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PERSPECTIVES

Post-approval regulatory strategies in drug commercialization: a risk-based and global perspective

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சுருக்கம்:
ஒரு மருந்தின் வாழ்க்கைச் சுழற்சியில் ஆய்வக அளவிலான உற்பத்தியிலிருந்து வணிக உற்பத்திக்கு மாறுவது ஒரு முக்கியமான கட்டமாகும். இந்த மாற்றம், வணிக அளவிலான செயல்பாடு தேவையான அளவு மற்றும் தரத்தில் மருந்து(களை) உற்பத்தி செய்வதற்கு சாத்தியமானது என்பதை அனைத்து பங்குதாரர்களுக்கும் உறுதிப்படுத்த வேண்டும். எனினும், ஆய்வகத்திலிருந்து வணிக அளவுக்கான வெற்றிகரமான மாற்றம் மட்டுமே மருந்து வணிகமயமாக்கலுக்கு முழுமையான உத்தரவாதம் அளிக்காது. உண்மையில், மருந்து தயாரிப்புகளின் வணிக விற்பனை என்பது ஒரு தொடர்ச்சியான செயல்முறையாகும், இது ஒழுங்குமுறை ஒப்புதலுக்குப் பிறகு சந்தை வாழ்க்கையின் போது மருந்துகளின் தரம், பாதுகாப்பு மற்றும் செயல்திறனை உறுதிசெய்ய தொடர்ந்து ஒழுங்குமுறை மேற்பார்வை தேவைப்படுகிறது. இந்த ஆய்வு, Title 21 Code of Federal Regulations 314.70 இல் விரிவாக விவரிக்கப்பட்டுள்ளபடி, ஒப்புதலுக்குப் பிந்தைய மாற்றங்களை நிர்வகிக்கும் அபாய அடிப்படையிலான மற்றும் அறிவியல் அடிப்படையிலான ஒழுங்குமுறை கட்டமைப்பை விளக்குகிறது. இந்த மாற்றங்களில் முக்கிய முன் ஒப்புதல் துணை நடவடிக்கைகள், மிதமான மாற்றங்கள் அறிவிப்புகள், மிதமான மற்றும் சிறிய வருடாந்திர அறிக்கைகள் ஆகியவை அடங்கும். மேலும், சந்தையில் மருந்து பற்றாக்குறை அல்லது பொது சுகாதார அவசரநிலைகளின் போது, ஒழுங்குமுறை அமைப்புகள் துணை நடவடிக்கைகளின் மதிப்பாய்வை விரைவுபடுத்த முன்-சமர்ப்பண வசதி தொடர்புகள் மற்றும்/அல்லது முன்னுரிமை மதிப்பாய்வு செயல்முறைகளை பயன்படுத்தலாம். சந்தைக்கு பிந்தைய பாதுகாப்பு தரவை மதிப்பீடு செய்வதற்கு உண்மையான உலக சாட்சியங்களின் பயன்பாடு பெருகிய முறையில் பொதுவானதாகி வருகிறது, குறிப்பாக ஒழுங்குமுறை முடிவெடுப்பதை ஆதரிக்க உண்மையான உலக தரவின் பயன்பாடு தொடர்பாக. இந்த உத்திகள் ஒட்டுமொத்தமாக நோயாளியின் பாதுகாப்பு, புத்தாக்கம் மற்றும் ஒழுங்குமுறை நெகிழ்வுத்தன்மை ஆகியவற்றை சமநிலைப்படுத்துவதற்கான அர்ப்பணிப்பை நிரூபிக்கின்றன, இதன் மூலம் மருந்துகளை வணிகமயமாக்குவதில் ஒப்புதலுக்குப் பிந்தைய மாற்றங்களுக்கான செயல்முறைகள் சாத்தியமான கூறுகளாக தொடர்வதை உறுதிசெய்கின்றன.

