Cambrex

White paper
Drug product

Pediatric dosage forms

Rising demand for pediatric dosage forms requires reformulation and development expertise but also to-scale manufacturing capabilities

Pharmaceutical companies are looking to pediatric indications of approved adult dosage forms (ADFs) to sustain and fuel growth. The desire to develop pediatric dosage forms (PDFs) of drugs with existing adult indications has two main drivers: (1) the US Food and Drug Administration's (FDA's) role in limiting off-label use in pediatric patients, which aligns with the FDA's role in ensuring the safety and efficacy of approved products for all patients; and (2) sustaining revenue growth through pediatric exclusivity that typically adds 180 days of intellectual property protection and thus almost 6 additional months of branded drug sales, which in some cases could translate to billions of dollars in revenue.

Many of today's largest pharma companies have selected Cambrex to reformulate their products and develop them in a variety of dosage forms appropriate for use in pediatric patients. Companies have come to rely on Cambrex as a trusted partner to provide specialized contract development and manufacturing services that meet the regulatory requirements of the US, Canada, and Europe, where Cambrex already manufactures PDFs for commercial sale through its customers.

As a result of a growing industry trend, Cambrex has a Pediatric Center of Excellence to meet the growing demand for PDFs and to develop and manufacture dosage forms for pediatric indications. In support of its Pediatric Center of Excellence, Cambrex has developed the infrastructure, process trains, and equipment needed for efficient, cost-effective, and rapid production of small- to medium-scale cGMP clinical drug products that are used in pediatric clinical studies.

> Cambrex's infrastructure and expertise cover the sweet spot for producing the small-to-medium-sized batches needed to meet industry demands for PDFs and Orphan Drugs, and also extend to large-scale manufacturing.

PDF scale and reformulation challenge manufacturers

The demand will likely continue to grow for PDFs of drugs spanning a broad range of therapeutic areas including pain management, respiratory diseases, anti-infectives, and central nervous system disorders. The challenges for drug producers developing PDFs are numerous and varied. These relate to the scale of manufacturing, the complexity of development and reformulation work required to support reduced dosing, a range of doses targeted to different age/weight levels, and often more than one formulation type required to meet the needs of toddlers through adolescents. Formulation decisions made in the development of PDFs can have important implications for drug stability, patient compliance, and accurate dosing. Various modifications to adult dosage forms (ADFs) are often needed to make a drug easier for children to take and easier for parents to administer.

The differences between adult and pediatric dosage forms are typically significant. In many cases, pharma companies select a contract development and manufacturing organization (CDMO) to develop products versus doing the work themselves for reasons related to cost, convenience, and capacity. First and foremost, CDMOs must have expertise in formulation sciences and proven formulation success in clinical development and commercial approvals. Many of today's drug products are complex

release and combination products that require innovative formulation approaches and technology. A formulator/developer must have the process and production equipment appropriate for quick turnaround of small- to medium-sized clinical, and ultimately commercial, batches that are typically required for PDFs that target smaller patient populations. Cambrex has a track record of success in partnering with several pharmaceutical companies in the development and commercialization of clinically suitable PDFs. Cambrex, along with several customers, has received both US and international regulatory approvals for PDFs as a result. Cambrex and its customers currently have multiple clinical and commercial PDF programs underway.

Advanced manufacturing technology and expertise in formulation sciences and process development are critical. In nearly all cases, developing a PDF from an ADF requires additional product development work. Cambrex has the capability to manufacture batches of PDFs that range in scale from 1kg to 1000kg, and most of the PDFs in Cambrex's pipeline require multiple processing steps.

When pharma companies approach Cambrex with an ADF for reformulation, the ADF is usually in the form of a tablet or capsule. While these dosage forms might be appropriate for adolescents (at a reduced dose), an ADF tablet or capsule would not be suitable for a young child or toddler. In most cases, the development of a PDF requires not only reduced dosage strengths, but also reformulation of the drug, perhaps as a liquid, an API suspension, or a powder for reconstitution. The solubility and stability of the API are some of the important factors to consider when deciding between liquid and solid oral dosage forms. The need to add flavoring, known as "taste-masking," to make a drug more palatable for children is another key facet of the reformulation process. Cambrex's broad range of formulation options includes all of these liquid-based dosing solutions in addition to solid dosage forms such as granules produced using fluid bed technology, beads, and the increasingly popular 2mm mini-tablets.

> Taste-masking can be challenging and is somewhat of an art form that benefits from experience and expertise.

Cambrex's formulation scientists and development and manufacturing teams work closely with pharma companies to identify the best options for reformulating a particular drug for the targeted pediatric patient population. Patient age and weight ranges, dosage strengths, frequency of dosing, and relevant disease factors (that might make it more difficult for a patient to swallow, for example) are all important aspects of formulation decisions. Sometimes parents just need the ease of being able to reach into the refrigerator and pull out a ready-to-use oral solution, without the need for reconstitution.

The trend toward combining 2 or more APIs in one formulation, the use of controlled-release medications, and, of course, cost considerations are all key factors that must be weighed during the design and development of a PDF.

While drugs for pediatric patients typically involve lower doses than those given to adults, concerns in minimizing drug toxicity in pediatric patients are always paramount. This can be overcome during formulation of PDFs by carefully choosing the dosage form, excipients, and concentrations used during the manufacture of the drug product.

