Special Series:

Small Molecule Drug Development

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Predictive AI in Drug Discovery: Five Steps to Success

The use of AI in small molecules drug discovery is driving the sector forwards in big ways – but there are big challenges too. Here are five steps to success.

The preclinical phase of drug discovery is the most time intensive stage of the R&D lifecycle – taking up to six years and accounting for more than 40 percent of total drug development costs. To reduce the billions spent on preclinical drug development, faster, more efficient R&D workflows must be a priority across the industry. So it's no surprise that pharmaceutical and biotechnology companies are looking to use machine learning (ML) to revolutionize R&D and AI to generate and validate small molecule drug discovery pipelines.

Research organizations that successfully deploy AI are already gaining a competitive edge. There is emerging evidence that these organizations get through preclinical stages quicker and cheaper than the traditional approach, with savings of around 30 percent of time and cost. The approach is already gaining traction; one study by the Boston Consulting Group found that biotech companies that have adopted an AI-first approach, "…have more than 150 small molecule drugs in discovery and more than 15 already in clinical trials."

Predictive AI is one AI approach that many pharmaceutical and biotech companies are exploring today. Here are five steps that research leaders should follow to realize success.

1. Identify the right use cases

Before investing in predictive AI, research leaders must define the problems, or use cases, that they want to tackle. Typically, the best applications for predictive AI are discrete tasks and processes where measurable, tangible gains can be achieved. In early drug discovery, examples of predictive AI use cases include predicting the 3D structure of a protein, relationships between molecules based on their chemical structure, and drug-target interactions.

In small molecule discovery, predictive retrosynthesis combines high-quality reaction data with AI to find structural or chemical patterns that correlate with specific compound properties and accelerate synthesis planning of novel molecular entities. The potential benefits of predictive retrosynthesis over traditional approaches are significant; routes can be generated for novel compounds in minutes rather than weeks.

2. Source accurate and high-quality data

The nuance of research questions in drug discovery demands a level of precision that requires high-quality, verified training data. Without accurate and high-quality data, researchers will lack confidence in predictive AI outcomes. For predictive models to work, researchers will want to include data from multiple sources in addition to their internal data. This will typically include data from scientific literature, plus other databases containing patent data, regulatory data, clinical trials data, safety data, and data from patient records.

For example, a predictive AI chemistry model requires a breadth of chemistry inputs that includes not only proprietary data and data on failed reactions, but also published literature. A predictive model that is fine tuned using incomplete data will produce inferior results whose shortcomings may not be immediately identified, leading to expensive incorrect decisions.

3. Prepare and structure the data

Once data is acquired it must be structured to power predictive AI successfully. Much of the data R&D organizations source are not AI-ready; datasets are siloed and stored in myriad formats with insufficient metadata, making it difficult to retrieve and use in predictive AI models. Standardizing and structuring datasets via the application of ontologies is a critical step.

Ontologies are human-generated, machine-readable descriptions of categories. They standardize data against an agreed vocabulary, providing a shared language across an organization. Vocabularies can include terms specific to an organization – such as product names – alongside industry recognized concepts and terms. Ontologies define semantic relationships to other classes and capture synonyms, which is essential where there are multiple ways to describe the same entity in scientific literature and other datasets. For example, the gene PSEN1 can also be referred to as PSNL1 or Presenilin-1.

4. Semantic enrichment

To extract insights, datasets must be enriched and annotated. Semantic enrichment is a key step that unlocks the full potential of data in structured and unstructured, public and proprietary, datasets. It transforms text into clean, contextualized data, free from ambiguities and synonyms, through annotation, tagging and adding metadata. It works by employing text analytics to extract key words, concepts, and terms for predictive models, and harmonizes synonymous terms for better accuracy.

Data harmonization is especially important when using databases from multiple sources as technical terms or abbreviations are often used. For example, sophisticated semantic enrichment software can identify and extract relevant terms or patterns in text and harmonize synonyms, such as “heart attack” and “myocardial infarction”, so they are identified as the same entity by a predictive model. This eliminates “noise” and ensures predictive AI models are underpinned by high-quality, enriched data.

5. Domain specificity

Structuring data for predictive AI through ontologies and applying semantic enrichment methods is highly specialized work that requires expert understanding of the domain under investigation. General purpose AI models developed by technology companies have utility in broad areas such as marketing and operations, but scientific research represents a set of niche challenges that necessitates domain expertise.

Few biopharma companies today will have the right mix of skills needed for tasks such as creating ontologies in-house. And though they are experts in their scientific field, researchers lack the technological capabilities required. Best positioned to solve this challenge are data scientists who can couple technology skills with scientific domain expertise. Such data scientists can bring an understanding of the context of questions asked in relation to the data available. They can further ensure ontologies and vocabularies are built so that predictive AI models return relevant results, and no essential data is missed.

The world is in agreement: AI will be a game-changer for every industry. For those working in preclinical drug discovery, the opportunity is huge – but so is the challenge. To accelerate drug discovery to meet the medical needs of patients around the world, pharma and biotech organizations need to bring together data, technology, and expertise. When these elements converge, AI can serve as a valuable support tool for researchers to usher in a new era of drug discovery.

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The Liquid Challenge

Regulators want more pediatric formulations. Companies often turn to liquids, but there are specific challenges that need to be considered.

In 2023 the FDA released Guidance for Industry, Pediatric Drug Development Under the Pediatric Research Equity Act and the best Pharmaceuticals for Children Act: Scientific Considerations, in which sponsors are advised to provide plans for developing age-appropriate formulations of drug products in cases where an adult formulation is not appropriate for pediatric patients (1). With many medicines, this can translate to a fairly straightforward formula: children = liquids.

This move from the FDA is not only vital to ensure availability of the right drug products for the right patient demographics and reducing off-label use in children; from a business standpoint, it presents a useful tactic towards sustaining and maintaining growth. Given that the market for oral liquids is predicted to increase at a compound annual growth rate of around 6.5 percent in the coming decade (2), the outlook for substantial gains in this segment are as promising as they are important. Crucially, pediatric exclusivity typically extends intellectual property protection by 180 days, providing nearly six additional months of branded drug sales.

Liquid formulations offer some advantages over traditional oral solid dose (OSD) products, particularly in terms of ease of

administration. Liquid formulations are easier to ingest compared to tablets or capsules, which can be particularly challenging for children (as well as seniors) who may struggle to swallow solid forms. They are also good for dosing flexibility. The same bottle of liquid medication can be used to administer different doses, simply by adjusting the volume given with a spoon, syringe, or dosing cup. This variability is good for supply chains too because it eliminates the need to develop a new stock-keeping unit for each dose variation, simplifying inventory management and reducing production costs.

Liquids also have increased drug absorption and bioavailability that can lead to faster onset of action, and allow for incorporation of sweetened or flavoured vehicles to mask the bitterness or unpleasant tastes of APIs.

