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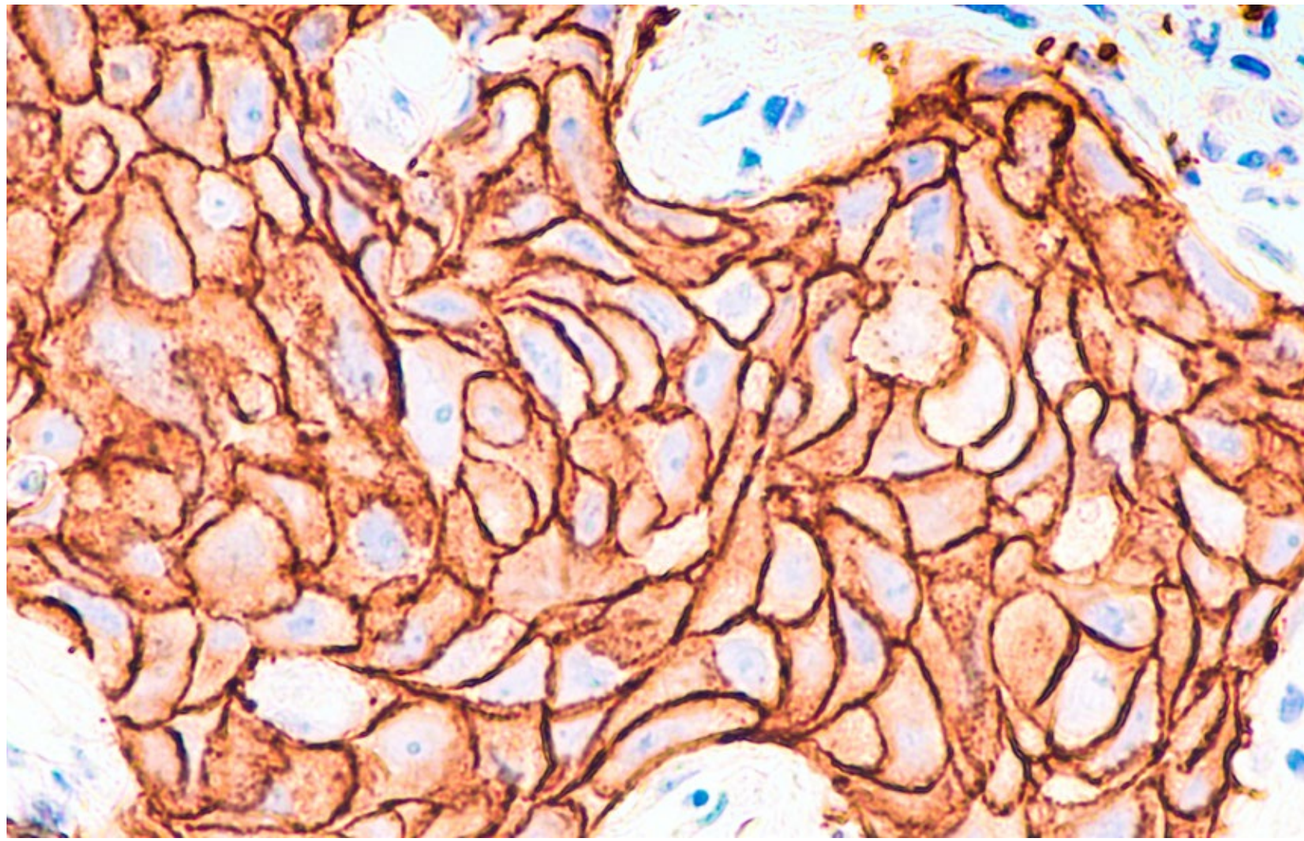

Consideration of Implementation for Postmarketing Carcinogenicity Studies Based on a Retrospective Analysis of Approved New Drugs by US FDA in the Past Ten Years

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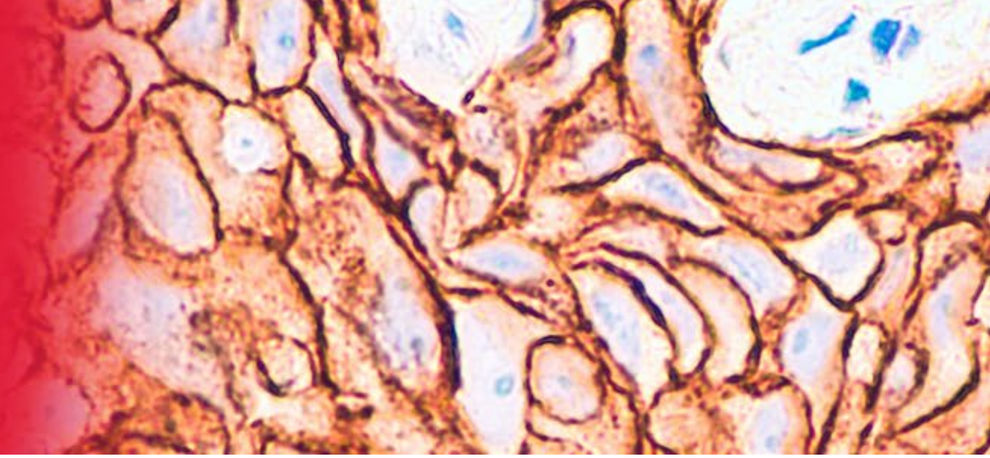