Not only are there many different ways to develop PDFs, but there are also multiple ways to package them. Cambrex can package pediatric drugs in various formats optimized for ease of administration. These include various types of bottles for dispensing liquids or suspensions, capsules containing powders that can be opened and poured out into water or apple juice, and Cambrex's unique stick-packs for packaging granules, powders, beads, or mini-tablets, which have been successfully used in several commercially approved PDFs.

Innovative solutions to complex challenges

Companies come to Cambrex with new and unique requests that require innovative solutions. One example is the request to design a pediatric formulation of a drug that could cover pediatric patients ranging in age from as young as a couple of months up to 17 years. Different age groupings required different doses and thus a range of product presentations and formulations.

> Cambrex is DEA-licensed to work with controlled products and has invested heavily to acquire the complex technologies and capabilities needed to give customers more choices for developing controlled-release products.

Another challenging and frequent example is the growing trend in which pharma companies are combining 2 or even 3 APIs in one formulation. This requires a fixed ratio of the drugs in a single dosage form. These types of scenarios become even more complicated when one of the 2 drugs must be released before the others. In one specific example, Cambrex developed a PDF containing 2 APIs in suspension in a 80/20 ratio. The API present at 20% was formulated for immediate release, whereas the API that comprised 80% of the total was formulated as extended release over 24 hours. Yet another example necessitated a formulation that allowed 2 of the APIs in a 3 drug combination to release before the third API.

One can imagine that these complex and challenging examples of PDFs could take many years to bring to fruition. The challenges include, but are not limited to:

- Just-in-time production of material for clinical trials in pediatric patients, which typically face recruitment challenges
- More stringent cleaning requirements (including situations where PDFs are manufactured on the same equipment as ADFs in the same plant) due to lower recovery carry-over limits versus larger batch/adult product batch-scale sizes

- Manufacturing clinical materials under full GMP conditions
- Having the bandwidth and lab support to conduct all method revalidations and stability studies on PDFs

None of these challenges are insurmountable however and the path from ADF to commercialization of a PDF can be shortened significantly by partnering with an experienced CDMO that has expertise and appropriate process and manufacturing capacity targeted to this niche application.

A key factor in time to market is manufacturing capacity and the ability of a CDMO partner to produce small batches on demand to allow for quick assessment of different formulation approaches. Waiting in a long queue of higher priority large-scale manufacturing runs makes for lengthy and uncertain delivery timelines. A dedicated team-based approach to project management from formulation and development through manufacturing, analytical, packaging, and regulatory review can also streamline PDF production.

3 years ago, Cambrex successfully developed a pediatric formulation of an adult drug for a customer with a total project duration time of only 3 years. This time horizon was from the start of the project through FDA approval of the PDF. Cambrex produced the drug in mini-tablets in two dosage strengths and packaged it in stick-packs. The use of a Design of Experiments (DoE) approach demonstrated robust processes, and 1-year expedited stability testing accelerated the analytical phase. Cambrex worked closely with the customer and the FDA throughout the project. This included pre-approval inspections to ensure a smooth regulatory review process and no surprises along the way. The importance of experience and a comfort level working in a highly regulated environment, with a proven track record with the FDA and international regulatory agencies, cannot be over-emphasized. For the project described here, the PDF developed and filed using Cambrex as the commercial manufacturing site received approval from the European Medicines Agency (EMA) a year after the FDA approval.

Should a CDMO be selected for developing a PDF, the relationship between the CDMO and the pharma company should be highly collaborative. The pharma company provides guidance on the patient population and the dosing targets based on age or weight groupings and clinical endpoints. Once the first clinical supplies are available, and dose ranging studies completed, Cambrex then works side-by-side with its customers to establish the final dosage strengths and formulations based on clinical efficacy and safety information obtained from the trials.

Faster to market

Collaborating with a partner that has its own in-house team of formulation scientists, a dedicated development group, and pilot and commercial-scale manufacturing in one location can yield direct benefits in the form of faster, more reliable turnaround and delivery times. At Cambrex, 3 shifts operate across 24 hours, allowing Cambrex to achieve an on-time rate for deliverables to clinical sites of greater than 96%. In a CDMO of Cambrex's size, customers get the advantage of all of the necessary technology and capabilities, but not the silos or bureaucracy of larger CDMOs. As a result, projects can progress more quickly, as a single, dedicated project management team can follow your project from start to finish. Furthermore, the experience that comes from having been through numerous FDA inspections – including general and pre-approval inspections – and familiarity with local teams of FDA inspectors are invaluable. Many pharmaceutical companies have already benefited from Cambrex's extensive expertise in formulation sciences and its fully integrated manufacturing capabilities across a broad range of scales and dosage forms to overcome the challenges in developing PDFs of already approved adult dosage forms.

> One solution will not work to reformulate all drugs. Every project has different challenges. Experienced formulation scientists can identify the best option with the shortest path to market.

About Cambrex

Cambrex is **the** small molecule company that provides drug substance, drug product and analytical services across the entire drug lifecycle. Enjoy working with our experts to accelerate your small molecule therapeutics into the market.

With over 35 years' experience and a growing team of over 2,000 experts servicing our global clients from our sites in North America and Europe, we are tried and trusted in branded and generic markets for API and dosage form development and manufacturing.