Clinical Trial Supply Chain Management: Changing Without Delay

By Adam Runsdorf, WDPrx President

SUPPLY CHAIN OLYMPICS

Compare clinical trial supply chain management to an Olympic sport and ‘balance beam’ would be an appropriate choice. Successful trials demand a blend of costs and benefits to achieve desired results.

Effective clinical trial supply chains increase efficiency and reduce risk while remaining on budget. This task is challenging within conventional clinical trial environments. New technologies for trial management may create more difficulties navigating between ease of use and complex data collection and privacy issues. With a total of 282,127 clinical trial studies1 being conducted around the world as of August 21, 2018, quality control is another vital factor affecting patient safety.

Vigorous evaluation should be undertaken before, during and after clinical trial programs to address deficiencies thereby strengthening positive outcomes. This collaborative effort involves internal and external stakeholders in order to establish best practices.

Analyzing clinical trial supply chain performance may initially seem as complex as the actual trial. Logistics is becoming an increasingly vital component of trial management. One practical solution involves breaking down overall clinical trial design into separate areas of examination.

By breaking down supply chain management for clinical trials into representative parts, it is possible to create a continuous improvement loop that will reduce error repetition and incorporate innovation into future programs.

Three primary areas where logistics impacts the clinical trial supply chain are trial design, location strategy and regulatory compliance.

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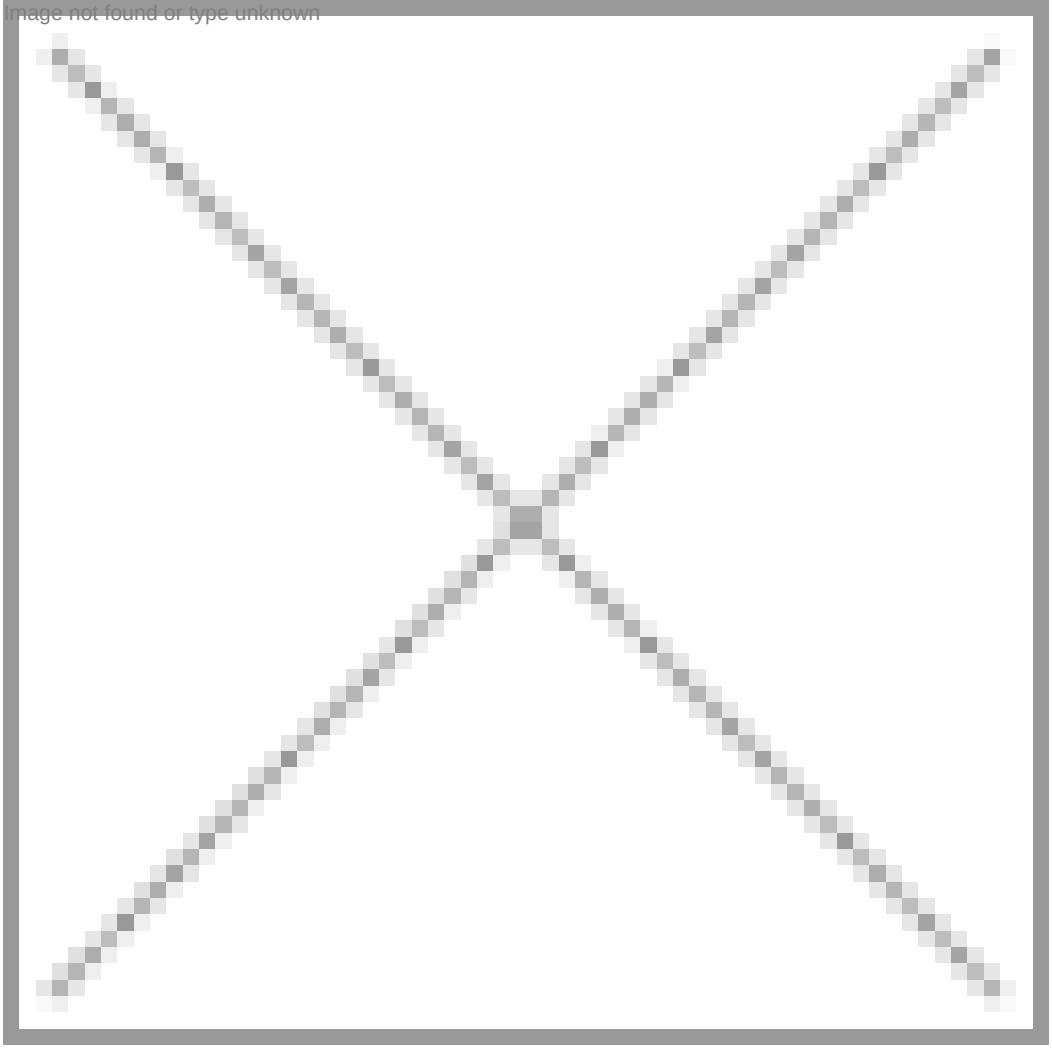


Collaboration between clinical and logistics teams early in the planning process improves successful outcomes.