So why don't more companies develop liquid formulations from the onset?

There are challenges. One key issue is the inherent instability of liquid formulations compared to their oral solid dose counterparts. Liquid forms are more susceptible to physical and chemical degradation, and the potential for microbial growth is significantly higher, necessitating rigorous preservation and/or sterilization processes to maintain product integrity.

Liquid formulations also require robust packaging solutions capable of preventing both breakage and formulation interaction. A broken container can result in the total loss of the product, posing significant logistical and financial concerns.

The containers are also relatively bulky and inconvenient for patients. Single-use sachets can be an attractive alternative for bolstered convenience, but this packaging format incurs its own obstacles; most notably ensuring dose accuracy. (It is worth noting here however, that a single-use sachet does have the added benefit of the option to nitrogen blanket, decreasing any potential oxidative issues with the formulation).

We also can't overlook the high potency angle. More than 25 percent of drugs on the market today are classed as highly potent, with 60 percent of oncology drugs in development involving highly potent active pharmaceutical ingredients (HPAPIs) (3). As more and more ADFs in development contain HPAPIs, this escalated high potency ratio will ultimately carry over into the development of pediatric formulations. The approach to handling such molecules requires stringent controls to ensure safety and efficacy, ideally involving contained engineering solutions to ensure drug product integrity and operator safety – including the use of dedicated facilities, HEPA filtration systems, rigorous cleaning validation procedures, and personnel highly trained in handling potent molecules.

Once the HPAPI is fully wetted, the risk to the operator is significantly reduced, but getting the HPAPI fully wetted safely can be a challenge. This is primarily because of the risk of airborne contamination, as HPAPIs are typically fine powders and can easily become airborne, posing a serious inhalation hazard to operators. The powder's propensity to accumulate static electricity further increases the likelihood of dusting, where particles can disperse into the air, especially during handling or transfer. Controlling the wetting process is therefore crucial; if the liquid is added too quickly or inappropriately, it can cause splashing or aerosolization, potentially releasing the HPAPI into the air. Effective containment is essential, requiring specialized equipment like isolators or closed systems to prevent any escape of the powder before it is fully wetted. Additionally, the variability in the physical properties of HPAPIs, such as particle size and hydrophobicity, can make the wetting process unpredictable, sometimes leading to prolonged periods of risk as the powder may resist wetting or form clumps.

Given the formulation-specific challenges, it's perhaps unsurprising that a pediatric dosage form "cottage industry" has sprung up to help pharma brand owners expand into liquids. If you choose the route of a CDMO, make sure they have dedicated expertise in liquid dosage formulation development and manufacturing, as well as the knowledge to navigate the regulatory landscape. Also look for advanced analytical testing and taste-testing facilities such as electronic tongues (e-tongues), which are a great way to help a product achieve patient compliance. The right taste masking is crucial for pediatric formulations because any disagreeable flavours are more pronounced in liquid form compared to solid dose products.

In summary, oral liquid dosage forms present unique benefits and challenges with additional considerations when the drug product is classified as being potent, but with the right expertise and technology, these hurdles can be effectively overcome and managed to deliver high-quality, patient-centric therapies.

LINKS

References
Available Online

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Hot Melt Extrusion

**Vision.
Expertise.
Success.**

AbbVie Contract Manufacturing offers proprietary hot melt extrusion (HME) technology in both the US and Europe. As the global leader and pioneer with more than thirty years of HME extrusion development experience, AbbVie has launched the most commercial products utilizing this technology. HME is widely recognized as an effective technology to transform poorly soluble APIs into amorphous solid dispersions.

Experience

- Unparalleled industry leader with >35+ years of formulation & manufacturing know-how
- Integrated formulation development, clinical & commercial manufacturing
- Most commercial products launched (>7), first product marketed in 2005
- Academic collaborations to drive innovation; highest rate of HME technical publications

Capability

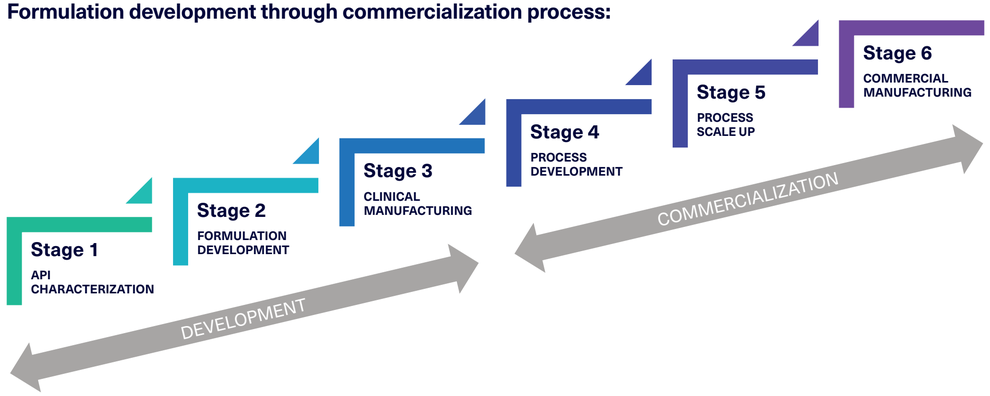
- 10+ extruders in network
- 18mm–70mm screw size
- Multiple OEMs (Liestritz, Coperion, Bosch)
- Potent capability (<1µg/m^3)
- Expertise in scale-up & technical transfer between sites
- Several simulation & scale-up models available for fast development to minimize API usage

Advantages & Value

- Continuous manufacturing without the use of solvents
- Wide range of scale to grow with product needs
- Ability to qualify multiple sites
- End to End manufacturing from extrudate to packaged drug product production
- Technical support & consultative services available
- Recognized leader in quality assurance

One proven pharma partner offering unique solutions to enhance bioavaibility

Formulation development through commercialization process:



AbbVie employs a stage-based process with clearly defined success criteria to develop a robust and successful formulation.

Analytical Services:

- HPLC (reverse phase, normal phase, ion exchange, gradient, and isocratic methods, pulsed amperemeter detection, UV visible, diode array, and MS detection)
- LC / MS & GC / MS
- GC (FID and TCD detection, capillary and glass columns, headspace, and residual solvents analysis)
- Spectrophotometry (FT- IR, UV visible)
- Atomic absorption, ICP and X-ray
- Optical and electron microscopy
- Surface area and particle size distribution
- Total organic carbon testing
- Microbiology lab for product testing and facility environmental testing
- Stability testing

Downstream Manufacturing Options:

(see Oral Solid Dose cutsheet for more details)

- Tablets (including multi-layer)
- Controlled Release
- Modified Release
- Capsules
- Milling

Packaging Options

- Blisters
- Bottles
- Sachets/Sticks
- Wallets

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Dosage Form Innovation| with Hot Melt Extrusion

What's going on with hot melt extrusion (HME)? We look at three recent studies that demonstrate the versatility of this manufacturing process for developing patient-centric dosage forms – from pediatric medicines to drug-loaded yarns.