Abstract:
The move from laboratory-scale production of a drug to commercial manufacturing is a critical milestone in the lifecycle of any drug. At this point, the transition from laboratory to commercial scale must provide assurance to all stakeholders that the commercial-scale operation is feasible for producing the product(s) at the needed quantity and quality as well as provide assurance that the commercial scale will produce effective product(s). However, the successful transition from laboratory to commercial scale alone does not fully account for the successful commercialization of drug products. In fact, the commercial sale of drug products is a continuous process that will require ongoing regulatory oversight to ensure the continued quality, safety, and efficacy of drug products during their market life following regulatory approval. This review will provide a description of the risk-based and science-based regulatory framework that governs post-approval changes (PAC), as detailed in Title 21 Code of Federal Regulations 314.70. Post approval changes may include major prior approval supplements, moderate changes being effected through notifications, moderate and minor annual reports, and so on. In addition to these regulatory pathways, regulatory agencies may also utilize pre-submission facility communications and/or priority review processes to expedite the review of supplements, particularly where there may be a shortage of medicines available on the market or during public health emergencies. The increasing use of real-world evidence to support

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the evaluation of post-marketing safety data is becoming commonplace, particularly as it relates to the use of real-world data to support regulatory decision-making. Collectively, these strategies demonstrate the commitment to balancing patient safety, innovation, and regulatory flexibility, thus ensuring that the processes for making PAC remain viable components of successfully commercializing pharmaceuticals.

Keywords: scale-up, post-approval adaptations, USFDA, priority review, PFC, real-world evidence, nanomaterials, drug commercialization

Introduction

Modifications made after regulatory approval post-approval changes (PACs) are an essential element of pharmaceutical product lifecycle management and usually have an unavoidable regulatory environment effect within every jurisdiction across the globe (1). Types of PACs are created for a variety of reasons: the need to upgrade equipment; renovate facilities; scale up manufacturing capacities; optimize processes; and implement continuous improvements to current processes, equipment, and/or personnel utilized in the manufacturing process, etc. To preserve the continued effectiveness, safety, and quality of marketed pharmaceutical products, all changes that occur post-approval must be supported by science and documentation and follow established regulatory processes through the appropriate regulatory agency (e.g., US FDA) to ensure the consistency of manufacturing & process changes will not negatively affect the clinical performance or critical quality attributes (CQAs) of the product throughout the life cycle of the product (2).

Effective management of PACs requires the use of strong chemistry, manufacturing, and controls (CMC) data; comprehensive knowledge of product risk; and established procedures or policies in place for change management systems (3). The purpose of regulatory monitoring after approval is to assure that manufacturing processes and/or changes made to a manufacturing process will not negatively impact the clinical performance or the CQAs of the product over the commercial life of the product (4).

Complexity regarding regulatory issues associated with PACs increases when the product is based on nanotechnology. Nanotechnology products (e.g., liposome, lipid nanoparticles, polymeric nanoparticles, nanosuspensions, etc.) continue to provide opportunities for growth through complex drug delivery systems with significant therapeutic benefits but also create unique regulatory challenges. Nanomaterials used in pharmaceutical applications are also subject to the same strict guidelines; however, they are subject to even stricter guidelines due to the larger number of variables that impact how the material behaves in vivo compared to traditional dosage forms. Because of the increased complexity and variability of nanomaterials, any and all modifications made after approval could have a significant impact on safety, efficacy, and in vivo performance. For these reasons, regulatory bodies emphasize much more comprehensive physicochemical characterization, CMC control systems, and a risk-based evaluation process of PACs for nanopharmaceuticals compared to PACs.

Methodology

This review article discusses the outcomes of a qualitative review of relevant guidelines, related policy documents, and scientific literature on the topic of pharmaceutical product PACs relating to formulation and composition (5). The primary sources of information for this review were official publications, guidelines, and scientific literature in the form of peer-reviewed journal articles from PubMed and Google Scholar related to PACs from the United States Food and Drug Administration (US FDA), European Medicines Agency (EMA), and International Council for Harmonization (ICH). The qualitative review utilized primary keywords such as "post-approval changes," "CMC variations," "regulation of nanopharmaceuticals," "priority review," and "pharmaceutical lifecycle management" to search for articles published between 2010 and 2025, as it is likely that research and literature before 2010 is no longer applicable to 21st-century pharmaceutical regulations. As literature was identified for analysis, data from all identified sources were collected and synthesized into a comprehensive overview.

