So, Your NDA Was Approved – Now What?!

Post-approval Responsibilities and Obligations

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FDA Disclaimer

The views and opinions presented here represent those of the speaker and should not be considered to represent official advice or guidance on behalf of the Food and Drug Administration.

Learning Objectives

Postmarketing Regulatory Requirements

- Postmarketing safety reports, other post-approval reports, waivers, and change of NDA ownership

Additional Post-Approval Activities

- Changes to an approved NDA (including pediatric assessments and efficacy supplements), PMRs/PMCs, REMS, and SLCs

CME Challenge Question #1

True or False? US-based applicants only need to submit <u>Postmarketing 15-day 'Alert reports'</u> for adverse drug experiences that occur within the US.

A. True

B. False

CME Challenge Question #2

Which of the following information does NOT need to be included in the NDA annual report?

A. The quantity of the drug product distributed

B. PMR/PMC status reports

C. Summaries of completed unpublished clinical trials

D. Current pricing data

CME Challenge Question #3

Once a CBE 30 labeling supplement has been approved, how long does an applicant have to implement the changes to the promotional labeling and advertising?

A. It must be updated promptly

B. 15 Days

C. One month

D. Prior to submitting the next NDA annual report

Postmarketing Regulatory Requirements

21 CFR 314.80(b)

Review of adverse drug experiences

- Must review any adverse drug experience (ADE) information obtained/received, regardless of the source
- Must also develop written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing ADEs to the FDA

21 CFR 314.80 (c)(1)

Postmarketing 15-day 'Alert reports'

- Must report all serious AND unexpected ADEs, whether foreign or domestic, within 15 calendar days of receipt as an initial Alert Report
- If new information becomes available concerning a previously reported ADE, must submit a follow up Alert Report within 15 calendar days
- Also applies to nonapplicants (e.g., manufacturers, packers, or distributors) that appear in the approved product labeling

21 CFR 314.80 (c)(2)

Periodic adverse drug experience reports

- Applicants must provide PADERs on a quarterly basis for 3 years post-approval and then annually afterwards
- Includes narrative summaries and analyses of the ADEs, history of any actions taken as a result of ADEs (e.g., labeling changes, 'Dear Doctor' letters), and a status update on clinical trials
- Applicants may request to submit a Periodic Benefit-Risk Evaluation Report (PBRER) in lieu of PADER

21 CFR 314.81

Other Postmarketing Reports

- NDA field alert report – 21 CFR 314.81(b)(1)
- Annual report – 21 CFR 314.81(b)(2)
- Advertisements and promotional labeling – 21 CFR 314.81(b)(3)(i)
- Special reports – 21 CFR 314.81(b)(3)(ii)
- Notification of a permanent discontinuance or an interruption in manufacturing – 314.81(b)(3)(iii)

21 CFR 314.90

Waivers

- Can request a waiver from any of the requirements outlined in 314.50 through 314.81
- May also request a waiver from any of the criteria of *"…an adequate and well-controlled study…"*
- Must contain sufficient justification why compliance with the requirement is unnecessary or cannot be achieved, OR a description of any alternative(s) to satisfy the purpose of the requirement, OR any other info supporting the waiver request

21 CFR 314.72

Change in ownership of an application

- Former owner provides documentation that states that all rights to the application have been transferred to the new owner
- New owner agrees to adhere to any agreements, promises, and conditions contained in the approved application and verifies the effective date of ownership
- Confirms receipt of a complete copy of the approved application
- Informs the FDA about any changes in conditions of the approved application as per 314.70

Additional Post-approval Activities

21 CFR 314.70(a)

Changes to an approved NDA

- Must notify FDA of any change(s) to an approved NDA and any revisions must be described “fully”
- For manufacturing changes, must also assess the effects of the proposed alteration(s) before distribution of the product
- For labeling changes, must promptly revise all promotional labeling and advertising to ensure consistency with the updates
- Confirmation that a field copy has been provided to the applicable FDA district office (except for labeling changes)

21 CFR 314.70(b)

Changes requiring supplement submission and approval prior to distribution of the product made using the change (major changes)

- AKA – Prior Approval Supplement (PAS)
- Any proposed changes that have the potential to substantially impact the safety/effectiveness of the product
- Review timelines depend on the supplement type (PDUFA goal)
- Can request a expedited review, if circumstances warrant

21 CFR 314.70(c)

Changes requiring supplement submission at least 30 days prior to distribution of the drug product made using the change (moderate changes)

- AKA – Changes Being Effected in 30 Days (CBE 30) supplement
- Submitted at least 30 days prior to distribution of modified product and includes appropriate information to assess the effects of the change
- Product cannot be distributed if the applicant is informed within 30 days of receipt that a PAS is required or if information is missing
- 21 CFR 314.70(c)(6) - Changes Being Effected (CBE 0) supplement

