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Aleon Regulatory Frontiers

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Welcome to the first edition of the Aleon Regulatory Frontiers newsletter! Staying informed about regulatory affairs in the pharmaceutical industry can be challenging. The field is constantly evolving, with new regulations, guidelines, and policies being introduced on a regular basis. As a regulatory consulting company, it is our responsibility to stay up to date on the latest regulatory developments and to help our clients navigate the complex world of regulatory affairs. In this quarterly newsletter, we will provide you with the latest news, updates, and insights on regulatory affairs. We hope you find this information useful, and we look forward to staying connected with you throughout your regulatory affairs journey. Thank you for your interest in our regulatory affairs consulting services!

INSIDE THIS ISSUE:

Fantastic News!!!
Congratulations and thank you Aleon team for your collaboration and great support!

Successful IND Submission

4:34 PM EST
December 9, 2022

Dedicated for Approval ®

Is a Pre-IND Meeting Necessary for your Program?

Editor's Choice

Is a Pre-IND Meeting Necessary for your Program?

Sponsors often ask Aleon : "is a pre-IND meeting necessary for my program?" This is just one of the many important questions for the sponsor as the early development project moves forward to the next vital stage. For most of the IND preparation and submission projects which Aleon Pharma International, Inc. ("Aleon") has managed, the sponsor ultimately decided that having a pre-IND meeting is necessary. These pre-IND meetings added significant value. We understand that every program is different and faces its own unique challenges. The decision on whether to have a pre-IND meeting is important to the sponsor and it should not be taken lightly. Typically, a pre-IND meeting is recommended if your program is intended to treat a serious or novel indication, or if your treatment itself is novel. Effectively planning your development strategy with feedback from the authority reviewing your submission is one of the most impactful steps a sponsor can take when approaching their IND submission.

The purpose of this article is to share examples of when a pre-IND meeting is critical for a program's success, to describe how your program might benefit from having a pre-IND meeting, to provide the overall timeline leading up to a pre-IND meeting, and to outline how a consulting group can help to prepare you and your team for a successful pre-IND meeting with the FDA.

Please note that for simplicity, we label the early interactions with the FDA as pre-IND meetings. Pre-IND meetings will have different names depending on the FDA division you are working with, and Aleon has extensive experience working with various divisions at FDA including Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), and Center for Devices and Radiological Health (CDRH).

When Having a Pre-IND Meeting is Critical for Your Program

There are many and varied instances where having a pre-IND meeting could be critical for your program's success. Such instances usually involve one or more of the following: If your program is intended to treat a serious or life-threatening condition, is treating a novel indication, is a new molecular entity (NME), was not previously approved or licensed, or is in a category for which there are no current guidance documents available from the FDA, the pre-IND meeting is especially important. In these cases, it is an opportunity for you to avoid guesswork and obtain valuable insight and/or confirmation of regulatory requirements as well as receiving direct guidance from the FDA. If the sponsor has potential pharmacology, pharmacokinetics, or toxicology concerns, the sponsor has specific questions for the FDA

related to the implementation of their development program or would like to obtain FDA's feedback on the proposed specifications for the drug substance and drug product, the pre-IND meeting can be invaluable.

We recognize that each program is unique, and ultimately the sponsor must decide if having a pre-IND meeting is right for their program. While having a pre-IND meeting with the FDA is not required, it may be beneficial to the sponsor based on our experience with the diverse projects we have worked on. By supporting you throughout the pre-IND process, Aleon will help guide you throughout the development process for your project.

How Your Program Can Benefit from Having a Pre-IND Meeting

Now that we have mentioned several situations in which having a pre-IND meeting is critical for your program, you may be wondering how you can benefit from having a pre-IND meeting with the FDA and if having a pre-IND meeting will delay your project timeline. As we mentioned earlier in the timeline section of this paper, you can be rest assured that Aleon can simultaneously work on both your pre-IND meeting and IND preparation and submission, so you do not waste your valuable time and still meet your project timeline while at the same time receiving important feedback from the FDA. Throughout our decades of experience, we have found an abundance of benefits that pre-IND meetings have provided to the sponsor. These benefits include refining the drug development strategy, expediting of the drug development activities, reducing the time to market, decreasing drug development costs by avoiding unnecessary and costly studies, minimizing the risk for a clinical hold, establishing a strong relationship with the FDA through early interactions, and obtaining new regulatory insights from the FDA. You can get the most out of your pre-IND meeting with the FDA and maximize your benefits by focusing on clear, specific regulatory and scientific questions related to pre-clinical, clinical, CMC, and other questions you may have. Aleon can maximize your benefits by sharing our expertise and experience with successful pre-IND meetings and advise you on how to best approach the FDA to ask your questions in the most advantageous manner possible.