Post-approval changes in USFDA

An understanding of product risks and how to effectively mitigate risks is critical to successful regulatory reviews of chemistry, manufacturing, and controls (CMC) improvements (6). In 2014, the Food and Drug Administration (FDA) published guidance documents outlining potential CMC improvements that require annual reporting and general approval. As outlined in these documents, an applicant will be required to select the most appropriate submission process by utilizing relevant scientific evidence and conducting a formal risk assessment. Depending on the applicant's risk assessment of the CMC improvement(s), an applicant may be required to submit their proposed changes to the appropriate agency via Prior Approval Supplement (PAS), Changes Being Effected in

30 Days (CBE-30), or annual report, and this will assist in determining how to change the CMC of a regulated product. The FDA must ensure that any change made to the chemistry, manufacture, or control of a regulated product receives appropriate evaluation and management (7, 8). To do this, there is a systematic process by which an applicant's risks and scientific data will enhance the applicant's ability to demonstrate the appropriate submission method for the change. In this way, CMC improvements will enhance the quality and safety of regulated products while also minimizing the need for extensive involvement from regulatory agencies (9).

Global regulatory perspectives on post-approval changes

The United States government, through its FDA, imposes a PAC management framework (21cfr314.70). However, there are varying degrees of regulatory oversight from one country to another. For example, the EMA classifies its post-approval variations into three categories (i.e., Type IA, IB, and II) according to their risk and potential impact on the quality, safety, and efficacy of a product. Meanwhile, the ICH has developed Harmonized Guidelines (i.e., ICH Q12), which focus on lifecycle management, risked-based decision-making and regulatory flexibility so that countries may have greater consistency between their drug review processes (10). In comparison to the PAS, CBE-30, and annual reports of the FDA, the EMA has a much more structured system for classifying variations; on the other hand, the ICH offers an even broader basis for harmonizing regulatory expectations worldwide. Despite this work, continued differences in the manner in which each country implements their regulations and records and processes are a constant challenge for pharmaceutical companies that operate in more than one regulatory jurisdiction.

The complexities introduced by today's pharmaceutical products, in particular products using advanced delivery systems and nanotechnology, create an even greater need for alignment amongst regulatory bodies. Enhanced harmonization and the adoption of science- and risk-based regulatory processes will be critical components in achieving effective life cycle management and maintaining comparable product quality across global markets. A comparison of post-approval change classification and regulatory focus across major regulatory authorities is presented in **Table 1** (11, 12).

TABLE 1 | Global regulatory comparison of post-approval change classification (FDA, EMA, ICH).

Aspect	FDA	EMA	ICH
Classification	PAS, CBE, annual	Type IA, IB, II	Risk-based (Q12)
Approach	Regulatory-driven	Structured variation	Harmonization
Focus	Compliance	Risk classification	Lifecycle management

TABLE 2 | Classification of post-approval changes (PAC) based on supplement type.

Type of changes	Rules	Type of application
Major change	21 CFR 314.70(b)	Prior approval supplement
Moderate change	21 CFR 314.70(c)(5)	CBE-30 days
	21 CFR 314.70(c)(6)	CBE-0 days
Minor change	21 CFR 314.70(d)	Annual report

Post-approval CMC changes in nanomaterial-based drug products

Post-approval changes to CMC become even more complex for nanomaterial-based pharmaceuticals since they are very sensitive to manufacturing and process changes. Unlike traditional dosage forms, more stringent controls must be placed on the manufacture of nanopharmaceuticals because even minor changes may have a considerable impact on clinical performance and product quality. Changes to CQAs, such as particle size distributions, are directly impacting the safety, biodistribution, and bioavailability of products made using nanomaterials (13). Critical process parameters controlling how nanoparticles are produced and stable can be changed from post-approval modifications such as equipment upgrades, process scaling, or changing the manufacturing facility location. Furthermore, any changes to the physicochemical characteristics of the raw materials used in the formulation and/or excipients will similarly affect the properties of nanoparticles.

