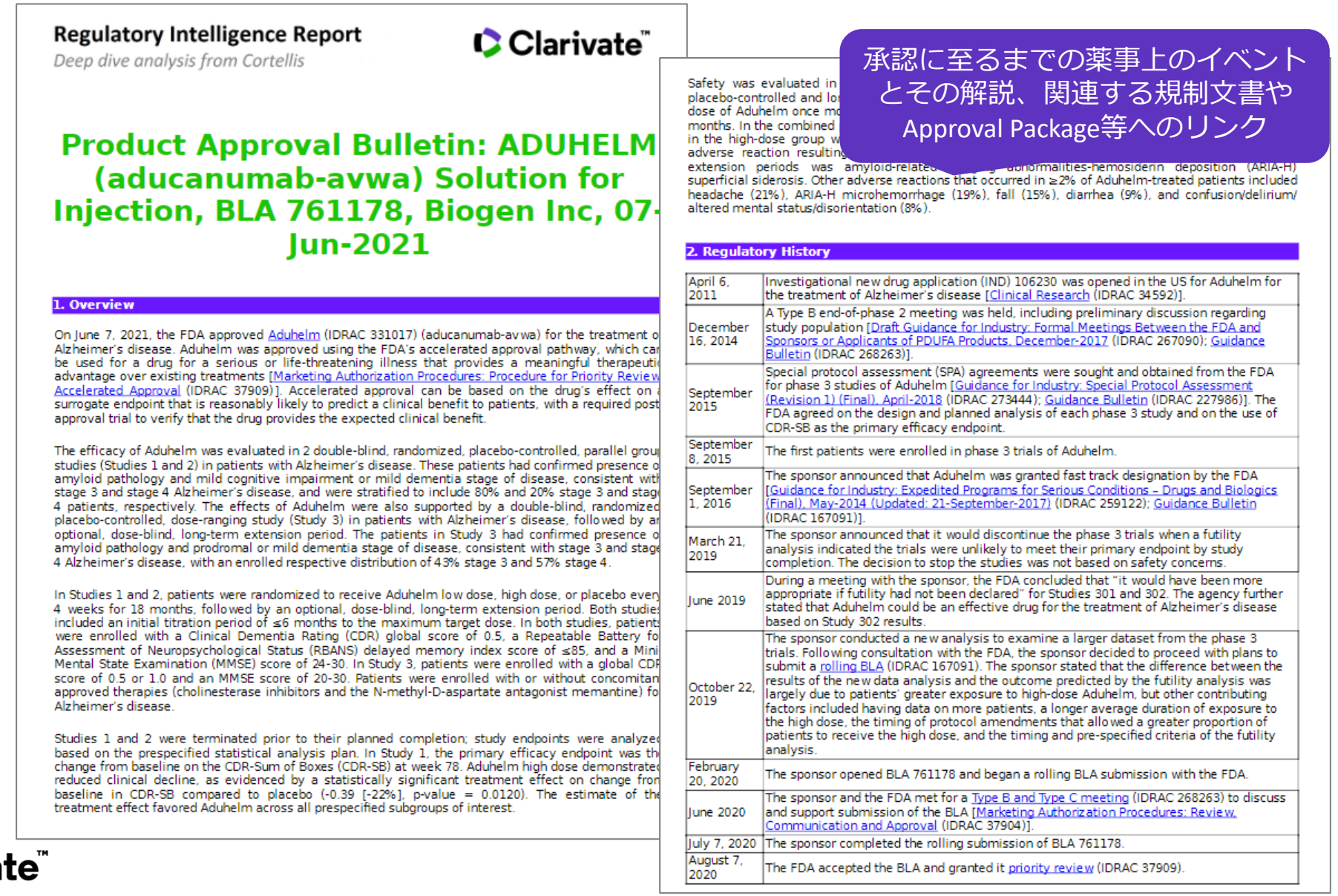
医薬品開発～承認に至る薬事上の重要マイルストーンと関連規制を効率的に整理する

Cortellis Regulatory Intelligenceで見る臨床開発～承認マイルストーン

Product Approval Bulletin （USモジュール）の活用



Regulatory Intelligence Report

Deep dive analysis from Cortellis

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Product Approval Bulletin: ADUHELM (aducanumab-avwa) Solution for Injection, BLA 761178, Biogen Inc, 07-Jun-2021