How Aleon Can Prepare You for a Successful Pre-IND

First, it is important to note that based on our experience, in recent years pre-IND meetings are usually granted as a Written Response Only (WRO), meaning that the FDA will provide written responses to the questions the sponsor has listed in the meeting request. If a WRO is granted, this will be documented in the

letter from the FDA. A video conference may also be granted as a form of a face-to-face meeting. In 2023, the FDA is resuming Type A face-to-face meetings as they implement a new hybrid workplace at the FDA's White Oak campus.

If the meeting is granted as a WRO, it is crucial that the sponsor provides specific information related to their drug development program in the meeting request and meeting package to receive the most comprehensive feedback from FDA in the WRO. If the meeting is granted as a face-to-face or video conference meeting, Aleon will work closely with the sponsor to conduct rehearsals to give the sponsor an opportunity to practice and find the best way to address FDA's responses in addition to the preparation and review of the meeting request and meeting package. Regardless of the form of the meeting, when you work with Aleon, our team will review the specific details of your drug development program and position you for a successful pre-IND meeting by providing expert strategic guidance and planning throughout the entire process. Our team will support you in developing the highest quality meeting request and meeting package in a timely manner to fit your timeline.

Timeline for Having a Pre-IND Meeting with the FDA

Understanding the overall pre-IND meeting timeline is important to effectively plan your pre-IND meeting with the FDA. After submitting the meeting request, the sponsor will be notified by the FDA stating if their meeting request has been granted or denied within 21 calendar days from FDA's receipt of the meeting request. If the meeting has been granted, the calendar days of receiving the meeting request. Similarly, if a WRO has been granted, the WRO response from the FDA will be within 60 calendar days of receipt of the meeting request. The meeting package must be submitted to the FDA within 30 calendar days of the meeting. In addition, for video conferences and face-to-face meetings, you will receive the FDA's preliminary responses no later than 2 days before the meeting.

Aleon can integrate the pre-IND meeting timeline into your IND preparation and submission timeline, simultaneously working on the meeting request and meeting package while moving forward with your IND document preparation and review to meet your development goal. This is one of the ways that Aleon gives the sponsor an opportunity to expedite the overall pre-IND and IND timeline. Typically, Aleon will complete all pre-IND meeting and IND preparation and submission activities within 4 months (120 calendar days). However, there have been many instances where our team expedited the timeline and completed the entire pre-IND and IND project sooner. We always work with the sponsor to review their unique study details and find the best timeline based on our experience that will suit the sponsor's needs.

Pre-pre-IND Meetings

An even earlier form of communication with the FDA is a pre-pre-IND meeting, or pre-IND consultation. The purpose of a pre-pre-IND meeting is to receive FDA's feedback in planning preclinical and clinical development programs. This early interaction should be requested if you have generated preliminary preclinical data, but you have not yet reached the stage of discussing preclinical safety studies. The feedback received from the FDA may be considered when preparing final protocols for preclinical studies, as well as when preparing the meeting package for the Pre-IND meeting. Aleon has had several successful experiences with pre-pre-IND meetings and our team can work directly with you to determine if you should consider having this interaction with the FDA before the pre-IND meeting.

Conclusion

Although not required by the FDA, pre-IND meetings are a great opportunity for sponsors to obtain valuable feedback from the FDA early in the drug development process. There are many benefits associated with having a pre-IND meeting, including, but not limited to, expediting drug development, reducing drug development costs, and establishing a strong relationship with the FDA. Our team can do this simultaneously while preparing your IND, so we save your time while still receiving valuable FDA feedback. Aleon will work with the sponsor from day one to prepare a high-quality meeting request and meeting package with clear, targeted questions to the FDA which will provide feedback for key decisions as your drug candidate moves forward.

Article authored by Aleon Staff

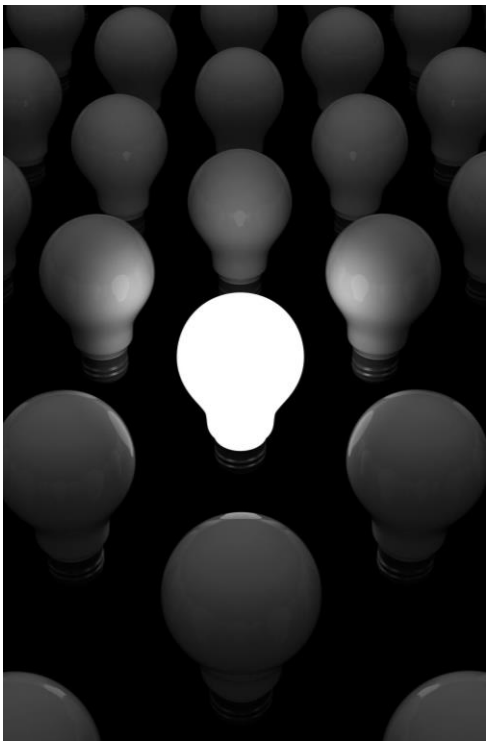
Increased Focus for Orphan Drug Development

Rare Diseases Remain Underserved, FDA Increases Focus on Orphan Drug Development

Rare diseases are defined in the US as diseases or conditions that affect fewer than 200,000 individuals. The relatively small patient population has historically meant therapies are harder to come by. Pharmaceutical companies were focused on more prevalent diseases given the larger number of patients in need, and trials for rare diseases were more costly to run, even finding patients was significantly more difficult.