Child-Friendly Tinidazole Tablets

Researchers in India used 3D printing and HME to create more child-friendly tinidazole (TNZ) tablets. TNZ is commonly used to treat several infections, such as giardiasis, but it suffers from poor solubility and a bitter taste – the latter of which can lead children to refuse the medicine.

The researchers set out to create tablets that could be customized for precise dosing tailored to a child's age, weight, and specific medical needs, selecting 3D printing as the most appropriate manufacturing approach. However, 3D printing requires that raw materials be evenly mixed and formed into a filament with the right mechanical qualities. To this end, HME was used to create amorphous solid dispersions of TNZ mixed with a polymer Kollidon25 (a soluble grade of polyvinylpyrrolidone). The polymer was selected for its ability to improve solubility and because tests confirmed good compatibility with TNZ.

With filaments in hand, the team used 3D printing to print dosage forms with different geometries that might appeal to pediatric patients. The tablets had a layer-by-layer pattern that helped improve the dissolution profile, with the tablets achieving 100 percent drug release within two hours in an acidic gastric medium. Finally, the bitter taste was also masked because TNZ was embedded within the polymer matrix, preventing direct contact with taste buds. *Read the Study*

High-Shear Melt Versus HME

High-shear (HS) melt granulation and HME were compared for the production of amorphous solid dispersions of carvedilol, a drug with poor water solubility that is used to treat cardiovascular conditions. The study, conducted by a team from the University of Ljubljana, University of Bologna, and the Research Centre for Pharmaceutical Engineering in Austria, aimed to improve carvedilol's dissolution using mesoporous carriers and polymer matrices. The research compared how well the two methods enhanced the drug's solubility and bioavailability.

Two mesoporous carriers, Syloid 244FP and Neusilin US2, were used to load the carvedilol-polymer mixtures. For the polymer matrix, either polyethylene glycol (PEG) 6000 or Soluplus were used, depending on the method.

One significant observation from the study was the difference in drug release profiles between the two methods. Syloid 244FP-based granules produced with HS melt granulation exhibited faster drug release than HME formulations. The researchers attributed this to the larger specific surface area and more porous structure of the HS granules, which allowed for faster interaction with the dissolution media. In contrast, HME extrudates had smoother surfaces and larger particle sizes, leading to slower but more controlled drug release.

The choice of polymer played a critical role in the performance of each formulation. PEG 6000 performed better than Soluplus in both technologies. Specifically, PEG 6000-based formulations, especially those made with HME, showed faster and more complete carvedilol release.

Despite the differences in drug release rates, both melt technologies offered advantages. HME was found to be more efficient and scalable, providing smoother particles with better flow properties, which could be beneficial for large-scale manufacturing. HS melt granulation, on the other hand, was superior in terms of rapid drug release, particularly for formulations using Syloid 244FP. The porous structure of the HS granules resulted in faster dissolution rates, which could be advantageous for drugs requiring immediate release.

Ultimately, the choice between the two technologies should be based on the specific needs of the formulation, such as desired release rate, scalability, and processing efficiency. *Read the Study*

READ THE STUDY

Knitting Drugs

Here's a more unusual type of dosage form: drug-loaded multifilament yarns. Created by HME, these yarns can then be processed into various shapes using a modified knitting machine, such as tubular structures or woven textiles, to deliver drugs in a controlled manner. Their large surface area and flexibility make them suitable for applications such as wound healing, implantable devices, or oral drug delivery systems. In the study below, researchers optimized the process with scalability in mind, successfully producing fibers containing polyvinyl alcohol and a model drug, fluorescein sodium, through a continuous melt extrusion process. The resulting fibers were smooth, uniform, and demonstrated consistent tensile strength, making them suitable for pharmaceutical applications.

Moving with the Times

Patient needs are changing, but small molecule drugs remain as important as ever. Here are some tips for development success.

Small molecules have many advantageous properties, including the ability to permeate via cell membranes to reach their intracellular targets – or not, in the case of the blood-brain barrier, where ingress may not be wanted.

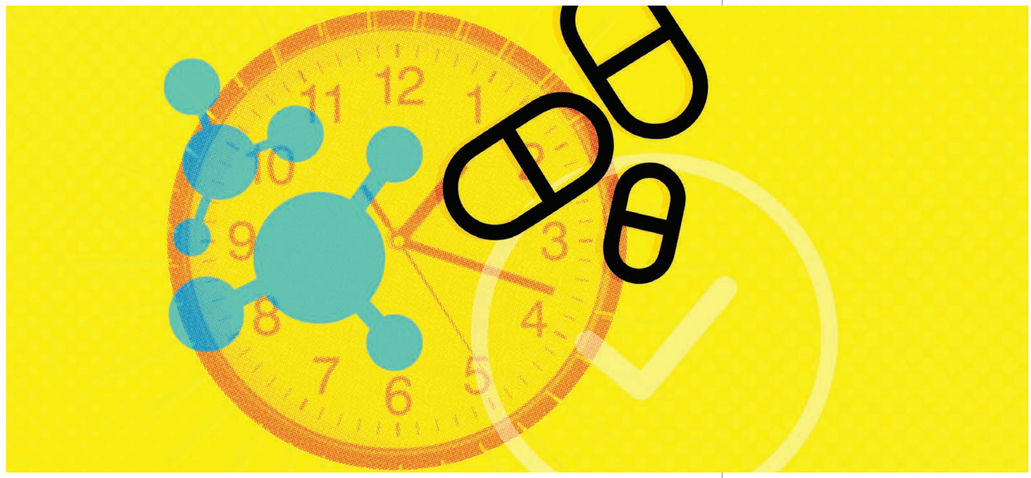
Since the early days of drug development, the needs of the population have changed. As the population ages, human behaviors and lifestyles change – which also affects the types of medicines in demand. Anti-infectives and cardiovascular drugs are obvious products that have improved health and longevity. However, living longer means that neurodegenerative conditions pose an increased burden that requires effective treatment (1). As the demands of a changing society evolve and continue to act as a driver for the identification of novel small molecules, the roles and diversity of the available medicines will also change.

Historically, it has been estimated that approximately 90 percent of all marketed drugs are represented by small molecules. Advances in the technologies available to scientists have seen a rise in the application of biologics, but technology is also impacting the small molecule space. The combined use of in silico screening tools and AI, for example, can create new leads in small molecules. Machine learning algorithms aim to significantly reduce the risk of failure and streamline the optimization process to provide stable, druggable target molecules that are sensible from both a synthetic and a toxicological perspective (3/4). Although machine learning is an exciting advancement in the complex process of developing new medicines, the need for the integration of more traditional medicinal chemistry expertise remains.