TRIAL PLANNING AND DESIGN STRATEGY

Initial trial design incorporates planning logistics and also clinical and material requirements. Early-stage involvement from the supply chain team helps coordinate the overall program plan and can anticipate potential hurdles that might otherwise be overlooked. Materials required for the study are determined during trial protocol development.

When the quantity of sites and patients is determined by the clinical team, the scope of logistics requirements becomes clearer. Trade regulations are confirmed to streamline flow of trial materials. Data analysis and forecasting provides insights about patient enrollment helping assure trial success. Techniques to maximize patient engagement may involve specific logistics approaches. For example, the use of smartphones or other relevant technologies affects information flow and may also impact patient engagement.

Organizations that stress inclusive collaboration at the outset of clinical trial development help assure greater success compared with siloed operations. This is primarily because all interested parties – CMOs, laboratories, logistics specialists and CROs – contribute expertise at every stage of trial planning, generating shared responsibility for creating efficiencies that assure a successful outcome.

TIME, TOUCH AND TRAVEL

One of the key components of clinical trial supply chain logistics is to determine the correct balance between successful trial resolution and trial expenditures. Logistics professionals involved early in trial development work with stakeholders to manage three major cost factors: time, touch and travel. Budget is affected when any of these elements is altered.

For example, reducing shipping time increases cost. A 'touch' is defined as any contact that disrupts the direct flow of the medication from manufacturer to patient. A requirement for in-home supervision of patients for greater program control requires additional budget. Shortening the distance traveled for medication to reach patients may reduce expenses.

Other considerations affecting time, touch and travel for clinical trial design include stock management control, randomization protocols, results testing procedures and data recording and collection.

Logistics professionals involved early in the planning process streamline program costs while achieving desired clinical results.

MANAGING DELAYS

A common theme in all clinical trials is that delays are inevitable. Clinical trial planning attempts to reconcile clinical possibilities with economic realities. Delays in project flow at various stages must be anticipated in advance and incorporated into contingency plans. Unanticipated delays cause budgetary disruption that may impact outcomes.

ENROLLMENT HURDLES

A common source of delays are derived from patient enrollment and retention problems. Patient acquisition is a complex game of numbers. Initial patient pools are drastically reduced due to pre-screening failures and refusals to give consent for the trial. If the initial pool was large enough to generate the desired patient group, all trials suffer from post-enrollment attrition with patients who leave after acceptance into the program.

DELAYS AT THE DEPOT AND INVESTIGATION SITES

Delays at the depot or clinical site are another major cause of delays in trial implementation. Clinical trials are complex clinically and organizationally. Sound medical practice is often at the mercy of shoddy training or record-keeping. Teaching policies and procedures so they are performed consistently and correctly is a difficult task under ideal circumstances. A trend toward increasing the number of countries per study and expanding the quantity of investigative trial sites is leading to long investigative site initiation timelines and longer durations for data transmission and updates2.

Multiple sites, countries and languages magnify the problem. Clearly defined administrative procedures along with properly calibrated equipment reduces false starts and maintains budget integrity. Proper

management of the deposit/site network entails timely distribution of inventory data across the supply chain.

CUSTOMS BROKER BREAKDOWNS

The import brokerage function is an important aspect of the clinical trial supply chain that adds uncertainty and volatility often leading to delays with negative budget implications.

The global nature of clinical trial administration requires knowledge of an intricate and often arcane set of rules and regulations concerning movement of materials across and within geographic borders. Coupled with this reality is that trial sites may be in locations lacking modern infrastructure.

Complete import/export documentation ahead of time and secure permissions from all authorities prior to trial launch. Conducting simulations and modeling exercises also help identify problems for pre-emptive resolution.

Despite recognizing these challenges, a recent study3 reveals that 54% of clinical trial sponsors are 'very concerned or 'concerned' about the ability of import brokers to successfully achieve objectives. This may be a function of the growth in outsourcing all but core clinical services to outside parties. Courier services are the primary source for import brokerage services, removing this critical process from direct study sponsor control.

LESSONS IN DRUG DEVELOPMENT

Unique challenges are associated with the drug development process for early stage clinical trials. Problems arise when early stage formulation begins too late after other components of the clinical trial plan have been implemented. To counter this situation, begin API development for production one year before trial launch4.