The FDA has taken great efforts to correct this problem as roughly 7,000 rare diseases affect more than 30 million people throughout the US. One major step the FDA took was the introduction of the Orphan Drug Designation program following the Orphan Drug act of 1983, a step quickly replicated by countries around the world. The policies are different in each country, but generally, they provide incentives (tax breaks, exclusive marketing rights, etc. The US Marketing Application fee can be waived which currently costs more than $3.2 million USD for a new NDA/BLA with clinical data) for companies to develop therapies targeting rare diseases, and since then the number of new therapies for rare diseases has increased dramatically. From 1967 to 1983 the FDA approved 34 drugs that would have qualified for the Orphan Drug Program. From 1983 to 2020 the FDA has granted more than 4,700 Orphan Drug Designations and approved more than 700 new treatments. Last year alone 26 of CDER's 50 new drug approvals were for rare diseases. However, many rare diseases are still lacking treatment. 90% of the rare diseases in the US still do not have approved treatments. It is therefore no surprise that FDA is increasing focus on rare disease treatments with the introduction of the Rare Disease Cures Accelerator-Data and Analytics Platform in 2018, the Standard Core Clinical Outcome Assessment Grant Program in 2019, Accelerating Rare Disease Cures Program in 2022, and the upcoming Rare Disease Endpoint Advancement Pilot program in 2023.

FDA is committed to seeing more therapies for rare diseases in the coming years, and we at Aleon are dedicated to supporting sponsors seeking Orphan Drug Designations and strategic guidance on orphan drug development. Aleon provides regulatory strategy during the process with up-to-date regulatory affairs knowledge and experience demonstrated by years of professional relationships with health authorities. Following best practices based on successful experience and past FDA feedback, Aleon develops a thorough internal review process to capture key items during the request preparation and review periods to ensure high-quality submissions. As a result, our sponsors gain designation even in challenging situations like Orphan subset or early-stage development with only *in vitro* data available. Aleon is proud to have helped with more than twenty successful ODD designations in the US, and in 2023 we are hard at work with sponsors on more designations in the coming months. If you are considering an Orphan Drug Designation request to FDA, please consult us today.



Article authored by Aleon Staff

eCTD Submissions in China

What you need to know

China's pharmaceutical industry has been growing exponentially over the past 20 years. In 2009, it had the 9th largest pharmaceutical industry in the world and within a decade it had become the second largest, only surpassed by the US. To keep pace with the growing needs, the NMPA recognized the need for a full electronic format to expedite the review and approval of new therapies and announced an eCTD submission system for New Drug Applications (NDAs) and Biologics License Applications (BLAs) in 2021.

There are a few interesting things to note about China's now active eCTD system. Foremost among them, the system's specifications are based on ICH 3.2.2., a technical standard, but one that very closely aligns with the FDA's specifications rather than the EMA's eCTD process. This will make the US and China submissions even more streamlined, especially for companies already deeply familiar with the FDA's eCTD process. There are still some differences, such as language and numbering requirements plus China is still developing this system – for the moment paper submissions are still needed,

and eCTD submissions themselves are completed via CD as the NMPA works on a portal for gateway submissions. Aleon's experienced eCTD team was prepared to support sponsors for their eventual eCTD submissions as soon as the announcement came from the NMPA, and this month engaged in our first eCTD submission project for an NDA in China.

Teams providing eCTD services will have to stay vigilant as the NMPA moves to finalize details of their new electronic system. Until then, sponsors in need of eCTD services for China will benefit from the support of companies with experience in electronic submissions. Aleon's eCTD function team has been supporting submissions to the FDA and EMA for more than a decade without issue thanks to our thorough vetting system for documents submitted to regulatory authorities. After our eCTD team has completed their review, they check the quality of the eCTDs via our in-house proprietary software as an additional review to ensure all documents will be accepted by the document submission portal of the relevant authorities. With more than 4,000 eCTD submissions by our team in the past 5 years, sponsors can rest easy knowing their documents will not be rejected upon submission. We look forward to expanding our eCTD team's work in China in 2023, making drug development more efficient, and helping companies get their treatments to patients in need without delay.

Article authored by Aleon Staff

IND Submissions in Multiple Markets

Where to begin?