1. Overview

On June 7, 2021, the FDA approved Aduhelm (IDRAC 331017) (aducanumab-avwa) for the treatment o Alzheimer's disease. Aduhelm was approved using the FDA's accelerated approval pathway, which ca be used for a drug for a serious or life-threatening illness that provides a meaningful therapeuti advantage over existing treatments [Marketing Authorization Procedures: Procedure for Priority Review Accelerated Approval (IDRAC 37909)]. Accelerated approval can be based on the drug's effect on surrogate endpoint that is reasonably likely to predict a clinical benefit to patients, with a required post approval trial to verify that the drug provides the expected clinical benefit.

The efficacy of Aduhelm was evaluated in 2 double-blind, randomized, placebo-controlled, parallel grou studies (Studies 1 and 2) in patients with Alzheimer's disease. These patients had confirmed presence o amyloid pathology and mild cognitive impairment or mild dementia stage of disease, consistent with stage 3 and stage 4 Alzheimer's disease, and were stratified to include 80% and 20% stage 3 and stage 4 patients, respectively. The effects of Aduhelm were also supported by a double-blind, randomized placebo-controlled, dose-ranging study (Study 3) in patients with Alzheimer's disease, followed by a optional, dose-blind, long-term extension period. The patients in Study 3 had confirmed presence o amyloid pathology and prodromal or mild dementia stage of disease, consistent with stage 3 and stage 4 Alzheimer's disease, with an enrolled respective distribution of 43% stage 3 and 57% stage 4.

In Studies 1 and 2, patients were randomized to receive Aduhelm low dose, high dose, or placebo every 4 weeks for 18 months, followed by an optional, dose-blind, long-term extension period. Both studies included an initial titration period of ≤6 months to the maximum target dose. In both studies, patients were enrolled with a Clinical Dementia Rating (CDR) global score of 0.5, a Repeatable Battery for Assessment of Neuropsychological Status (RBANS) delayed memory index score of ≤85, and a Mini Mental State Examination (MMSE) score of 24-30. In Study 3, patients were enrolled with a global CDR score of 0.5 or 1.0 and an MMSE score of 20-30. Patients were enrolled with or without concomitant approved therapies (cholinesterase inhibitors and the N-methyl-D-aspartate antagonist memantine) for Alzheimer's disease.

Studies 1 and 2 were terminated prior to their planned completion; study endpoints were analyzed based on the prespecified statistical analysis plan. In Study 1, the primary efficacy endpoint was the change from baseline on the CDR-Sum of Boxes (CDR-SB) at week 78. Aduhelm high dose demonstrated reduced clinical decline, as evidenced by a statistically significant treatment effect on change from baseline in CDR-SB compared to placebo (-0.39 [-22%], p-value = 0.0120). The estimate of the treatment effect favored Aduhelm across all prespecified subgroups of interest.

Safety was evaluated in placebo-controlled and lo dose of Aduhelm once mo months. In the combined in the high-dose group w adverse reaction resulting extension periods was amyloid-related abnormalities-hemosiderin deposition (ARIA-H) superficial siderosis. Other adverse reactions that occurred in ≥2% of Aduhelm-treated patients included headache (21%), ARIA-H microhemorrhage (19%), fall (15%), diarrhea (9%), and confusion/delirium/altered mental status/disorientation (8%).