21 CFR 314.70(d)

Changes to be described in an annual report (minor changes)

- Does NOT require a separate submission to the FDA; only need to be included in the NDA annual report
- Refer to the relevant sections of 314.70 and the *Guidance for Industry – Changes to an Approved NDA or ANDA – Apr 2004* for additional examples
- FDA makes final determination on reporting category (PAS vs. CBE vs. AR changes)

Efficacy Supplement

A supplement to an approved NDA proposing to make one or more related changes from among the following changes to product labeling:

- Add or modify an indication or claim; revise the dose or dose regimen; provide for a new route of administration; make a comparative efficacy claim naming another drug product; significantly alter the intended patient population; change the marketing status from prescription to over-the-counter use; provide for, or provide evidence of effectiveness necessary for, the traditional approval of a product originally approved under subpart H of this part; or incorporate other information based on at least one adequate and well-controlled clinical study

Section 505(B) of the FD&C Act

Pediatric Assessments

- Each application for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration shall contain data that are adequate to assess the safety and effectiveness of the product for the claimed indication(s), and to support dosing and administration for relevant pediatric subpopulations
- Applicants may request a deferral or waiver (full or partial) from these requirements

Section 505(O)(3) of the FD&C Act

Postmarketing Studies/Clinical Trials

- FDA can require at the time of approval that an applicant conduct further postmarketing studies/clinical trials, and may also require the applicant to initiate studies/clinical trials for an approved product if new safety/serious risk information becomes available
- FDA must determine that adverse event reporting under section 505(k)(1) and the active postmarketing risk identification and analysis system per section 505(k)(3) would be insufficient before requiring postmarketing studies/clinical trials be conducted

Postmarketing Requirement (PMR)

- Postmarketing studies or clinical trials to assess a serious risk that the applicant is required to conduct either following initial product approval, or if a serious risk is identified post-approval
- PMR describes the study/clinical trial to be conducted to ensure that the study/clinical trial is well designed and adequate, and provides a milestone timetable for completion
- PMRs can be applied to products approved under the Animal Efficacy Rule or accelerated approval, studies required under the PREA, and for safety studies/clinical trials required under FDAAA

Postmarketing Commitment (PMC)

- Postmarketing studies or clinical trials that the applicant has agreed to conduct following initial product approval
- These are studies or clinical trials concerning issues related to clinical safety or efficacy, clinical pharmacology, nonclinical toxicology, and/or product quality that don't meet the statutory purposes for PMRs
- Applicant is required to provide updates on the status of ALL PMRs and certain PMCs in their annual report
- FDA maintains a publicly available webpage of these PMRs/PMCs

Section 505-1 of the FD&C Act

Risk Evaluation and Mitigation Strategies (REMS)

- Designed to focus on preventing, monitoring and/or managing a specific serious risk by informing, educating and/or reinforcing actions to reduce the frequency and/or severity of the event
- A required risk management plan can include one or more elements to ensure that the benefits of using a product outweigh the risks associated with it
- REMS may be released or modified if it's subsequently determined that the extra measures are no longer necessary

Section 505(O)(4) of the FD&C Act

Safety Labeling Changes

- Can require applicants to make safety labeling changes (SLC) based on new safety information that becomes available after approval of the product; must notify applicant in writing
- May include (but not limited to) updates to the BOXED WARNINGS, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, DRUG INTERACTIONS, and ADVERSE REACTIONS labeling sections
- If the labeling is changed, any REMS may need to be modified

Summary

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Resources

- Electronic Code of Federal Regulations (eCFR) webpage
- FDA Guidance Documents webpage
- CDER Manual of Policies & Procedures (MaPPs) webpage
- Guidance for Industry: Providing Postmarketing Periodic Safety Reports in the ICH E2C(R2) Format (Periodic Benefit-Risk Evaluation Report) – Nov 2016
- Pediatric Product Development webpage
- Guidance for Industry: Changes to an Approved NDA or ANDA – Apr 2004
- Guidance for Industry: Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees – Jan 2005
- Guidance for Industry: Postmarketing Studies and Clinical Trials – Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act – Oct 2019

Resources

- Guidance for Industry: Reports on the Status of Postmarketing Study Commitments – Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997 – Feb 2006
- Postmarket Requirements and Commitments webpage
- Guidance for Industry: FDA's Application of Statutory Factors in Determining When a REMS Is Necessary – Apr 2019
- Guidance for Industry: Format and Content of a REMS Document – Oct 2017
- Risk Evaluation and Mitigation Strategies (REMS) webpage
- Approved Risk Evaluation and Mitigation Strategies (REMS) webpage
- Guidance for Industry: Safety Labeling Changes – Implementation of Section 505(o)(4) of the FD&C Act – Jul 2013
- Drug Safety-related Labeling Changes (SrLC) webpage

U.S. FOOD & DRUG ADMINISTRATION

Thank you!

Questions?

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