Over the past 20 years, there has been a shift in the demographic of those companies taking small molecules into later-stage clinical development. This was a journey undertaken predominantly by big pharmaceutical players, but the number of SMEs that hold on to their assets after phase I has grown. Although the risk of possible failure remains high, the rewards are significant.

Another trend has been a growth in the number of products on an accelerated development pathway, typically because of the unmet needs of a particular patient group. This accelerated trajectory poses a burden on those planning for success as a significant amount of data relating to manufacture, stability, solid form landscape, and formulation are required early in the development timeline to support safe and rapid progression.

Despite the integration of in silico modeling and AI approaches, there are increasing numbers of small molecules entering development that exhibit sub-optimal physicochemical characteristics, such as inadequate solubility or poor permeability. The effort involved in maintaining an appropriate level of efficacy for molecules that demonstrate such issues can be significant. A rather succinct representation of this trend was published in Molecular Pharmaceutics over a decade ago (5).



Just as medicinal chemists may use in silico screening and AI to aid in the design of new structures, the pharmaceutical chemist has access to AI and screening tools to help with the prediction of solvate formation, propensity toward polymorphism, and the likelihood of forming salt or cocrystal versions (6). AI and screening tools represent a growing part of the development toolbox and function to supplement the more traditional screening and manufacturing activities. Perhaps better put, they help streamline those experiments applied and validate the results obtained.

De-risking development

There is no one size fits all when it comes to development. Compounds should be developed on a material basis, as screening and selection should never be formulaic. The entire process must be both iterative and pragmatic. Having the ability to integrate the various aspects of pharmaceutical development, especially in the early phases, is ideal.

Given the pace of early-phase development and the challenging nature of many new chemical entities, having a team of synthetic chemists coordinating with solid state experts enables rapid progression. Taking the time to understand what is important from the beginning will also facilitate the construction of tailored programs. If this is combined with robust understanding and communication of what early formulation strategies might look like, a risk-mitigating development plan can be implemented.

One crucial benefit of integration is easy access to material. As a synthetic process is optimized, the impurity profile changes. If material behavior is brought to the forefront of the initial interactions between the chemist and the solid state scientist, early batches can be profiled with only a few milligrams cost in terms of spent API, forming the foundations of future development. Ideally, this work starts to build a data set that correlates solubility characteristics with solid form and impurity profiles. Solid form characterization normally includes (but is not limited to) crystallography and thermal properties, such as melting point and decomposition temperature.

For BCS class II and IV candidates, this solubility correlation can be of particular significance if an early amorphous batch was positioned toward the lower end of acceptable. Form change to a crystalline (or a more stable crystalline polymorph) would likely reduce efficacy and require a more complex formulation strategy or salt formation, if applicable.

Another benefit of integration is the opportunity to profile each stage of the synthetic process. For highly insoluble molecules, it is likely that, as you progress toward the final structure, solubility will drop. If this is combined with a propensity to polymorphism, control of the critical quality attributes (CQA) of intermediates, as well as the final product, can be more than problematic.

Understanding form change reduces the risk of failure at a later stage, when more is at stake from a production perspective. This issue is particularly evident during early phase batch isolation, when well-designed crystallizations are less common and precipitative methods are more often innocently applied before sufficient data is in hand to understand where additional resources and quality by design are required.

A pragmatic approach to development should enable choices from an early stage and answer the question: "Will a salt be required, or is size reduction the initial option ahead of more complex strategies?" These decisions are critical – and the integration of solid form with chemistry and early pre-formulation activities is a significant benefit to a risk-mitigating program.

Preformulation evaluations are vital where a molecule has a pKa profile that makes salt formation likely but not without challenge – the main risk being that of facile disproportionation back to the parent. Having a well-characterized batch, solubility data, and a pH solubility profile in aqueous, biorelevant, and common formulation solvent/excipients can make the choice of salt or parent less of a challenge and for very little material cost.

A useful reference to consider is that of Butler and Dressman (7), who created a Developability Classification System (DCS) for oral immediate-release compounds to address the question of what aspects of a molecule's performance characteristics would limit oral absorption. It can be used to help derive strategies for formulation and the identification of the CQAs of the drug substance that should be the target deliverables from the integrated solid form and chemical development process.

Small molecules continue to play a pivotal role in developing effective medicines for an aging population. Those molecules that are classified or predicted to sit within BCS class II and IV are of particular significance. However, realizing the benefits of integrating solid form and chemical development teams from an early phase, plus making use of in silico and AI technology, can provide a streamlined and risk-mitigated journey from the early phase to the clinic.

References Available Online

ABOUT THE AUTHOR

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Oligonucleotide & Peptide
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Biocatalysis
Biologics
Drug Product
Small Molecule

Nonprofit Model for Manufacturing

All companies claim to put patients first, but how true is that really when the corporate pharma business revolves around profits? Civica Rx is approaching generic drug manufacturing using a nonprofit model – and it's working. We get the story behind their facility in Petersburg.

Civica Rx was launched in 2018 as a nonprofit drug firm with a focus on essential generic medicines that were being under-delivered in the US market. The problem – in Civica's words: "Unfortunately, when a supplier is able to concentrate market power with [essential generic] drugs, they are able to wield an exorbitant amount of influence on the price."

The company was founded by several US health systems (Catholic Health Initiatives; now CommonSpirit Health, HCA Healthcare, Intermountain Healthcare, Mayo Clinic, Providence St. Joseph Health; now Providence, SSM Health, and Trinity Health) and philanthropic organizations (the Gary and Mary West Foundation, the Laura & John Arnold Foundation, and the Peterson Center on Healthcare). Martin Van Trieste, former chief quality officer at Amgen, came out of retirement to sign on as Civica's CEO – a role he took on with no compensation. At first, 14 generic medicines were identified by the company as being a priority.

Groninger nest filling line with SKAN isolator

Six years later, Civica is supplying nearly 80 different generic medicines to member hospitals – and has provided over 185 million doses to date. It has also opened its own manufacturing facility in Petersburg, Virginia, with the capacity to produce 90 million vials and 50 million pre-filled syringes of medicines every year. Crucially, a study published in NEJM Catalyst found that the company had been able to improve generic drug access through its unique model (1). Civica has also expanded its ambitions to new areas, such as insulin. In 2023, the state of California announced a 10-year agreement with Civica for the manufacture of "CalRx" insulin.

Jason Winfield, site director of engineering and technical services at Civica, thinks that much of the success comes from the company's can-do attitude and the lack of bureaucracy. "From the start, Martin made it our mission to do what's in the best interest of the patients. We continue that motto today. A lot of people are very engaged in our mission – there are a lot of good names on our executive team. As a nonprofit, we are able to come to work to help patients rather than earning extra dollars shareholders. Not having to go through third party distributors, distribution centers, and pharmacy managers has allowed us to get products to hospitals and patients at a reasonable cost."