2. Regulatory History

April 6, 2011	Investigational new drug application (IND) 106230 was opened in the US for Aduhelm for the treatment of Alzheimer's disease [Clinical Research (IDRAC 34592)].
December 16, 2014	A Type B end-of-phase 2 meeting was held, including preliminary discussion regarding study population [Draft Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products, December-2017 (IDRAC 267090); Guidance Bulletin (IDRAC 268263)].
September 2015	Special protocol assessment (SPA) agreements were sought and obtained from the FDA for phase 3 studies of Aduhelm [Guidance for Industry: Special Protocol Assessment (Revision 1) (Final), April-2018 (IDRAC 273444); Guidance Bulletin (IDRAC 227986)]. The FDA agreed on the design and planned analysis of each phase 3 study and on the use of CDR-SB as the primary efficacy endpoint.
September 8, 2015	The first patients were enrolled in phase 3 trials of Aduhelm.
September 1, 2016	The sponsor announced that Aduhelm was granted fast track designation by the FDA [Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics (Final), May-2014 (Updated: 21-September-2017) (IDRAC 259122); Guidance Bulletin (IDRAC 167091)].
March 21, 2019	The sponsor announced that it would discontinue the phase 3 trials when a futility analysis indicated the trials were unlikely to meet their primary endpoint by study completion. The decision to stop the studies was not based on safety concerns.
June 2019	During a meeting with the sponsor, the FDA concluded that "it would have been more appropriate if futility had not been declared" for Studies 301 and 302. The agency further stated that Aduhelm could be an effective drug for the treatment of Alzheimer's disease based on Study 302 results.
October 22, 2019	The sponsor conducted a new analysis to examine a larger dataset from the phase 3 trials. Following consultation with the FDA, the sponsor decided to proceed with plans to submit a rolling BLA (IDRAC 167091). The sponsor stated that the difference between the results of the new data analysis and the outcome predicted by the futility analysis was largely due to patients' greater exposure to high-dose Aduhelm, but other contributing factors included having data on more patients, a longer average duration of exposure to the high dose, the timing of protocol amendments that allowed a greater proportion of patients to receive the high dose, and the timing and pre-specified criteria of the futility analysis.
February 20, 2020	The sponsor opened BLA 761178 and began a rolling BLA submission with the FDA.
June 2020	The sponsor and the FDA met for a Type B and Type C meeting (IDRAC 268263) to discuss and support submission of the BLA [Marketing Authorization Procedures: Review, Communication and Approval (IDRAC 37904)].
July 7, 2020	The sponsor completed the rolling submission of BLA 761178.
August 7, 2020	The FDA accepted the BLA and granted it priority review (IDRAC 37909).

承認に至るまでの薬事上のイベントとその解説、関連する規制文書やApproval Package等へのリンク

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Cortellis Regulatory Intelligenceで見る臨床開発～承認マイルストーン