In late stage trials, sufficient time must be allocated to refine the active ingredient and modify components and production techniques to enable large-scale manufacturing. Failure to anticipate the steps necessary to scale up from trial quantities to commercial production could cause a significant financial burden.

SHIP SHIP DELAY!

The clinical trial supply chain addresses similar challenges with additional unique considerations faced by all businesses caused by shipping delays. Clinical trial clinicians are extremely sensitive to lost or mishandled shipments due to the nature of the package contents. Each shipment contains samples that are difficult or impossible to replace. Special circumstances exist for samples that require temperature regulated environments.

Sample viability of cellular structures relies on transport within specific temperature and seismic vibration ranges. Variation from established guidelines may render samples unacceptable for study results. Verification of temperature maintenance within acceptable range must also be monitored throughout the

duration of shipment to assure sample viability.

Selecting a reliable transportation provider is essential for successful trial outcomes. This function is becoming more significant as the clinical trial supply chain expands into multiple countries with differing abilities to provide the specialized transportation modes required for modern trials.

LOCATION STRATEGY

Budget considerations for many trials require establishing locations in several countries to satisfy patient recruitment goals as efficiently as possible. Considerations affecting international investigation site selection include regulatory burden, financial issues, study drug accessibility, data quality and monitoring, transportation and training.

According to the National Institutes of Health5, Over half (54%) of registered clinical studies in the world as of August 23, 2018 occur only outside the United States or combine sites within and outside the U.S. Studies contained within the United States account for 35% of the total study quantity.

The dispersion of sites requires increased vigilance, effort and risk to record data accurately and in a timely manner. A majority of clinical trial sponsors in a recent poll6 selected 'challenging' to describe logistics issues between depot and clinical sites in four of six world regions: South America, Central America, Asia and Eastern Europe.

The main location-based issues concerning supply chain logistics involve regulatory procedures, drug access and transportation.

REGULATORY FACTORS

Any study with human subjects requires regulatory approvals prior to patient recruitment. Regulations vary by country and affect authorization to conduct the study as well as movement of samples within and outside national borders. Trials originating in the United States must submit a list for approval to the U.S. Department of State of all foreign nations with investigational sites.

The optimal time to resolve issues involving international locations is during the initial study planning stage as it may take a considerable length of time for application and approval processes to be completed for multiple country locations. This process may also need to be conducted in several different languages.

Without precise record-keeping and follow-up at this early phase, more costly delays further into the program can be expected. Thorough research must be conducted to assure study approvals for import permits, licenses, special packaging and labeling requirements, customs valuation regulations and other trade-specific agreements and protocols.

STUDY DRUG ACCESS

Clinical trial requirements must be realized with close coordination of the logistics team. For example, a drug used for a trial may not be authorized for use in all countries selected as investigation sites. The drug or equivalent formulation may need to be locally sourced requiring further training and dispensing protocols.

Although international locations enable trial requirements to be satisfied quickly, these advantages may be lost if regulations for specific countries are overlooked. For instance, import requirements may affect the randomization sequence for international trial participants.

TRANSPORTATION MANAGEMENT

Geographic diversity adds to the transportation complexity of the clinical trial supply chain.

Multiple transportation partners are required for a successful trial outcome. The quantity and type of transportation partners may vary within different countries in order to maintain regulatory and safety requirements. The logistics team evaluates potential transportation partners according to their ability to function efficiently within the requirements for each specific trial. Transportation logistics solutions may involve a combination of outside couriers, customs brokers and internal capabilities.

With multiple international locations, ‘on-the-ground’ expertise is preferred to navigate local transportation issues that often arise unexpectedly and that may change without notice. Correct documentation, travel time within and between countries, security protocols, labeling, packaging and monitoring requirements to maintain sample viability in transit are key transportation considerations for clinical trials.