Bringing it home

Van Trieste has now headed (back) to a well-deserved retirement, but Civica continues to grow. In March 2024, the company announced a collaboration with groninger and SKAN for new filling lines for their facility. Winfield told me more about the decision – and groninger and SKAN also gave their input.

"This was a really rewarding project to work on," says Matt Clifton, business development manager at groninger. "A lot of people are affected by drug shortages – including people I know personally – in the US. Civica has a real patient-centric focus. I always focus on getting the best machine for the client but this project felt close to the heart."

But why build your own facility – especially in an expensive Western country like the US?

According to Winfield, there has been a big focus for some time on bringing production closer to home. Indeed, the challenges of globalized supply chains is something that Van Trieste has previously discussed with The Medicine Maker. Winfield says, "A lot of pharmaceutical manufacturing takes place in India and China, but there have been widely publicized issues with sterile injectables. And although India is a great provider of APIs, they get a lot of their precursors from China. During the COVID-19 pandemic, materials stopped moving – and this hasn't ended with COVID; there are still ongoing challenges in supply chains."

Civica already had diversified suppliers of APIs from the start, prioritizing the US and Europe, but drug shortages and the industry's reliance on existing supply chains inspired the company to open the Petersburg plant. But even with its own manufacturing capacity, Civica doesn't put all of its eggs in one basket.

Groninger outer bag removal

"No more than 50 percent of our hospitals' demand comes from any one facility," says Winfield. "We've moved things around strategically; if there is an upset in any facility manufacturing our private-label drugs, we can source it from a different place. We have second and third line suppliers, but our Petersburg facility

is the ultimate control. We can manufacture our own medicines, across the spectrum of presentations, including vials, syringes, and cartridges. If any of our suppliers are unreliable or if there is a market shortage, we can quickly ramp up manufacturing at Petersburg. We've also got technologies at the plant that allow us to have quick transfer of products in and out."

Choosing equipment – and suppliers

Winfield got his role at Civica in 2020 – after the decision to build a facility had already been made. Two weeks before he was officially due to start his new role, he was brought in for critical decision making on what filling lines to purchase. An architect engineering general construction firm had proposed using filling lines from different vendors – as well as isolators from different vendors. "It didn't make sense to me. At the time [COVID], there were big challenges in resources – including people, materials and equipment. I wanted to standardize how we ran the facility," explains Winfield.

"Big challenges" is perhaps an understatement. During the pandemic, companies with large manufacturing contracts, such as for vaccines, were buying out equipment, consumables, and PPE. Many companies didn't yet know what their manufacturing processes were going to be so they hedged their bets. "Folks were buying every single-use mixer they could," says Winfield. "At one point, there was an 80-week lead time on single-use bags. After COVID, many items were thrown away because they were never used at the commercial scale. Regulators are now starting to look at manufacturing processes and controls – and encouraging companies to be more careful. For example, if you throw away 25 percent of your product because the containers aren't sealed, it's not okay to do that anymore because you are taking away consumables that could be used by someone with a more controlled process."

Winfield made calls to vendors he had worked with previously. After a bidding process, a deal for filling machines and isolators was agreed with groninger and SKAN. Although they are separate companies, only one contract was involved because the companies already have their own corporate partnership in place.

"SKAN has always focused on high quality containment," says SKAN's Marc Suter. "Back in the 1990s, the industry started thinking about separating the filling process and began looking into isolator technology. We were one of the first companies to build a commercial-scale filling isolator in Switzerland and with the industry heading this way it made sense to partner with a filling company. groninger is an expert with filling lines, and we had a similar mindset and similar leadership in technology, so we joined forces. Our goals are the same: to make reliable lines that are easy to handle for manufacturing products. Today, we collaborate together on a lot of different products."

The companies have their own separate products and different areas they want to grow in, but where there is crossover there is close collaboration. Nevertheless, they did need to reassure Civica that two companies were definitely better than one. Clifton says, "We've been working together for years. Many of the long-standing staff at each company are very familiar with one another. In many cases, machines are designed together. However, some people do have questions about how the process works when you have two separate companies involved. They may feel they have to send two purchase orders and worry about things falling through the cracks. But we trust one another enough that one company takes the lead and responsibility for the project. A turnkey approach makes it easier for the client."

Laura Sildon, Executive Director of the Civica Foundation with Brian & Joshua Davis, who live with Type 1 Diabetes

Talking about the Civica project, Suter adds: "Civica were using a greenfield site and it was a very ambitious project. As a vendor you see a lot of ambitious plans – and you also see plans that fail. How

Civica approached everything was amazing. Today, the facilities are up and running. Everything has been installed and qualified."

One of the main reasons that Civica went with well-known companies for process equipment was simple: you know what you're getting from an established name in the market because the reputation is clear. "Quality and reliability should always be at the forefront. Cheap capital ultimately leads to bad operations," says Winfield. "Saving a few million dollars on a piece of capital or other shortcut will cost you a lot more in unreliability and rejected batches in the future. Buying good quality, reliable equipment sets you up for a culture of success. Bad equipment also affects people – who wants to fail? I wouldn't hang around for long at a company that was taking shortcuts."

Shortcuts aren't just investing in the wrong equipment; many companies try to cut costs by getting more life out of older technologies as opposed to investing in something new. Networks that don't invest run the risk of requiring complete remediation in the future. "Unreliable lines also mean that you're asking staff to do more with less," adds Winfield. "This type of cultural pounding can really demoralize people over time."

The technology itself is only one aspect of selecting the right suppliers. You also need to consider how the vendor will support you. Suter says, "There are many vendors out there that will all give you a great sales pitch, but it comes down to trust. Before committing, you need to ask yourself: do I trust this partner? Can this partner get me to the finish line on time? The finish line is not equipment delivery; it is when everything is qualified and approved by the authorities."

"Find a vendor that will help you install and qualify the equipment – and do whatever else it takes to make the project a reality and maintain the equipment for its life cycle," adds Clifton. "Don't forget to check out your vendor's service capabilities because this is something companies often don't look at until they actually need it."

As well as technological support with servicing, Winfield explains that time zones are a common issue. "There are a lot of amazing technology companies in Europe, but when you're stateside you really need stateside support," he says. "If I have something that is broken, I need your help today. I can't wait 8 or 12 hours until the clock resets on the other side. Everything in this project from installation, to start up, commissioning, and so on was based out of the US."

Also think about the capabilities when times are rough. The COVID-19 pandemic has taught us all about preparing for unexpected disasters. "Since this project took place during the pandemic, travel was curtailed for many," said Suter. "Usually, vendors offer facility tours or site tours of other facilities using their technology, but we had to use virtual reality for mock ups and tailoring the line. This worked really well, but you have to have those capabilities in place and be adept at using them to make the project a success."