Selecting the right country to start your product's regulatory journey can be challenging enough on its own, but it can cause serious headaches when a company is considering seeking approval in multiple markets. Some companies will benefit from a coordinated, simultaneous approach while others will be better suited by a sequential approach, using what they learned during the first submission process to inform the next. There is no easy rule to understanding which approach is right for you, and sponsors should put serious thought into the regulatory strategy to which they are committing themselves.

Certain companies will find a simultaneous approach is more suitable for their overall regulatory strategy and try to provide patients globally with the care they need sooner. However, there can be benefits to a sequential approach as well. Let's take a dual submission to the US and China as an example. Many sponsors correctly recognize that these are two of the largest, and therefore most important, markets for their future product. Although the approval process in China and the US may have looked very different a decade ago, the approval processes today have many similar features. The increased push towards global regulatory harmonization means that a lot of the feedback provided by one of the regulatory authorities will be directly applicable with the other.

For instance, let's consider a recent submission Aleon supported for a small molecule program targeting oncology indications. After a careful examination of the details of the program's history and discussions with the sponsor about the trajectory of the program, we elected to start with the submission in the US first, and then carry out the submission in China. The feedback provided by the FDA in the Pre-IND meeting better informed the sponsors strategy, and the later submission to the NMPA was made considerably easier by incorporating feedback from the FDA into their NMPA submission.

Regulatory authorities and their markets can look similar and different in many ways at a distance, the key to an effective approach is careful planning and actively refining your strategy from a global perspective – one of Aleon's main strengths as a global regulatory affairs expert.

Article authored by Aleon Staff

FDA Drug Development Outlook in 2023 & Beyond

Regulatory Affairs outlook in 2023 and Beyond

2022 was a year filled with developments in US drug Policy, and 2023 will likely be the same with the FDA's Budget expanded by an additional $226 million for the year. The planned $3.5 billion USD budget for 2023 is complemented by roughly $3 billion USD in user fees.

2022 saw several major developments in the US market including: the Inflation Reduction Act (authorizing Medicare/Medicaid to negotiate drug prices), reauthorization of PDUFA (including a series of orphan drug grants and other initiatives), Accelerated Approval reforms (per FDA's request following 06/2021 approval of Biogen's aducanumab), and FDA's continued expansion of regulatory Flexibility (with the rejection, then approval of Amylyx's Relyvrio).

Looking ahead in 2023 there are several developments on the horizon that savvy sponsors should keep an eye on. The first item to consider is the implementation of the Inflation Reduction Act (IRA). The law permits Medicare and Medicaid to negotiate drug pricing, but effects will likely not be seen for a few years. The first drugs for negotiation will be announced in early fall 2023, and the first prices changes will likely not be introduced until 2026. So far, no lawsuits have begun to challenge the implementation of this part of the law, but if litigation comes it will likely be in 2023.

Another item to take note of is the first new drug approved in 2023, Eisai's Leqembi. This new Alzheimer's treatment was submitted through the Accelerated Approval pathway much like Biogen's aducanumab, and the upcoming changes to the FDA's Accelerated Approval pathway will likely be affected by the post-market success of this new treatment.

Perhaps the most notable development for readers of this newsletter will be the FDA's announcement of the new PDUFA fees for fiscal year (FY) 2023. The new fees (available via the federal register (Docket Number FDA-2022-N-2355) are part of the new 5-year term established by PDUFA VII for FY 2023 through FY 2027.

2023 is poised to be an interesting year for regulatory affairs. From new FDA guidance on AI in medical devices to improved focus on orphan drugs there are many new initiatives to pay attention to at the FDA. Keeping up with all the developments can be challenging, but your partners at Aleon are hard at work getting ready for any challenge that may come your way in 2023!

Article authored by Aleon Staff

A Message from Aleon's President

Founding Aleon

I founded Aleon in 2010 to provide high-quality regulatory services for innovative sponsors to move their drug and biologics programs forward. Our focus was simple: use our expertise to help companies of all sizes—particularly startups—better understand and accelerate novel drug development from IND all the way to NDA/BLA approval.

In the time since we began

We've helped many sponsor companies achieve regulatory success in the development of small molecules, monoclonal antibodies, bispecific antibodies, antibody-drug conjugates, cell & gene therapies and more with the FDA, NMPA, and EMA. Countless partners, many of which are now publicly traded on the NASDAQ, NYSE, SSE, and HKSE, have gained the approvals they needed to bring their novel drugs to market. We're honored to have been a part of their journeys, and thrilled to see their innovations succeed.

Looking ahead, we're focused on being the leading regulatory consulting company for new drug and biotech advances and continuing to help bring innovative treatments to market and patients in need. We're committed to promoting and elevating the amazing work our partners do every single day.

Andrew Jiang, President

Aleon Pharma International, Inc.

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