Therefore, post-approval modifications for drug products made using nanomaterials will generally be classified as either moderate or severe changes, where modifications that would be considered minor for traditional formulations would typically be classified as moderate to severe for nanomaterial drug products. The FDA applies a very conservative and risk-based regulatory approach to the development of drug products made using nanomaterials with an emphasis on detailed characterization and strong CMC justification to ensure consistency of product quality and safety for patients over the entire product lifecycle.

Classification of PAC based on regulatory submission type and applicable regulations is summarized in **Table 2** (**Figure 1**) (14).

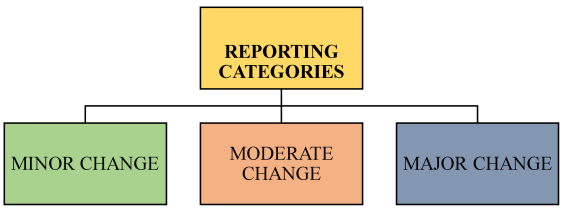

FIGURE 1 | Classification based on the type of supplement and rules.

Reporting categories of changes and estimated timeline for approval according to USFDA regulations

The reporting categories and estimated timelines for approval of PAC according to regulatory requirements are shown in **Table 3** (14).

Case studies in post-approval regulatory adaptations

The following case studies illustrate how non-approved regulatory changes can have real-world effects on the approved product after marketing approval has been granted: the manufacturing and regulatory changes that have occurred to commercialize a medicinal product.

Case study no. 1: impact of particle size modification in nanopharmaceuticals

During the scale-up of a lipid nanoparticle-based drug product, a minor variation in particle size distribution (i.e., size variations) resulted in manufacturing process changes. These small differences in particle size distribution resulted in a very significant impact on the release of drug from lipid nanoparticles and, therefore, on the biodistribution of drug at the target site. Both release of drug from lipid nanoparticles and biodistribution of drug at the target site are CQAs of any nanomedicine product; thus, this change was classified as a major variation and subsequently required an approved PAS from the FDA. Additionally, this case study clearly illustrates the high sensitivity of nanomedicine products to small variations in the manufacturing process, thus necessitating stringent regulatory oversight/approval (12).

Case study 2: facility relocation and its regulatory implications

Pharmaceutical companies have to worry about their manufacturing plants moving locations and trying to meet increased manufacturer capacity or keep their supplies flowing after relocation due to several reasons, which can include but not limited to, differences in the equipment used at each plant, the processes that each manufacturing facility uses, and the environmental conditions of each facility, will present a risk of potential regulatory authority requiring companies to have comparable data prior to moving into a new facility. This case study demonstrates how a new facility is considered a high-risk change within the lifecycle management framework (11).

Case study 3: priority review in response to drug shortages

A company faced a drug shortage and requested priority review on a supplement submission to implement a manufacturing change in order to allow time to do a priority review to help expedite their regulatory review process so that their patients could have faster access to their drugs, as obtaining flexibility from the manufactures, while at the same time providing regulatory flexibility is important for preventing interruptions to the supply of their drug products, and expedited pathways for drugs provide a way to facilitate public health goals while still maintaining drug quality and safety (15, 16).

TABLE 3 | Reporting categories and estimated timelines for FDA submissions.