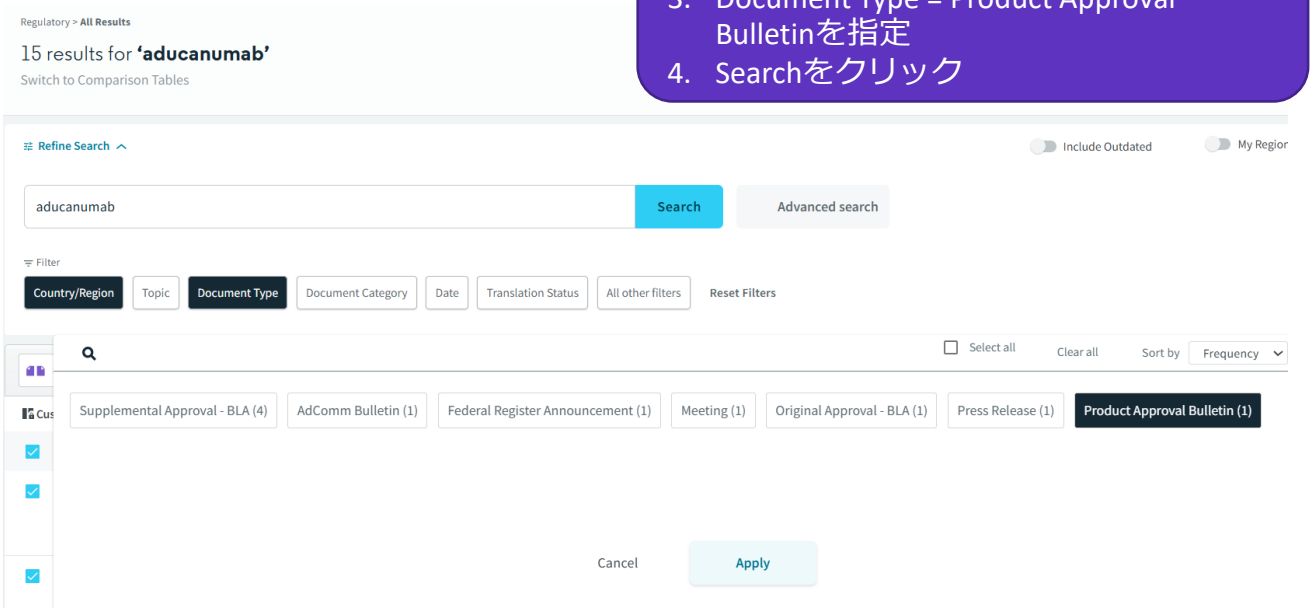
Product Approval Bulletin （USモジュール）の活用

Product Approval Bulletin

- 収録対象モジュール：Drugs & Biologics US モジュール
- 医薬品が承認に至るまでの経緯と、各ステージにおける関連規制、FDA諮問委員会の履歴、競合医薬品の情報等を提供
- レポート作成対象医薬品
  - 新規化合物
  - バイオロジクス製品（疾患治療用途のもの）
  - FDA諮問委員会のレビューを経てFDA承認された品目

検索によるアクセス方法

1. 検索ボックスに医薬品名を入力
2. Country/Region = USAを指定
3. Document Type = Product Approval Bulletinを指定
4. Searchをクリック



Applyボタンによるフィルターの確定を忘れずに!

5. 検索結果画面で目的の文書タイトルをクリック

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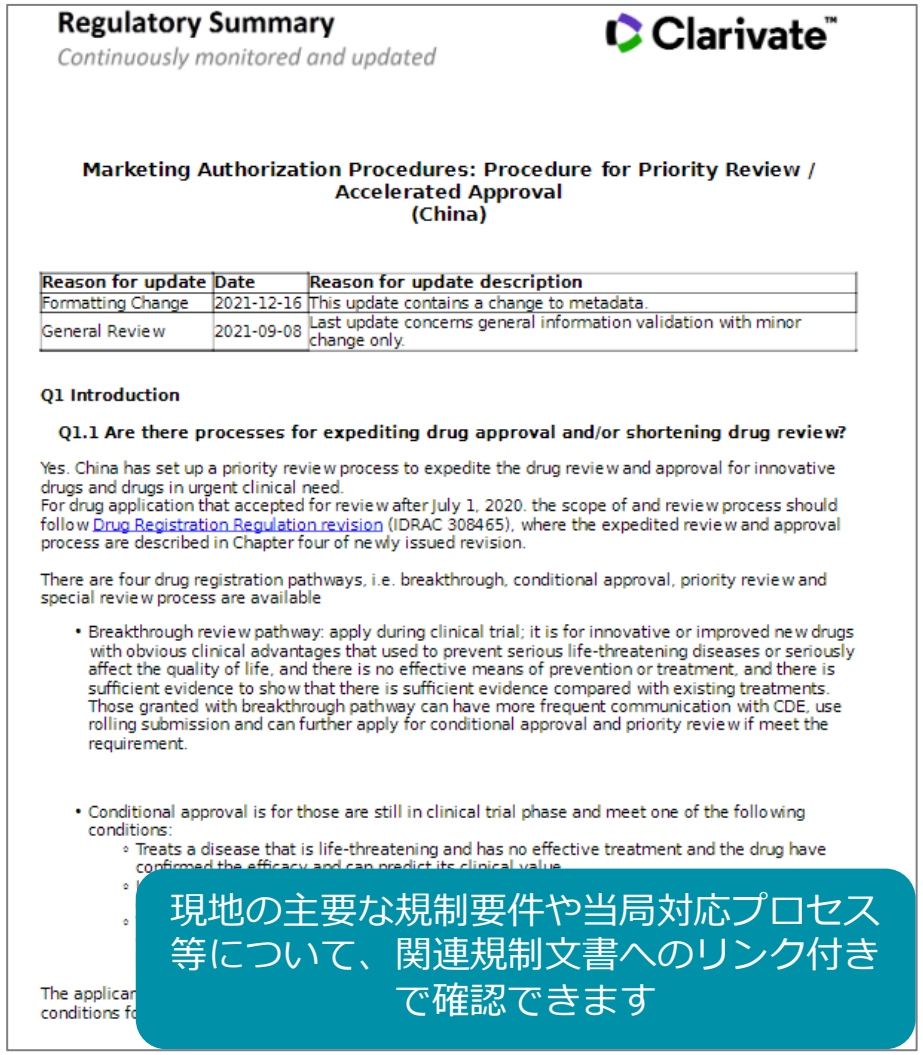
関連Tips：迅速承認、例外的使用、オーファン指定などの薬事対応プロセスの調査