COMPLIANCE STRATEGY

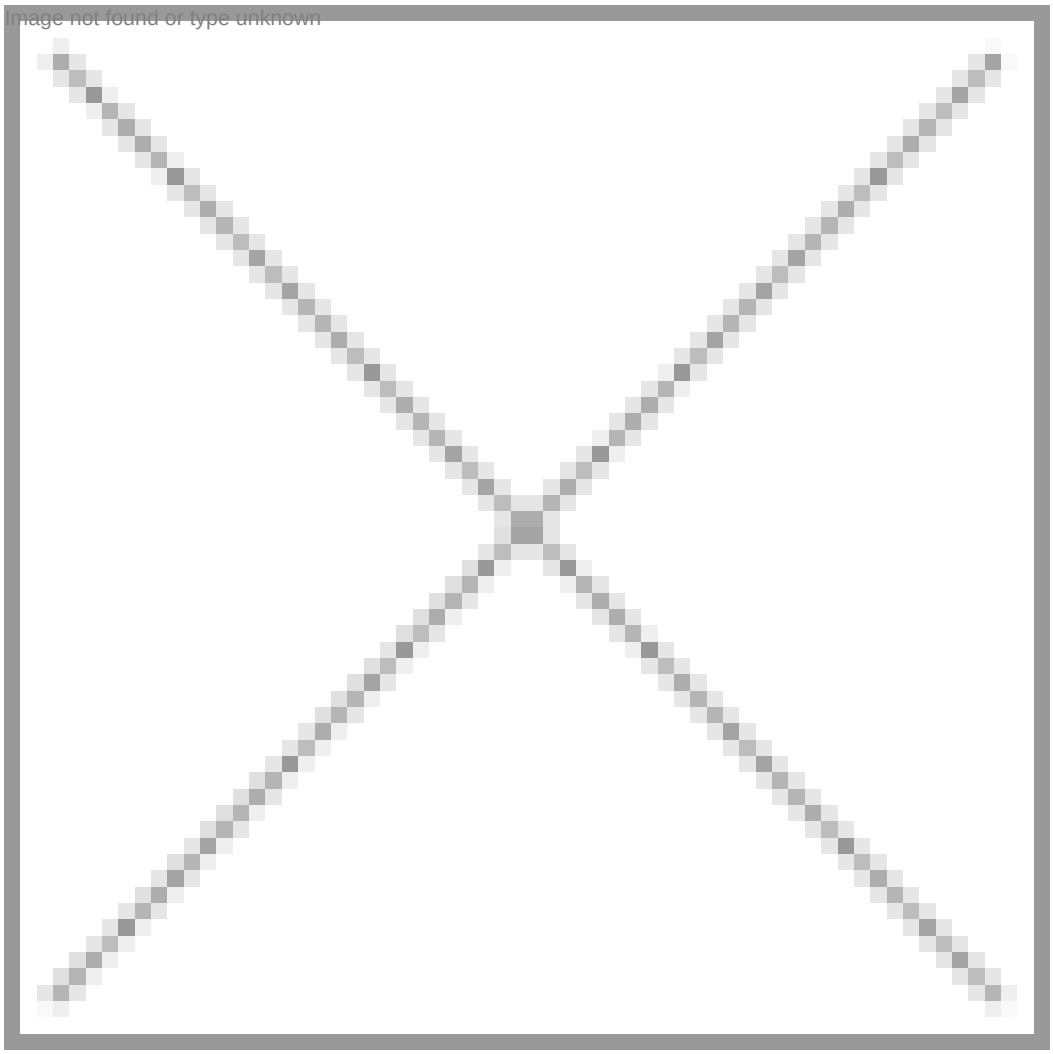
Due to the biological nature of clinical trial shipments, their transport is highly regulated. Rules for shipping diagnostic specimens change regularly affecting documentation requirements that vary internationally and at times may differ within areas of a single nation. The selection of an experienced transportation provider may save costs by developing optimal routes that shorten transit duration.

PACKAGING

Security of samples must be prioritized in every trial location but this function becomes more complicated when investigation sites are in locations with weak infrastructure or equipment to maintain study requirements. Effective security of clinical trial materials in transit is dependant on the nature of specimens and packaging. Ambient specimens may require a specific maximum duration for their transport. Clinical specimens must be handled with more urgency due to the need for a temperature regulated environment which may stipulate a refrigerated (2-8 degrees Celsius) or frozen (-78.5 degrees Celsius) state.

Logistics members of the study planning team will determine the safest, most efficient packaging option for transport based on distance and time and package contents. For cold chain solutions, phase-change, active and passive shipping systems are among potential options. Depending on study requirements, shipper

validation with documentation may be advised.



Correct packaging helps assure integrity of clinical trial sample contents and minimizes damage in transport between investigation site and hub.

DATA ANALYSIS

Maintaining accurate record-keeping of materials in transit demands constant monitoring. Temperature excursions can invalidate samples and data. When studies are conducted in various parts of the world where seasonal temperature shifts may vary widely, the planning team should evaluate the costs and benefits of temperature monitoring on some or all shipments based on time of year, travel time, mode of transport and location.

LABORATORY LOGISTICS

The logistics pipeline for clinical trial management increasingly relies on the location and quantity of laboratories to analyze samples received from investigation sites. A central hub for analysis of received samples from multiple investigation sites may simplify transit logistics and training requirements. However, creating an integrated network of strategically located laboratories may reduce processing time, minimize potential for temperature excursions and reduce transportation costs by increasing road travel compared with air travel.