Change	Major change	Moderate change		Minor change
Supplement to be filed	Prior approval supplement (tell, wait, and do after getting approval procedure)	CBE-30 (tell, wait, and do procedure)	CBE-0 (tell and do the procedure)	Annual report (do and tell procedure)
When to notify to agency	Before implementing the change	Before implementing the change	Can be implemented simultaneously	A list of changes should be annually reported right from the drug approval date till withdrawn from the market.
Estimated timeline for approval (6)	6 months (no pre-approval inspection) 10 months (with pre-approval inspection)	30 days (timeline may vary based on queries addressing to the agency in due course)	Change can be implemented (the very next day after notifying the agency, but best to wait for 15 days)	NA

In conclusion, these case studies demonstrate the importance of regulatory systems that are based on risk-based processes for managing regulatory compliance due to the complex nature of drug products and being able to adapt as the manner in which drug products are manufactured continues to change.

Regulatory strategy: priority review

Beyond its regulatory processes, priority reviews represent a tool that can be used strategically throughout the pharmaceutical life cycle (17). In some situations (i.e., drug shortages, emergencies affecting public health, changes in manufacturing), priority reviews allow the FDA to expedite reviews of supplements and applications (NDA), and when done effectively, can reduce time-to-market and help ensure drug supply reliability (1, 18). Furthermore, the flexibility of the regulatory process used to assign priority status reflects a changing paradigm for regulators concerning patient-centric, risk-based decision-making. Finally, whilst requiring ample scientific justification and being closely aligned with public health priorities, priority review designations are inherently restrictive and extremely powerful in terms of regulation. MAPP 5240.3 Rev. 5 governs the Priority Review of Abbreviated New Drug Applications (ANDAs), amendments, and supplements. This allows for accelerated FDA review for submissions pertaining to public health emergencies, drug shortages, specific government purchasing programs, or circumstances where review delays may result in undue hardship under Section 505(j)(11)(A) of the FD&C Act. When you request a priority review, it is very important to put "Priority Review Requested" on the letter to help us identify your submission as such and include both the appropriate ANDA number followed by an appropriate justification letter (which must also be supported by adequate documentation). Although it is encouraged that requests for prioritization be made by applicants, the FDA will also independently designate a submission as priority review if it determines that its contribution to public health is significant enough to recommend prioritizing it as a priority. For appropriate submissions, the FDA may expedite review or assign an earlier goal date. If eligibility is determined after submission, qualifying for priority review does not change the original goal date, and fulfilling more than one prioritization criterion does not provide an extra benefit. An ANDA, amendment, or supplement may be eligible for expedited review if any of its components meet the requirements. Except in cases when prioritizing is required to address a serious public health issue, submissions related to facilities that are officially action-indicated are typically not eligible for priority consideration. The Office of Generic Drugs (OGD) consults with the Office of Pharmaceutical Quality (OPQ) and other pertinent FDA offices before making final decisions about priority designation.

TABLE 4 | Categories eligible for priority review under MAPP 5240.3 Rev. 5.

Category	Description/regulatory basis
Submissions related to drug shortages	Submissions for products listed on the FDA Drug Shortage List with the status "Currently in Shortage" at the time of prioritization. Such submissions may help mitigate, resolve, or prevent future drug shortages.
Special review programs (e.g., PEPFAR)	Submissions for antiretroviral drug products intended to support global HIV/AIDS treatment programs, including the President's Emergency Plan for AIDS Relief (PEPFAR). Paragraph IV certification is not required for eligibility under this category.
Public health emergencies	Submissions that support or address a public health emergency declared by the U.S. Department of Health and Human Services under Section 319 of the Public Health Service Act (42 U.S.C. §247d).
Government purchasing programs	Submissions associated with government procurement activities, including packaging modifications or expiration date extensions, are supported by documentation such as requests for proposals from agencies such as the Department of Veterans Affairs or Department of Defense.
Legal and statutory requirements	Submissions required to comply with federal or state laws, regulatory mandates, or other statutory obligations.
Nanomaterial-based drug products	Submissions involving nanomaterial-based formulations where PAC may impact CQAs (e.g., particle size, surface characteristics, or stability) and where expedited review may be warranted to address public health needs, manufacturing complexity, or supply continuity concerns.