Civica has installed two full filling lines, which include four SKAN isolators (three as part of the filling lines and one as a material transfer isolator). One line is an integra line for bulk vials, and includes a tunnel and capper. The second line is for nested RTU containers. Both are flexible enough to cope with frequent format and product changes, and they have been designed to minimize product loss.

Docking a Beta Canister on an MTI (Material Transfer Isolator) from SKAN

"Because the isolators are all manufactured by SKAN, it allows me to reduce my overall spare parts in the facility because

there's a common spare part to each one," says Winfield. "I also have increased operational savings when it comes to HEPA certifications because I don't have to call in different vendors. This is also useful for audits and inspections. The true cost of ownership goes far beyond what the capital is."

Disrupting the status quo

From the very start of Civica, Clifton says that the company was unique. "A lot of people in the industry were watching them closely. They had smart people on the business side and significant industry leadership with a ton of manufacturing experience. However, I think there was some doubt early on about whether they could pull it off and if there would be any compromises on quality. But they've done it – their products are excellent and their facility is one of the best facilities I've visited. They use high-end solutions and they understand what they are doing. They are top tier in the industry."

"It's hard not to feel personally moved when you hear the story behind Civica," adds Suter. "Somebody needs to tackle drug shortages, but it may not be profitable to do so for some companies. The result is that patients have to go without their medicines. I'm proud to be part of a project that is trying to change that. Civica isn't just focused on generic drugs; they also have plans to make affordable insulin. I really wasn't aware of how difficult the situation is in the US compared with Europe, where I am based. If you follow through and stand with something, you can make changes in this industry. It's been amazing to watch what Civica has done."

In some ways, it can be said that Civica found success in its insulin plans before supplying a single vial. In 2022, Civica announced plans for an insulin with a price of $30 for a 10 mL vial, and $55 for a five pack of 3 mL – which includes the cost of distribution and pharmacy dispensing. In 2023, the price of insulin in the US was capped at $35 per month for Medicare Part D, as part of the US government's Inflation Reduction Act. Insulin makers Eli Lilly, Sanofi and Novo Nordisk have all since reduced their insulin prices. Although the Inflation Reduction Act will have played a large part in the companies' decisions, it's also likely that they were feeling pressure from Civica's 2022 announcement.

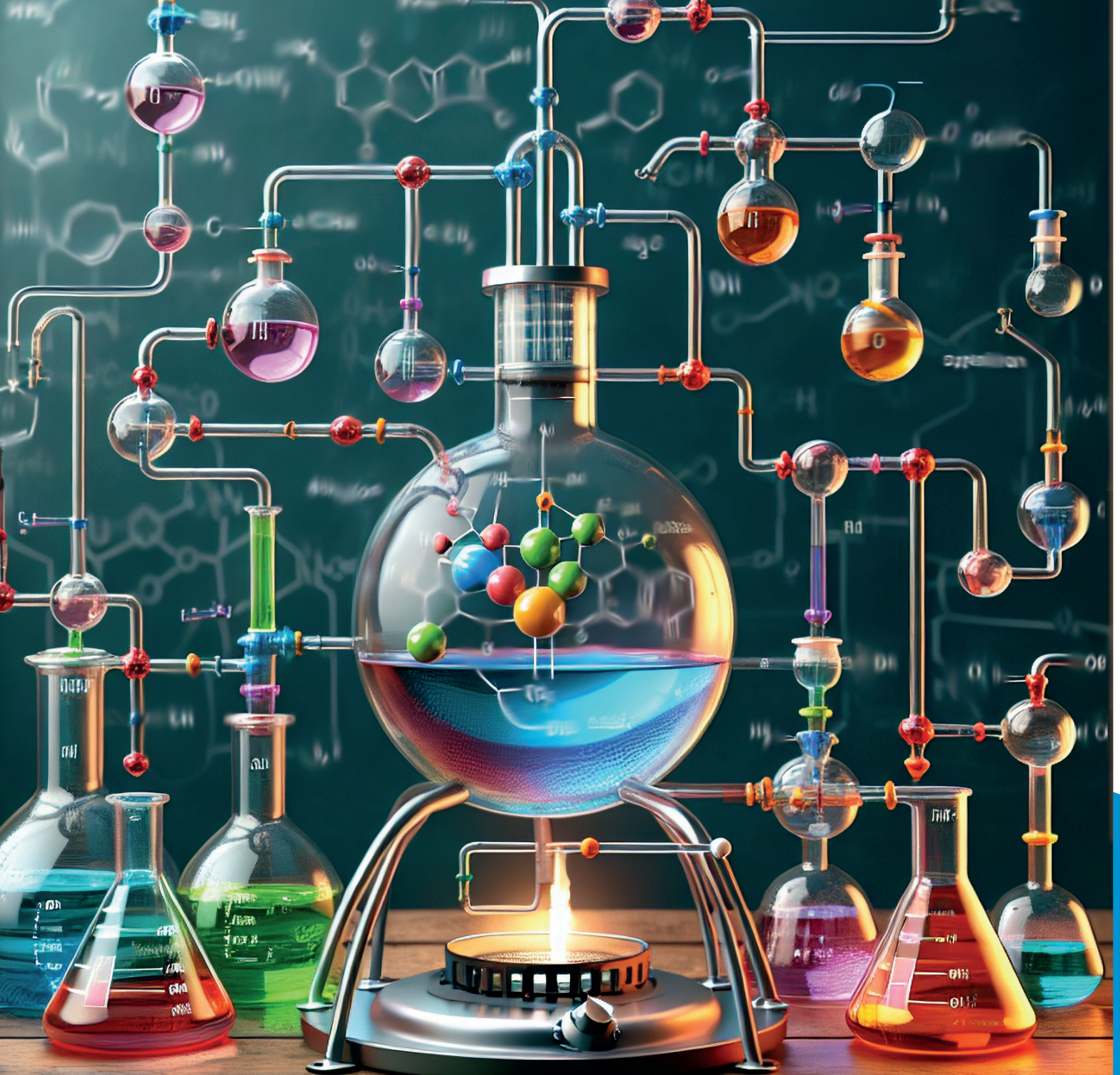
Winfield says, "Civica put out a public statement in 2022 and we meant it. I'm not an industry expert on pricing or pharmacies, but ultimately other countries are able to provide affordable insulin to their citizens so there's no reason why this can't be done in the US too. We're not naive to think that we will take over and supply the world with insulin from our Petersburg site, but we hope we can prove to the industry that it is possible to sell insulin for less – and that others will follow."