THE NEW NORMAL: DIRECT-TO-PATIENT

The conventional clinical trial supply chain is being disrupted by direct-to-patient distribution and related uses of widely available technology to transmit data to trial sponsors for analysis. According to a recent report,7 24% of trial sponsors report utilizing direct-to-patient distribution.

Virtual trials affect logistics decisions about patient acquisition and enrollment, patient administration of the sample drug, data transmission, transportation, study duration and other factors. The potential benefit of virtual trials focuses on reducing bottlenecks that negatively affect traditional trials structure.

For example, patients in virtual trials may be solicited online, enabling a faster method to pinpoint appropriate candidates from a wider population compared with traditional advertising methods where potential patients must show up to be properly screened. Virtual trial patients administer the treatment themselves.

Program adherence is supported by video-chats with trained personnel at regular intervals. Many transportation related issues may be minimized as more patients with more diverse backgrounds may be able to be secured in a more limited geographic area. Proprietary applications downloaded by smartphones may gather and transmit data to a centralized evaluation site for near real-time analysis.

These developments may help to shorten trial duration with commensurate cost reductions. Further transportation innovations including Uber Health8 may benefit traditional and virtual trial logistics by bringing patients and trial materials closer together.

CLOSING ARGUMENT

The clinical trial supply chain resembles a set of dominos organized in a complicated pattern where the first one to fall triggers subsequent pieces which move at exactly the correct moment in an uninterrupted path to create a desired design.

The logistics process enables the dominos to reach the finish. Proactive forecasting of potential issues involving planning, supplies, timing and delays, geography and lab logistics help assure smooth progress. Virtual trials show significant promise by conquering some problem areas in certain types of conventional trials.

The march to create more streamlined clinical trials is increasing the importance of supply chain logistics as an integral component for successful outcomes.

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Rising CMO Business Fortunes, by Adam Runsdorf

The current business climate favors forward-thinking contract manufacturing organizations that improve ties with manufacturers for services across the entire value chain, writes WDPrx President Adam Runsdorf in the May 2018 issue of Contract Pharma magazine.

Read the article on the Contract Pharma site .

The relationship of pharmaceutical manufacturers with contract manufacturing organizations (CMO) and contract development and manufacturing organizations (CDMO) is increasingly evolving from one-dimensional product outsourcing into a broad partnership model involving several aspects of development, testing, production and research.

Several developments occurring from within and outside the pharmaceutical industry are converging to promote a favorable business climate for progressive CMO firms that align their corporate strategies to take advantage of the signs and signals occurring around them.

Reasons To Be Cheerful: Two Parts

The growth of the global CMO industry is most clearly observed in the projected increase in revenues, expected to grow from $62 billion in 2016 to $83.9 billion in 2020.

Two sets of factors are shaping the promising fortunes of the outsourced manufacturing business: external factors that are occurring outside the direct control of the CMO industry involve financial, economic, structural and regulatory developments; internal factors are driven from within the industry including continuing breakthroughs in large- and small-molecule formulations, an emphasis on services across the value chain, capital investments in technology and persistent cost pressures on manufacturers.

Consistent quality and reliability are common threads woven through all external and internal factors that manufacturers demand as important measures of project success.

A Little History

The origins of the CMO industry were brought about by lack of production capacity at manufacturer facilities. The relationship began with contractual agreements to produce active pharmaceutical ingredients (API) or finished dosage forms (FDF). The model operated essentially unchanged until internal and external forces set the stage for growth.

Dedicated CMO firms as we know them today began operating around 1996 and were dominated by companies in Europe. Prior to this time, pharmaceutical manufacturers maintained loosely defined ‘gentlemen’s agreements’ to produce chemicals and API for each other in order to discourage competition.

The North American Free Trade Agreement (NAFTA) adopted in 1994 and other similar agreements around the same time opened the floodgates for the CMO industry to derive benefits working with international manufacturers sharing technology across borders.

The Trans-Pacific Partnership (TPP) trade agreement being negotiated without the United States includes 12 countries representing 40% of the global economy. If we stay on the sidelines, U.S. biopharma companies may be negatively impacted by the agreement concerning intellectual property protections.

Biopharma manufacturers based in the U.S. are protected from biosimilar competition for 12 years. Any data collected from clinical trials and other R&D initiatives remain the exclusive property of the manufacturer and cannot be utilized by prospective copy-cat organizations.

The U.S. was the strongest voice in favor of maintaining multi-year protections for data exclusivity. Now that the U.S. is no longer at the negotiating table, the other nations may shorten or eliminate these provisions, increasing competition in the biopharma industry with global repercussions.