Categories of submissions eligible for priority review under MAPP 5240.3 REV. 5

Categories of submissions eligible for priority review under the regulatory framework are outlined in **Table 4** (15).

Supplements for which a priority review is requested under 21 CFR 314.70(B)(4)

According to 21 CFR 314.70(b)(4), an applicant may ask the FDA to give a supplement a priority review for public health concerns or if the applicant would suffer undue hardship if the changes outlined in the supplement were not implemented right away. In this context, undue hardship for the applicant is a relevant consideration. The priority review procedures for single-source abbreviated new drug applications and nanomaterial-based products are summarized in **Table 5** (11).

Examples include:

Unexpected cessation of an active substance, packaging material, or container closing mechanism; Facility relocation

or modification due to a catastrophic occurrence; significant changes or supply interruption of a critical nanomaterial component used in the drug product that may impact safety, efficacy, or stability.

The pre-submission facility correspondence (PFC)

The Pre-Submission Facility Correspondence (PFC) is an initial application that enables priority ANDAs, PAS, and related modifications to be processed more efficiently. Applicants submit details of their manufacturing and bioequivalence (BE) facilities before ANDA submission, allowing the FDA to determine whether facility inspections are necessary and to plan them earlier in the review process (19). The PFC must be submitted at least 2 months prior to the planned ANDA, and facility information cannot be changed once the ANDA is approved. Containing information similar to an original ANDA, the PFC is valid in the U.S. for predetermined facility inspections and can allow the applicant to introduce the drug product before the standard ANDA goal date of 8 months. Applications eligible for PFC include Original ANDAs, PAS, and PAS Amendments (20). The FDA approves PFCs for reasons such as drug shortages, public health emergencies (e.g., COVID-19), invalid or non-infringing patents, or when only one reference listed drug and generic exist. All submissions are completed electronically via eCTD through the Electronic Submission Gateway (ESG).

List of facility information that should be submitted in the PFC for a priority ANDA

The facility information required for PFC is summarized in **Table 6** (19).

Establishment information

The establishment information required for manufacturing facilities is presented in **Table 7** (14).

Receipt and assessment process for pre-submission facility correspondence

The following section describes the process for the receipt and assessment of the PFC related to a priority Supplement.

Using the FDA's electronic submissions gateway (ESG) to submit the PFC

1. Obtaining an Abbreviated New Drug application number that has been pre-assigned, if applicable

Before submitting the PFC, the applicant for original abbreviated new drug applications should ask for a pre-assigned ANDA number. On Form FDA 356h, the applicant should enter the pertinent ANDA application number for PASs, PAS amendments, and ANDA amendments.

2. Forwarding PFC via FDA's ESG 200

According to the Agency's guidelines, PFC must be provided online in eCTD format (22). To send the PFC through the ESG, select the relevant Center by choosing "CDER" and the submission type by selecting "eCTD." As stated in section V.B. (below), the applicant must submit the priority Abbreviated New Drug application following the "ANDA Submission Timing." FDA shall be informed in writing if the applicant chooses not to file the ANDA after submitting the PFC. The notification of the decision not to submit the ANDA must be sent to eCTD section 1.2, Cover Letter, with reference to the submission number.

3. The FDA's Evaluation of PFC

As soon as the Agency receives the PFC, it will begin assessing it. The FDA will notify the applicant in writing that the PFC has been received. As further explained in Section VI, the FDA will determine the ANDA's priority status after it is submitted and set the proper review goal date.

Submission timing

PFC must be submitted at least 60 days prior to the ANDA itself in order for an abbreviated new drug application to be eligible for priority review. The timely filing enables the regulatory body to review the facility details before receiving the ANDA.

Additionally, there should be no significant changes made to the information in the PFC in the Abbreviated New Drug application. The FDA urges applicants to submit the PFC no later than 90 days before the ANDA submission in order to minimize the possibility of major changes to facility information between the ANDA and PFC submissions, which could compromise the priority review status. It is advised that applicants read the advice document "Providing Regulatory Submissions in Electronic Format – Receipt Dates," which was published in February 2014.