Companies need to make money and they should be allowed to do so. Not everyone can be a nonprofit (although more nonprofits may certainly benefit the world), but the industry must find a way to address drug shortages while balancing profits. Perhaps this means rethinking certain aspects of business. Civica will continue to pursue its unique model, but companies like groninger and SKAN also have a role to play.

Groninger nest filling line with SKAN isolator2

Clifton says, "It's our job to make the most efficient machines possible that can deliver the best products while helping to lower manufacturing costs. That has all come through innovation, which we don't want stifled by companies becoming unprofitable. I don't think the problem lies with the companies, but more with certain healthcare systems. Change is possible though – as Civica has shown."

Civica is supported by a number of partners and supporters. If you are interested in helping the cause, get in touch.



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Continuous Processing. Continuous Evolution

Continuous processing for small molecule products has been a hot topic for years, but where does the industry stand with it today? We speak with Doug Hausner, Senior Manager, Continuous Manufacturing, Oral Solid Dose, Pharma Services at Thermo Fisher Scientific, to find out.

What progress and success stories have been seen in continuous processing over the past several years?

Continuous processing got started commercially with oral solid dose about 10 years ago, and then a lot of the focus shifted toward using the approach for both small molecule drug substance and bioprocessing. Today, there are commercially approved continuous processes for both small and large molecules.

Oral solid dosage is still often the main modality when people refer to continuous manufacturing. There have been close to 20 oral solid dose new chemical entity (NCE) pharma products or similar OTC products approved for commercial manufacturing using continuous in the last decade. Approvals using the technology are poised for an uptick because, despite the initial wave of continuous manufacturing-based product approvals, companies bringing these products to market didn't integrate continuous manufacturing into development programs until after the initial wave of approvals. Since then, these products have been coming through pipelines being developed as continuous processes as opposed to being initially developed as a batch process and then converted to a continuous process in late-stage development.

Now that the approach has been demonstrated and de-risked, companies are revisiting their pipelines and putting programs on a pathway to use continuous manufacturing technology from the very start. As evidenced by activity among equipment vendors, there has been a significant amount of infrastructure put in place over the past few years, which will result in a number of those pipeline programs reaching the market soon.

And what have been the biggest lessons that the industry has learned?

The rate of adoption, even for technologies that provide significant benefit over the course of a product lifecycle, will be slow when the technology does not enable a new dosage form. This is certainly the case for small molecule continuous manufacturing. While the benefits of continuous are clear, the traditional approach for manufacturing these products is still readily available. This allows for delayed adoption, particularly among companies who are more conservative and looking for a highly de-risked entry point. A few years ago, there was a sentiment within the industry that the rate of adoption would increase significantly once CMOs started offering continuous manufacturing capabilities, but this has not been the case; the rate of adoption or conversion to the technology has remained at a similar level. This is because CMOs are required to demonstrate their capability with the technology beyond physical infrastructure by having commercially manufactured products – as a means of demonstrating that continuous manufacturing technology has been fully derisked. Although many large-scale innovators are already using continuous technology on their internal pipelines, many small and emerging companies are waiting for further adoption and carefully evaluating their pipelines to find their entry point.

This has not been the case for other technology adoptions, such as pre-filled syringes relative to vials. In that example, even though the product remains the same, the delivery has changed to provide benefits to the patient and improved margins to the manufacturer. Making the pivot to continuous manufacturing is more akin to the Industry 4.0 transition to electronic batch records and digital notebooks or, for an example outside of pharma, the transition to electric vehicles. The growth curve remains, but there is a delay relative to technology readiness because older technology remains viable and available.

What type of equipment is required for a continuous process and how does it differ from batch?

Much of the equipment used for continuous processing of small molecule drugs is not all that different than batch, with some components such as table presses changing very little when used in a continuous process. Typically, the equipment is smaller scale than its equivalent for batch process, specifically for the material handling and blending components.

The real difference with continuous manufacturing is that all equipment is connected and working in unison. This requires automation and software, so that the process can be properly coordinated and controlled as each step runs simultaneously. In this way, continuous versus batch processing is an Industry 4.0 modernization that brings real-time quality monitoring and control to the shop floor.

Moreso than the equipment itself, the use of modern automation, software and real-time sensors within the process makes a significant difference. This has led to greater generalization of the term "continuous processing" in recent years and use of "advanced manufacturing" in its place. While there is a clear difference between continuous and highly automated batch processes from an engineering perspective, from a practical and, more importantly, regulatory perspective, they fall under the same umbrella.

What are the biggest challenges?

The biggest challenge is, in some ways, related to one of the technology's primary benefits: its flexibility. Because of the flexibility in batch size and ability to go directly from clinical to commercial production without scale up, it is important for companies to determine what benefits they are seeking to obtain from the technology and how to achieve them with a specific approach. There is not a one-size-fits-all solution to leveraging the technology. Business cases can be made for its benefits in clinical, lack of scale up, speed to market, launch, initial market launch, ramp up or life cycle management. Therefore, it is important to understand how a continuous manufacturing strategy will address and enhance specific processing needs so that organizations can make the appropriate decisions for each of their programs.

What new innovations are drug manufacturers requesting when it comes to new equipment and technologies?

While not necessarily new, drug manufacturers often want to see that we have process analytical technology (PAT) capabilities, both in terms of people and equipment. In some cases, they may be looking for this as part of a real-time release approach, but there is a general expectation that this capability should support the control strategy for a continuous manufacturing product.

The skillset for PAT is unique and does not exist within all organizations. As a result, the pool of qualified personnel is limited and requires a focus on recruitment and retention. Just as important is a strong automation team. Pulling together the real-time data from multiple systems working together in a validated environment is a key element to achieving real-time quality control when leveraging continuous manufacturing and real-time release.

What advice and tips can you offer when it comes to implementing and running a continuous process?

Understanding the near- and long-term scope of your program relating to continuous manufacturing is key. Will the benefits be greater initially within development or early commercial, through transitional market growth or primarily through long-term cost of goods sold savings? Is leveraging the technology about enhanced quality assurance, nimbleness in the market, cost, or being an innovator?

Prioritizing the benefits you seek to gain from the technology will help shape the pathway your program should take, basing decision-making around how to maximize key benefits and the impact that has for the lifecycle.

What would you like to see change in the coming years?

With further adoption, continuous processing or approaches may be more broadly referred to as "advanced manufacturing." In that light, it would be great to see further reliance on what the technology enables in comparison to past approaches. Using highly automated systems with real-time quality control capabilities, we can speed development without additional risk to the commercial control strategy. The industry should revisit how we approach validation, filing, process improvement and more given the use of real-time process monitoring and control.

Where Have All the Drugs Gone?

Drug shortages are everywhere. We speak with Vimala Raghavendran, Vice President, Informatics Product Development at the US Pharmacopeia (USP) to get the full picture.

How bad is the drug shortage crisis?