Drugs & Biologics全モジュール共通



Regulatory Summary

Continuously monitored and updated

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Marketing Authorization Procedures: Procedure for Priority Review / Accelerated Approval (China)

Reason for update	Date	Reason for update description
Formatting Change	2021-12-16	This update contains a change to metadata.
General Review	2021-09-08	Last update concerns general information validation with minor change only.

Q1 Introduction

Q1.1 Are there processes for expediting drug approval and/or shortening drug review?

Yes. China has set up a priority review process to expedite the drug review and approval for innovative drugs and drugs in urgent clinical need.
For drug application that accepted for review after July 1, 2020, the scope of and review process should follow Drug Registration Regulation revision (IDRAC 308465), where the expedited review and approval process are described in Chapter four of newly issued revision.

There are four drug registration pathways, i.e. breakthrough, conditional approval, priority review and special review process are available

- Breakthrough review pathway: apply during clinical trial; it is for innovative or improved new drugs with obvious clinical advantages that used to prevent serious life-threatening diseases or seriously affect the quality of life, and there is no effective means of prevention or treatment, and there is sufficient evidence to show that there is sufficient evidence compared with existing treatments. Those granted with breakthrough pathway can have more frequent communication with CDE, use rolling submission and can further apply for conditional approval and priority review if meet the requirement.

- Conditional approval is for those are still in clinical trial phase and meet one of the following conditions:
  - Treats a disease that is life-threatening and has no effective treatment and the drug have confirmed the efficacy and can predict its clinical value

The applicar
conditions fo

現地の主要な規制要件や当局対応プロセス等について、関連規制文書へのリンク付きで確認できます

Regulatory Summaries（規制の解説レポート）の活用

- 各国規制の解説文を活用して、様々な薬事上の指定を受けて医薬品承認申請を行う際の要件、手続きプロセスを効率的に調査できます
- 主な関連レポート
  - Marketing Authorization Procedures
    - Priority Review/Accelerated Approval Procedure
  - Marketing Authorization Procedures
    - Unapproved Drug Use/Compassionate Use Procedure
  - How to Market...
    - Orphan Drugs
    - Drugs for Pediatric Use etc...
- Regulatory Summariesへのアクセス方法は以下の資料も参考にしてください
  - Cortellisユーザーサポートサイト「各国の規制要件や慣行についての英語の解説文を読む」

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