1. To comply with the requirement that the PFC must be submitted at least 60 days before the Abbreviated New Drug Application, if the ANDA is submitted on Monday, February 19, 2024, the PFC submission deadline is Thursday, December 21, 2023.

TABLE 5 | Priority review procedures for single-source and nanomaterial ANDAs.

Procedure	Single-source ANDA's	Nanomaterials
1	The OGD Division of Filing Review staff identifies applications requesting prioritization during a filing review of an original ANDA or new strength supplement and relays info to OGD staff, including OGD RPM.	OGD identifies ANDAs for nanomaterial-based drugs requesting priority review due to unique nanomaterial use.
2	The OGD RPM, OGD labeling review project manager, or OPQ RBPM evaluates submissions for prioritization if requested, even if no filing review occurs, and communicates info with OGD/OPQ staff to ensure uniform prioritization.	Evaluation of nanomaterial ANDAs to ensure consistent priority review across OGD and OPQ offices.
3	Under section 505(j)(11)(A) of the FD&C Act, OGD/OPQ personnel may select submissions meeting prioritization conditions for drug shortages or public health emergencies and forward info to OGD RPM and OPQ RBPM.	Nanomaterial-based drugs critical for public health or in shortage (e.g., nanomedicine for rare diseases) may be prioritized.
4	Prioritizing a review is decided only when a submission is received, following 21 CFR 314.101(b).	Nanomaterial ANDA priority review is granted upon submission receipt as per 21 CFR 314.101(b).
5	OGD, OGD review disciplines, and OPQ RBPMs collaborate with OGD RPMs to ensure applications are ranked according to the MAPP.	Coordination ensures uniform prioritization for nanomaterial-based generic products.

TABLE 6 | Facility information required for pre-submission facility correspondence (PFC).

eCTD module	Description/content	Application for pharmaceuticals	Application for nanomaterials
1.1	Form FDA 356h	Filed with Form FDA 356h; select "Product Correspondence" + "Other" → specify "Pre-Submission of Facility Information for Priority ANDA/PAS/Amendments."	Same procedure; critical for nanomaterial-based ANDAs to ensure expedited review of complex formulations.
1.2	Cover Letter	Includes inspection readiness, RLD identification, and anticipated submission date.	Must highlight nanomaterial-specific inspection readiness and any unique RLD reference for nanomedicines.
1.3.1.2	U.S. Agent Appointment Letter	If applicable for pharma ANDA submission.	Same requirement for nanomaterial drug submissions.
1.4.2	Statement of Right of Reference	DMF Right of Reference letter, if applicable.	DMF reference for nanomaterial drug substances or excipients.
2.7	Biopharmaceutic Studies Summary	Summary tables of BE studies and analytical methods.	Includes additional studies on nanomaterial absorption, distribution, and analytical characterization.
3.2.S.1.1 to 3.2.S.1.3	Nomenclature, Structure, General Properties	Standard drug substance info.	Include nanomaterial-specific properties (particle size, surface area, zeta potential).
3.2.S.2.1 to 3.2.S.2.6	Manufacturer info, manufacturing process, control of critical steps, process development	Conventional pharma process description and controls.	Must include nanomaterial-specific process details (e.g., nanoparticle synthesis, encapsulation, critical CQAs).
3.2.S.4.1 to 3.2.S.4.4	Drug Substance Specifications & Batch Analyses	Standard specifications and batch testing.	Additional tests for nanomaterial characterization (size distribution, aggregation, stability).
3.2.P.1 to 3.2.P.3.5	Drug Product Description, Composition, Manufacturing Process, Controls, Sterilization	Standard pharma product details.	Include nanomaterial drug product formulation details, process validation, and sterilization/handling of nanoscale materials (21).
3.2.P.5.1 to 3.2.P.5.4	Drug Product Specifications & Batch Analyses	Standard product testing and release.	Nanomaterial-specific QC tests (particle integrity, surface chemistry, release profile).
3.2.P.7	Facility Info for Non-Drug Constituent Parts	Info for combination product components.	Includes nanomaterial-specific facility info if used in combination products.
5.3.1.2	Bioequivalence & Clinical Studies	Site info, study titles/numbers, investigators, protocols, study reports.	Add nanomaterial-specific PK/PD studies, nanoparticle tracking, and any unique clinical considerations.
5.3.1.4	Analytical Studies	Site info, study details, analytical validation, study reports.	Include nanomaterial characterization methods (e.g., TEM, DLS, surface analysis) and validation results.