Since 2019, the severity and length of shortages have increased. As of December 31, 2023, 125 total drug shortages were listed on the US FDA drug shortage database, affecting a variety of therapeutic classes. Our analysis using data from USP's Medicine Supply Map, a platform that uses artificial intelligence and predictive analytics to identify, characterize and predict risk in the complex medicine supply chain, also showed an increase in the average time duration of drug shortages, which was over three years in 2023, compared to two years in 2020. Persistence in drug shortages is caused by compounding economic forces and the market's inability to resolve these with traditional market economy responses.

What types of medicines are affected?

Although any medicine or therapeutic area can experience a drug shortage, some medicines are more at risk based on certain vulnerability factors. For example, in 2023, 53 percent of the drugs

in shortage were sterile injectables. The medicines in shortage cost 8.5 times less than those not in shortage ($46 versus $392), and over half of the injectables in shortage were priced at just under $5.

When looking at solid oral medications in shortage, which accounted for 32 percent of all drugs in shortage, we found that more than half of these medications cost less than $3. These low prices likely resulted in low margins for drug manufacturers, reducing the incentive for them to continue producing the medicine – along with a lack of incentive for manufacturers of these drugs to invest in next generation quality management systems – and may have contributed to their shortage.

What are the risk factors for a shortage?

There is no one cause of drug shortages; however, the leading and root cause of most drug shortages are unsustainably low prices. For example, data shows that lower-priced drugs – commonly generic medicines – have a higher likelihood of being in shortage because manufacturers lack incentives to continue producing these products. Findings from USP's Annual Drug Shortages Report show that there is a race to the bottom in pricing dynamics for generic medicines, which resulted in product discontinuations (mainly for low-priced generic solid oral medications) increasing by 40 percent from 2022 to 2023, from 100 drug products in 2022 to 140 in 2023.

Lower margins also undermine initiatives to ensure supply chain resiliency by limiting the ability of manufacturers to reinvest in manufacturing facility maintenance, manufacturing updates and quality assurance and management.

Aside from low prices, USP has identified three other risk factors associated with drug shortages:

- Geographic manufacturing concentration. Drugs that are made up of APIs and/or finished-dose products that are manufactured or produced in one or only few locations are more susceptible to shortages. Geographic concentration can also result in more significant impacts when a shortage does occur because there are limited options for sourcing/producing APIs or other materials.
- Manufacturing quality concerns. Facilities with a history of quality issues can predict increased vulnerabilities for medicines made there.
- Manufacturing complexity: Drugs with higher manufacturing complexity, such as sterile injectables, are more vulnerable to shortage. A need for dedicated lines for certain product categories (e.g., antibiotics such as amoxicillin) and/or complex chemical synthesis of the active ingredient can limit a manufacturer's ability to produce a drug in the case of supply chain disruption. The complexity of pharmaceutical formulations can be assessed using:
- dosage forms
- number of underlying ingredients and key starting materials
- expertise needed to synthesize the molecule
- storage requirements
- size and molecular structure of the API

Although there is no one-size-fits-all solution, short-term actions can be taken to reduce the risk of future shortages, while policymakers and industry regulators work on developing long-term solutions.

In the short term, manufacturers can continue to track and immediately report supply chain disruptions to the FDA to help regulatory agencies mitigate the impact of a disruption and reduce the risk of shortages. Having a strong understanding of the global supply chain and vulnerability factors using data can also better equip manufacturers to prevent fallout from drug shortages. In particular, there are data blind spots for key starting materials and excipients. Many supply chain risks associated with the key starting materials used to manufacture APIs are largely unknown because no single entity has a grasp on the sourcing [MM1] for these materials. Increased transparency into the volume and geographic location of API production would allow manufacturers to strengthen their ability to monitor their suppliers and understand how best to pivot when disruptions occur.

Going forward, policy adjustments and diversification of the geographic locations of manufacturing facilities are necessary. Policymakers and regulators from federal agencies, as well as non-governmental organizations, should develop safeguards that build on early warning capabilities, establish a vulnerable medicines list,

coordinate supply chain resilience and reliability efforts through payment and purchasing models that value and incentivize supply chain quality, strengthen the manufacturing capacity for drug products through the development and adoption of advanced manufacturing technologies, and align incentives to promote sustainable prices for generic medicines.

We need a fundamental shift in the market to realign supply and demand forces and create a predictable, sustainable, resilient supply chain that can reliably provide critical medicines to patients. Policymakers and public and private drug purchasers must value quality and resiliency through sustainable prices of drugs. This shift will also require us to broaden the geographic diversification of manufacturing sites and encourage domestic manufacturing of key critical drug components with pricing incentives that encourage utilization of excess domestic manufacturing capacity.

In addition to a marketplace shift, both governmental and non-governmental stakeholders must invest in early warning capabilities and utilize a vulnerable medicines list that highlights medicines most susceptible to shortages based on key risk factors to help provide insights that can inform policy and purchasing decisions.

Have there been any success stories in resolving issues?

Increased transparency, collaboration and new technologies have led to some progress when it comes to addressing drug shortages. We are encouraged that there seems to be recognition among policymakers that a fundamental shift is needed to make the market for generic drugs more sustainable. For example, the Senate Finance Committee's proposal to address shortages is one example of how policymakers are attempting to address these economic factors. Many of the concepts in the proposal align with USP's recommendations, but we would add three areas for consideration: identify risks, reward resilience, and incentivize modern manufacturing technologies.

There will continue to be a need in the near term for better tools to understand supply chain vulnerabilities and shortage risks, and ways to proactively intervene in a coordinated manner. Only by addressing both the short-term and long-term aspects of this issue will we be able to minimize the impacts of the ongoing drug shortage crisis.

What is the USP position on drug shortages?

Shortages are systemic and have long-lasting impacts on patients, health systems, and future innovation. Policymakers, regulators, industry, payors, health systems, and other stakeholders must act to identify and respond to the risks and vulnerabilities in the medicines supply chain to ensure patients have access to the therapies they need.

Actions should address both short-term and long-term needs and include risk mitigation strategies, public and private investment and partnerships, payment reform to reward reliability and manufacturing quality, coordination and accountability and policy reforms. Major areas include:

- Building early warning capabilities
- Establishing a vulnerable medicines list
- Coordinating supply chain resilience and reliability efforts
- Strengthening the manufacturing base for drug products
- Promoting sustainable prices for generic medicines by valuing supply chain resiliency

To advance the conversation on drug shortages to action, USP, ACS-CAN and more than a dozen other organizations have signed on to a Call-to-Action – a suite of options designed to urge US Congress to create meaningful reform to prevent and mitigate shortages – enabling patient access to a consistent supply of quality medicines. USP has also published several papers on topics related to supply chain resilience and remains engaged with decision-makers to advance solutions to end drug shortages.

Without significant market interventions, current drug shortage trends will likely continue or worsen.