Then came an influx of bio-pharmaceutical companies backed by venture capital funding. These companies focused on securing a molecule for promising therapeutic value and relied on outsourcing for most business activities, which in turn supported the rise of the contract research organization (CRO).

These forces built the solid foundation for the fertile business landscape that exists today for the CMO industry.

Dividing The Pie

Currently the majority of revenue in the CMO sector is derived from API manufacture followed by finished dosage forms and then drug and process development including laboratory work. Business from all categories is expected to rise with API maintaining the prominent revenue position in future.

Although the largest slice of the CMO revenue pie is generated by API, the fastest growth vehicle in the international CMO market is finished dosage form manufacturing, forecasted at a 6.9% CAGR through 2026 due mainly to strength of oncology and immunology therapies.

Closely related to the CMO function are CROs, which provide drug discovery and critical data support as well as contract packaging organizations (CPO) for secondary packaging and labeling. Clearly defined lines of responsibility are now blurring.

External Factors Driving CMO Business

The pharmaceutical industry is profoundly affected by external forces that have a direct impact on

profitability. All businesses must allow for unforeseen or unexpected circumstances that might disrupt operations. But pharmaceutical manufacturers are in the midst of several developments occurring simultaneously. Leadership of these companies must combine sound financial management with forward-looking strategies in order to prosper.

Key external challenges for pharmaceutical manufacturers involve more stringent government and regulatory compliance, industry consolidation, continued erosion of traditional corporate structures and economic pressures cutting profit margins.

The consensus solution among manufacturers to most of these external considerations is their increased reliance on contract manufacturers.

Regulatory Requirements

Government and other authorities require that manufacturers adhere to stringent standards for regulatory compliance. In some cases, scientific advances in the medical field have occurred faster than the government's ability to keep current with relevant testing to assure patient safety.

For example, a new requirement of the United States Pharmacopeial Convention (USP), enforced as of January 2018, sets new analytical and validation requirements for measuring elemental impurities. This new standard replaces a test for heavy metals that was accepted for almost a century.

Another example of government compliance: the U.S. Food and Drug Administration (FDA) is charged with implementing Federal laws assuring the safety of medications. The most recent FDA Guidance concerning analytical testing requires greater details about drugs and process development than previously published.

Adding to the administrative obligations, the Drug Supply Chain Security Act (DSCSA) passed into law in by Congress in 2013 imposes many new requirements on manufacturers designed to reduce drug diversion and minimize counterfeit products.

Manufacturers must make significant investments in internal personnel, external consultants, facilities, equipment and machinery to maintain compliance. The development of more complex molecules and the increasingly sophisticated infrastructure required to successfully process them are prompting corporate leaders to constantly re-examine the costs and benefits of maintaining in-house capabilities to fulfill this purpose.

Outsourcing regulatory compliance responsibilities to CMO partners is an increasingly popular solution.

Industry Consolidation and Rationalization

Global investment firms search for industries with a healthy number of profitable players, a diverse supply chain as well as a burgeoning niche of smaller companies exploiting new technologies. The pharmaceutical industry fits this strategy which has historically resulted in industry consolidation, enabling the acquiring company to create internal efficiencies, expand product offerings and incorporate new technologies that

would be more expensive to develop from scratch.

Although 2017 saw fewer mergers compared with preceding years, there were many significant transactions.

The takeover of Patheon by Thermo Fisher Scientific in May 2017 was valued at $7.2 billion. Johnson & Johnson acquired Actelion, a biopharma company based in Switzerland, for $30 billion and Gilead paid $11.9 billion for the privilege of swallowing Kite Pharma.

These examples demonstrate the desire for companies to create a ‘one-stop-shop’ for pharmaceutical outsourcing with expertise along the entire supply chain from drug discovery, development, API production, formulation and packaging.

Industry consolidation is followed by rationalization of resources to streamline administration and increase profitability of the combined venture. For example, a manufacturer with ten CMO relationships taken over by a manufacturer with the same number of CMO vendors may produce an unwieldy total of 20 possible CMO firms under the same corporate umbrella.

Decisions are made about how best to reallocate the catalog of outsourced products to the smallest quantity of their best-performing CMO partners. This process results in more business spread out among fewer CMO firms, increasing business volume for the most highly regarded partners.

Faster Approval Process

A faster approval process for drug approvals also contributes to more business for the CMO industry.

President Trump made quicker drug approval an issue in the Presidential election. Dr. Scott Gottlieb, Commissioner of the FDA, is capitalizing on recent statements and the passage of the Advancing Breakthrough Therapies for Patients Act of 2012. The Act authorized a new abbreviated approval process for breakthrough therapy drugs to “expedite the development and review of drugs which may demonstrate substantial improvement over available therapy,” according to the FDA.