2. If an ANDA is submitted on Tuesday, November 14, 2023, the PFC must be submitted by Friday, September 15, 2023, to meet the 60-day prior submission requirement, even if the 60-day period ends on a weekend.
3. For an ANDA submission date of Thursday, July 4, 2024, the PFC should be submitted by Monday, May 6, 2024, to satisfy the 60-day advance submission rule, considering that the due date coincides with a federal holiday.

A signed certification statement must be submitted by the applicant when submitting an Abbreviated New Drug Application in section 1.2 of the electronic Common Technical Document (eCTD) format. One of the following must be attested to by this statement:

1. According to the GDUFA III commitment letter, the applicant attests that no material changes have been made to the information contained in the PFC.

TABLE 7 | Establishment information for manufacturing facilities.

Drug substance manufacturers, drug product manufacturers, drug product testing facilities and other facilities	
Manufacturing site name and address	ABC Pharma Ltd, Hyderabad, India
FEI number	3001234567
DUNS number	65-123-9876
FDA's last inspected date	12 March 2023
EIR received	Yes

2. In accordance with section 505(j)(11)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), the applicant acknowledges that the only modifications made were the removal of a facility that did not contribute to the generation of data for the application.

Notification to the applicant

Letter of Acceptance: The agency will issue a letter as part of the PFC assessment to Let the applicant know that the goal date, including any priority designation determination, will be supplied upon submission and receipt for the review of the abbreviated new drug application, and to avoid losing priority review target stake, the applicant is urged not to submit their ANDA and PAS before 60 days following the PFC date submission (14).

Conclusion

Effective management of PACs is critical among the components involved in lifecycle management of a pharmaceutical product to ensure continued product quality, safety, and efficacy through the entire period of commercialization (7, 23). Regulatory frameworks created by the FDA, in conjunction with the existing and evolving approaches by the EMA and harmonization-related activities of the International Council for Harmonisation (ICH), are establishing a greater emphasis on science and risk in the evaluation of PAC.

Post-approval changes involving pharmaceutical products are increasing in complexity and regulation. This is particularly true for nanopharmaceuticals that are highly susceptible to manufacturing variation, which will affect the CQAs of the products.

In the context of the evolving regulatory landscape for pharmaceutical products, several regulatory mechanisms exist to help manage the regulatory control of PAC and help the manufacturer achieve timely product availability in the market, such as prior approval supplements, CBE, PFC, and priority reviews.

An internationally growing uniformity in law related to drug approvals throughout the world in the years ahead will also allow for greater uniformity between the various legal systems found in different countries as they try to harmonize their operations with each other, which means providing more opportunities for the use of new innovative technologies such as nanoparticles and newer advanced delivery systems. There are going to be increased demands by regulators on technology and data utilized in the regulation of drugs, and therefore, regulatory agencies must adjust and change to be able to respond to the increased challenges of meeting the goals set by drug manufacturers, delivering appropriate medicine to patients, enhancing the regulatory processes, and creating more flexible and risk-adjusted regulatory frameworks (21).

In order to foster innovation in the development of new drugs, it is essential that the law that governs drug approval processes remains flexible and forward-looking so that patients everywhere will be able to have confidence that they are receiving safe and effective treatment for their ailments (24).

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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