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BACKGROUND & PURPOSE

The term *postmarketing requirement* (PMR) is used to describe all required postmarketing studies and clinical trials. According to FDA guidance *Post-marketing Studies and Clinical Trials — Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act Guidance for Industry and ICH S1 Guideline On The Need For Carcinogenicity Studies Of Pharmaceuticals*, for pharmaceuticals developed to treat certain serious diseases, carcinogenicity testing need not be conducted before market approval although these studies should be conducted post-approval. While there are no examples about postmarketing carcinogenicity studies to be conducted for pharmaceuticals treating serious diseases in these guidelines, in the China NMPA's guideline *Guidelines for the Necessity of Carcinogenicity Studies of Pharmaceuticals*, only HIV is mentioned as an example of a serious disease. This research aims to systematically analyze the postmarketing requirements for carcinogenicity studies in the United States, to elucidate how postmarketing carcinogenicity studies are proposed, to provide some reference for enterprises for research and development of new drugs and drug evaluation agencies.

METHODS

This study delved into 465 drug approvals by US FDA from 2015 to 2024, either as new molecular entities (NMEs) under New Drug Applications (NDAs), or as new therapeutic biologics under Biologics License Applications (BLAs), and examined all the 25 FDA approvals that contain postmarketing requirements for carcinogenicity studies in the past ten years, leveraging review documents from the FDA, comprehensive data on product characteristics, all post-marketing requirements and commitments for carcinogenicity studies.

RESULTS

This study found that the overriding consideration for all post-marketing carcinogenicity studies were the disease indications of these drugs, which were life-threatening or severely debilitating diseases, and there was unmet medical need for therapies to treat these diseases.

Some of the diseases included cystic fibrosis (CF), Duchenne muscular dystrophy (DMD), spinal muscular atrophy (SMA), carcinoid syndrome diarrhea, early stage HER-2 positive breast cancer, amyotrophic lateral sclerosis (ALS), seizures associated with Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS), hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis), HIV-1 infection, Lambert-Eaton myasthenic syndrome (LEMS), extensively drug-resistant (XDR) and treatment-intolerant/nonresponsive (TI/NR) multidrug-resistant (MDR) tuberculosis, acute hepatic porphyria (AHP), primary hyperoxaluria type 1 (PH1), chronic idiopathic constipation (CIC), Alagille syndrome (ALGS), hypertrophic cardiomyopathy (HCM), epidermolysis bullosa (EB), low-grade gliomas (LGGs), and warts, hypogammaglobulinemia, infections and myelokathexis (WHIM) syndrome.

For example, Alagille syndrome (ALGS) is a rare (incidence of 1 in 30,000-70,000), autosomal dominant, multi-organ disease. Bile duct paucity in the liver occurs in approximately 90% of patients with ALGS. The disease can progress to cirrhosis leading to liver failure. Before the approval of the drug Livmarli, there was no FDA-approved medical therapy for treatment of pruritus in patients with ALGS. Additionally, the available non-clinical and clinical data for these drugs supported this strategy.

RESULTS

For example, besides the indication, the justification of deferred carcinogenicity studies for the drug Eteplirsen were:

1) Eteplirsen was not genotoxic in the ICH standard battery of assays: *in vitro* bacterial mutation and mammalian chromosome aberration, and *in vivo* mouse bone marrow micronucleus.

2) No pre-neoplastic or other proliferative lesions were observed in 39-week NHP toxicity study.

3) No treatment-related clinically significant adverse events have been observed in clinical studies of > 3 years of once-weekly IV administration.

CONCLUSION

Postmarketing carcinogenicity studies strategy accelerates the availability of pharmaceuticals for life-threatening or severely debilitating diseases, that have no available therapy. Our analysis of drug approvals in the US FDA reveals diverse drug patterns approved for post-marketing carcinogenicity studies and provides clear cases. This study provides valuable insights for regulatory decision-making in a dynamic pharmaceutical landscape. Balancing the risks and rewards of conditional approvals is crucial in ensuring both patient safety and timely access to innovative treatments.

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