According to the FDA Center for Drug Evaluation and Research (CDER), 46 drugs were approved in 2017 compared with 22 in 2016, 45 in 2015 and 41 in 2014, the most since 1996.

The Commissioner, in written testimony from April 2018 to the House Appropriations subcommittee, further committed to compacting the approval process when he stated is agency will “sharply increase” release of guidance documents designed to assist manufacturers to derive new treatments.

Summary

Outside forces are sometimes detrimental to business. Weather-related disasters including the destructive hurricane season of 2017 create significant damage with little warning and with long-lasting effects.

At other times, outside forces combine to boost business success. Several external circumstances in government and in business are propelling the CMO industry to greater opportunities. Some of the key

factors responsible for this business upswing are increasingly stringent regulatory and compliance requirements, financial opportunities creating compelling logic for pharmaceutical industry consolidation and the creation of more efficient drug approval processes resulting in more manufacturing resources being devoted to bringing new products to market.

Internal Factors Driving CMO Business

Internal factors positively affecting the CMO industry are issues within the direct control of pharmaceutical manufacturers. These include technological advancements in processes and equipment, additional service offerings and efficiency enhancements. Unlike external forces, internal factors facilitate long-term planning and they are often developed in response to external factors.

Virtual Reality

Virtual pharma companies reduce fixed costs to a minimum by outsourcing some or most marketing and manufacturing activities to businesses including CMO firms. Typically, virtual pharma companies may employ quality and regulatory professionals and financial and commercial staff. The rise in virtual pharma benefits the CMO industry in several ways.

First, the investor community has pivoted from focusing on company assets to concentrating on project ownership. The lion’s share of investment funds in virtual operations are available for CMO firms to help the project succeed.

Second, the rise of the virtual business model shifts more responsibility to the CMO to perform more work compared with a conventional manufacturer. For example, laboratory work including analytical testing and additional services, plus clinical trial management provide expanded opportunities for the CMO to develop deep, long-term relationships with virtual manufacturers.

Cost Pressures Create Bold CMO Initiatives

The search for profits in a world of shrinking margins is not unique to pharmaceutical manufacturers. However, there are many issues weighing on industry profitability that favor entrepreneurial CMO leaders.

Pharmaceutical manufacturers face stiff challenges to success including price pressures, raw materials shortages, government oversight, litigation and insurance liabilities. In a nod to the virtual model, the solution for many conventional manufacturers is to reduce operational expenses to achieve greater profit potential. Focusing on core capabilities, primarily marketing, research and development, necessitates the downsizing of internal manufacturing capabilities at traditional manufacturers to trusted CMO firms.

A related development spurring transition to CMO operations is high capital expenditures required for equipment and facilities to meet testing and manufacturing requirements for large molecule APIs, high-potency APIs, biopharmaceuticals and other new molecules. As an example, expensive new high-resolution accurate-mass instruments and other technologies allow for the necessary testing and measurement of biologics. Existing testing equipment may not be able to be upgraded to new standards.

Conventional manufacturers that have previously spent large sums to upgrade facilities and build new infrastructure based on finite projects or over-enthusiastic sales forecasts are more reticent to make those investments themselves. Entrepreneurial CMO companies offer a solution for risk-averse manufacturers by committing to absorb capital costs up front for new production capacity, strengthening the business relationship with priority manufacturers over a longer contract term. This includes increasing capacity for production of highly potent APIs (HPAPIs) to satisfy increased demand for biologics.

Ultimately, prudent reliance on reputable CMOs returns additional benefits to traditional manufacturers including a stronger risk management position by producing product at multiple external sites and also reducing potential shortages with advance preparation for manufacturing drugs in short supply at multiple CMO facilities.

Continuous Manufacturing

Harnessing technology is enabling CMO firms to increase revenues with more cost-effective alternatives to current production methods. To further improve the existing efficiencies for manufacturers, more CMO firms are investing heavily in continuous manufacturing methods in addition to conventional batch processing methods.

Compared with batch processing, which creates a finished dosage form (FDF) after preliminary phases are performed by multiple parties all converging at the production line, continuous manufacturing involves a single end-to-end production line beginning with the raw materials and ending with a final product or packaged unit ready for sale.

Batch processing is better suited for smaller runs with multiple products, while continuous manufacturing is designed for production of a specific drug. Compared with batch processing, continuous manufacturing increases speed to market, reduces risk because fewer people from fewer facilities are involved in the manufacturing process and requires a smaller footprint.

With continuous manufacturing, quality assurance protocols must be adjusted to consistently test and monitor the production line. Progressive CMOs are transitioning to automated testing solutions to meet the requirements of these new production methods.

