the FDA will generally perform a pre-approval inspection (PAI) of the drug substance and drug product manufacturers and testing sites. The decision to conduct an on-site inspection is risk-based and considers factors such as the manufacturer’s experience, any history of cGMPs concerns, and the complexity of the manufacturing process. Similarly, the FDA will also inspect investigative sites from the pivotal clinical trials and can choose to inspect the sponsor as well.

Conclusion

Although the FDA’s submission, review and approval process can be daunting, it has implemented activities to increase the transparency and predictability of the process. This article has provided an overview. However, numerous guidance documents and FDA policies and procedures are available on the FDA’s website with more detailed information. Sponsors and applicants are encouraged to take advantage of the opportunities available for meetings with FDA officials. Topics of the meetings might include the issues on the product’s development plans or avenues to ensure that the submission’s data will meet FDA requirements. With advance research, careful planning, and partnership with FDA experts, regulatory professionals can better understand the FDA’s processes for reviewing applications and explain the process to their colleagues and management.

References

1. Information on the PDUFA VI reauthorization is available at: https://www.fda.gov/forindustry/userfees/prescriptiondruguserfee/ucm444608.htm (accessed 10 October 2018).
2. An applicant can be an individual, a company, an agency, an academic institution, a private organisation, or another organisation. The term “Applicant” is defined in 21 CFR 314.1. “Applicant means a person who submits an application or abbreviated application or an amendment or supplement to them under this part to obtain FDA approval of a new drug or an antibiotic drug and any person who owns an approved application or abbreviated application.”
7. Information on Advisory Committees is available at: https://www.fda.gov/AdvisoryCommittees/default.htm (accessed 10 October 2018).
11. The term “Sponsor” is defined in 21 CFR 312.3(a): “Sponsor means a person who takes responsibility for and initiates a clinical investigation.” Generally, the sponsor and the applicant are the same organisation. However, this is not always the case.
The initial review and approval of prasugrel hydrochloride* (Effient™, Eli Lilly and Company) demonstrates the multidisciplinary nature of US FDA reviews, as well as ways in which FDA considers benefit-risk assessments and conducts consultations external to the primary review division. The NDA for prasugrel was submitted in December 2007 as a 505(b)(1) application, and was granted priority review with a Prescription Drug User Fee Act (PDUFA) goal date of June, 2008.

Prasugrel is a thienopyridine adenosine diphosphate (ADP) receptor antagonist that irreversibly inhibits the platelet P2Y12 receptor, inhibiting platelet activation and aggregation. The indication sought by the sponsor was for “the reduction of atherothrombotic events and the reduction of stent thrombosis in acute coronary syndromes (ACS)”, with a specific definition of the patient population included in the indication statement. The sponsor also sought to add that prasugrel had “been shown to reduce the rate of a combined endpoint of cardiovascular (CV) death, non-fatal myocardial infarction (MI), or non-fatal stroke”.

In support of the new drug application (NDA), the sponsor conducted a Phase 3, multinational, randomised, double-blind, double-dummy, active controlled (clopidogrel) study in subjects with ACS who were scheduled to undergo percutaneous coronary intervention. The study enrolled over 13,000 patients and followed them for a median of more than one year. At final analysis, prasugrel demonstrated a statistically significant reduction in the triple composite endpoint (CV death, non-fatal MI, non-fatal stroke) when compared with clopidogrel. During the FDA’s review of the application, three issues arose that required significant multidisciplinary input and careful consideration by the review team.

Salt-to-base conversion and bioequivalence

Late in development, the applicant discovered that the prasugrel hydrochloride salt form could undergo an acid/base reaction with an excipient that converted the prasugrel HCl salt to the free base form. Because the sponsor had already demonstrated that the hydrochloride (HCl) salt had better bioavailability at high gastric pH, this was potentially clinically meaningful since many of the patients in the indicated population use proton pump inhibitors, which impact gastric acidity. The FDA carefully evaluated the chemistry, manufacturing and controls (CMC), and pharmacokinetic data to determine if additional CMC work was needed to ensure the identity, purity and potency of the drug for marketing. The FDA also evaluated the efficacy data to determine if the compound efficacy was reliable in the face of potentially variable bioavailability during the pivotal trial. Following discussions among the CMC reviewers, the clinical pharmacology review team, and the clinical reviewers in the division, it was determined that the mixture of HCl salt and free base forms did not have a significant impact on clinical efficacy or safety.

Imbalance in cases of cancer

The final safety analysis of the pivotal trial demonstrated an imbalance in the number of cancers associated with the prasugrel versus clopidogrel arms of the study. However, the analysis was complicated by several factors, including a lack of clarity regarding which cancers were pre-existing and which were diagnosed during the study, specificity of malignant versus non-malignant tumours, and whether to include non-melanomatous skin cancers in the calculations of the imbalance. Following FDA requests to the sponsor to gather additional data regarding number and types of cancers identified, the reviewers conducted multiple analyses of the data. They also requested consultations with the Division of Oncology Products, and the Division of Surveillance and Epidemiology, and carefully reviewed the results of two-year rat carcinogenicity studies with the preclinical pharmacology and toxicology reviewers. Although acknowledging the concern raised in the study, the reviewers concluded that the apparent signal of prasugrel use potentially promoting development or acceleration of cancer was spurious. A statement regarding the imbalance was included in the adverse reactions section of the approved label.

Risk of bleeding and assessment benefits and risks

Prasugrel use was associated with a higher risk of bleeding compared with clopidogrel in the pivotal trial. Bleeding is an on-target safety event, given that the mechanism of prasugrel efficacy is related to inhibition of platelet function, so the assessment of benefit-risk in this scenario is difficult. The FDA ultimately approved the therapy, but required the sponsor to include warnings for use of the drug in patients over 75 years of age and patients who are intended to undergo a coronary artery bypass graft procedure. Additionally, the FDA required that the labelling include a contraindication for use in patients with prior history of a transient ischemic attack or cerebrovascular accident.

These issues demonstrate some of the complex review decisions that the FDA faces when approving new therapies, especially those intended to address unmet medical needs in very sick patient populations. They also provide insight into the careful review and analysis process the FDA uses when considering whether to approve a new drug application.

*Product information in this case study is summarised from the FDA Cross Discipline Team Leader review document, available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022307s000_SumR.pdf. We thank the authors for their permission to use their content in this supplement.

Quiz: Test your knowledge

Now you have read the supplement, complete the self-assessment exercise at topra.org/CPDsupplements and answering the questions online. Successful completion and submission of the assessment form means that you can claim your lifelong learning (LLL) hour for the task, which members can add to their CPD recording tool.