HOW TO KEEP THE GRANDFATHER DILEMMA FROM INTERRUPTING DRUG REDEVELOPMENT

In this article, Pfizer CentreOne's Associate Director, Regulatory Affairs, Chris Rojewski, provides programme insights into approval pathways for the redevelopment of pharmaceutical compounds.

Clearer approval pathways and new administration technologies are driving interest in redeveloping a range of legacy over-the-counter and generic compounds. Destined for new indications and better patient performance, rehabilitating old formulations is a growing part of pharma's business models and product strategies.

Many of these compounds have been on the market and used safely for a long time, in certain cases, even predating the requirement for a compliant regulatory application being approved by US FDA in order to market the product; these products are termed as "marketed unapproved drugs", sometimes referred to as "grandfathered". In the context of new development paths, these legacy products may not be compliant with current regulatory standards, and thus can't be referenced – requiring specific remediation before an old drug can win new approval.

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ROBUST REMEDIATION RESPONSE REQUIRED

The majority of Pfizer CentreOne customers (i.e. drug innovators) seek approval for their US product(s) along the 505(b)(2) regulatory pathway. Although every aspect of the drug product and its manufacture may have been previously approved, a robust programme to remediate critical filings is needed – even for seemingly straightforward, highly prescribed drug products.

Two key pieces of FDA guidance in 2011 and 2013 set the stage for the necessity to contemporise the regulatory filings of drug products being redeveloped and approved for renewed manufacture. This guidance helped set regulatory filing expectations for new drugs intended for new markets, as per the FDA's stance on marketed unapproved drugs and combination products.

Two recent sterile injectable programmes delivered by Pfizer CentreOne, came up against complexities related to a grandfathered product and a combination product. Challenges included the "compliance-readiness" of the application reference, design history file and similar regulatory filings.

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Case #1: Revitalising A Vintage Combination Product For Modern Medicine

A long-term customer engaged Pfizer CentreOne to revitalise one of its mature finished drug products. Marketed commercially for more than a decade, the formulation was packaged as a combination product in a prefilled syringe (PFS). This combination product was originally approved through the FDA Center for Drug Evaluation and Research as a new drug.

The device component of the product is owned by Pfizer and was referenced through a Type III drug master file (DMF) that was managed by Pfizer. FDA combination product regulations have evolved over the years, which added the risk of having to apply new compliance standards for this product with post-approval modifications. Thankfully, in 2013, the FDA offered guidance to clarify how to handle some of the uncertainties related to this situation.[1]

As the programme ramped up, it soon became clear that key reference files could not meet today's combination product regulatory requirements. This roadblock introduced additional complexity into an already complex sterile parenteral programme. To keep project timelines on track, the company's regulatory team quickly pivoted, implementing a robust remediation programme for how the product referenced the device DMF and how it tied into the device design history file (DHF).

Like many relationships with contract development and manufacturing organisations (CDMOs), manufacturing a finished drug form may involve the legacy intellectual property of several parties. One of the complexities involved in this sterile injectable fill/finish project was the fact that the DHF for the PFS was owned by a third party. Fortunately, that third party was Pfizer Global Supply (PGS), which pushed through remediation of the package's DHF in parallel with the drug innovator's combination product remediation programme.

The complexities of this programme and the demands of the product required a phased approach to regulatory filings. This enabled the team to complete the product-specific validation studies necessary to include the product within the scope of the device DHF.

Once DHF remediation was complete, the product application was able to reference the DMF for the PFS, which made the drug innovator's application compliant with current regulatory expectations. Ultimately, the process took nearly 12 months, but all filings across the finished drug product were compliant with current combination product regulations, and ready for post-approval changes when submitted by the drug innovator.

Case #2: The Absent Regulatory Application

Another customer engaged Pfizer CentreOne to help renew manufacturing an extremely mature sterile injectable diluent, which was being repurposed for use with a commercial biologic product as part of a convenience pack. This product predated current regulatory approval practices, and was considered a marketed unapproved drug that was grandfathered. The FDA encourages the manufacturers of these products to obtain the required evidence and comply with the approval provisions of the Federal Food, Drug and Cosmetic Act, or run the risk of removal of the products from the market.[2]

As this product was the asset of a third party (in this case PGS), providing the product intellectual property to the customer for submission as part of their application was not preferred. A programme was needed to formalise this grandfathered product into a compliant regulatory application for approval, which could then be referenced by the drug innovator.

This was more than a regulatory exercise, however, as some revalidation effort was necessary to bring the product up to current standards. The customer's remediation programme required a focus on framing the design correctly for the intended use with the biologic product, then building a new regulatory application from scratch.

A ROBUST PROGRAMMATIC APPROACH TO REMEDIATION IS REQUIRED

These cases are not unique and drug innovators are encountering these hurdles more frequently as they pursue drug strategies leveraging the 505(b)(2) approval pathway. According to the FDA, 64 products were developed under this guidance in 2019, and tremendous growth is expected for the category.[3]

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Both examples demonstrate how regulatory complexities can crop up unexpectedly, even with previously approved or grandfathered compounds, and during long-term commercial manufacturing relationships. Fortunately, a robust approach provided the necessary remediation responses to achieve product compliance and win subsequent product approvals from regulators.

DRESS PRODUCT FILES FOR SUCCESS

To align documentation for compliance and regulatory filing success, Pfizer CentreOne follows a methodology adopted by Pfizer for its own internal documentation remediation. Offering a structured approach to the process, the company can ensure compliance with current standards, which should lessen the risk of regulatory scrutiny with customers' applications.

With more of these kinds of products being renewed commercially, the issues related to grandfathered product data will need a focused programmatic approach. Regulatory application remediation can help keep 505(b)(2) programme timelines on track, while assuring compliance and market approval.

ABOUT THE COMPANY

Pfizer CentreOne is a global CDMO embedded within Pfizer and a leading supplier of specialty APIs. Pfizer CentreOne's global manufacturing network includes more than 35 sites across six continents. Backed by Pfizer resources, the company delivers technical expertise, global regulatory support and long-term supply. Working together with its customers, Pfizer CentreOne combines its knowledge with open dialogue to solve challenges as part of an intelligent collaboration.

REFERENCES

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ABOUT THE AUTHOR

Chris Rojewski has over 10 years of experience in regulatory affairs and more than 25 years in the pharmaceutical industry. After obtaining his Bachelor of Science in Chemistry from the University of Iowa, US, Mr Rojewski began his career as an Analytical Chemist at Abbott Laboratories, later joining Pfizer in 2016. With extensive experience in chemistry, manufacturing and controls, Mr Rojewski now expertly manages Pfizer CentreOne's Regulatory team as Associate Director of Regulatory Affairs.

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IMAGE

Two polymorphs of cholesteryl acetate recrystallised from the melt Gary Nichols, Materials Characterisation, Sandwich, UK.

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