Arriving Early and Staying Late

To spur growth, the CMO industry is taking on capital projects and investing in new technology to share risk with manufacturers. The outcome of these strategies creates a mutual dependence for CMO and client that

helps assure long-term and profitable relationships.

As manufacturers shed non-core business practices, preferred CMO firms take on responsibilities at the earliest stages of the chain that may begin with formulation development and pre-clinical studies, then move on to main business lines of drug development, API production and formulation. As industry consolidation continues, efficiencies may be found in the same CMO becoming involved with end-stage operations that may include packaging responsibilities.

The results include stronger partnerships and increased involvement between CMO and manufacturer that benefit both parties.

Conclusion

Developments within the pharmaceutical industry are creating a favorable environment for CMO growth. The continued popularity of the virtual pharma business model, cost pressures on conventional manufacturers, the ascendency of continuous manufacturing and the efficiencies gained from relying on CMO partners at every stage of the value chain, all point to continued prosperity.

External factors outside the industry bolster the optimistic outlook. The challenge of adhering to changing and expanding regulatory requirements, disruptive M&A activity from global financial interests and the accelerated pace of drug development and approval all work in favor of broadening ties between manufacturers and the CMO industry.

One foreseeable challenge to future growth concerns global biopharma companies that are building their own infrastructure to produce their own technologically advanced formulations. New drugs often are produced in very small quantities as specialty pharmaceuticals to treat specific rare conditions. The high profit margins that are realized from these therapies provide justification for these manufacturers to control production internally.

Another situation with potential effects on future business is the outcome of the Trans-Pacific Partnership (TPP) negotiations, which may jeopardize U.S. interests related to intellectual property rights concerning data collection and results for pharmaceutical development.

Despite these potential pitfalls, the outlook remains positive for continued rise in business performance for progressive contract manufacturers.

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Adam Runsdorf is President of WDPrx – Woodfield Pharmaceutical, LLC, which specializes in the manufacture and production of non-sterile liquids, gels, semi-solids and suspensions for prescription and OTC products. The on-site laboratory conducts all QA and micro testing and also manages full technology transfer. A complete range of modern equipment supports multiple batch quantities from clinical trial samples to full commercial production. Packaging options include a wide range of plastic and glass bottles and jars, nasal spray devices, metal and laminate tubes.

Quality Factors Influencing Semi-Solid Manufacturing

This story appears in the January 2018 issue of Contract Pharma magazine. Read it *here.*

QUALITY FACTORS INFLUENCING SEMI-SOLID MANUFACTURING

Kalpen Patel, Research and Development Manager, WDPrx
Angela Holley, Business Development Director, WDPrx

Although the name suggests otherwise, manufacturing semi-solid pharmaceutical drug products cannot be done ‘half-way.’ The making of semi-solid dosage forms, including pastes, ointments, gels and creams, requires specialized production techniques to assure high-quality results.

TRAITS OF QUALITY SEMI-SOLIDS

Several characteristics define the quality of semi-solid pharmaceuticals. Under cGMP compliant manufacturing and production conditions, semi-solid pharmaceutical drug products are generally smooth to the touch. They minimize dehydration, grittiness, and are cosmetically elegant. Their application does not irritate the skin and offers a pleasant scent. They also apply easily to the affected area with the appropriate use of plastic or aluminum tubes and other unique delivery mechanisms.

Poorly manufactured semi-solids may produce undesirable results that affect patient outcomes.

Several domestic and international standards have been adopted to create efficiencies in the manufacturing process including QbD (Quality by Design), DoE (statistical Design of Experiments) and FMEA (Failure Mode and Effects Analysis) to mitigate risk.

Producing quality semi-solids literally boils down to five key physical characteristics: homogeneity, particle distribution, spreadability, grittiness and use of surfactants. If one element fails, then the entire process breaks down. Each element must be closely monitored from beginning to end and after sale to assure patients receive the correct medication in the specified concentration throughout the life of the product.

PHYSICAL PROPERTIES AFFECTING QUALITY

HOMOGENEITY – Homogeneity is the state of being all of one kind.

The manufacturing process for creams involves two separate phases: an oil phase and a water phase. The degree to which these two phases are properly treated is the key element of quality semi-solid manufacturing.

For manufacturing semi-solids, homogeneity refers to the proportionate distribution of ingredients. Unlike liquid medications, proper homogeneity must exist within the large vessels used in the manufacturing process as well as within each individual tube and jar of product marked for commercial sale. The distribution of API and other ingredients must be uniform in all container closure systems. For example, the same proportional distribution of medication must exist in a 2,000 gallon tank and also within a 1.75 ounce tube.

A faulty homogenization process may result in significant deficiencies in semi-solid quality. Poor homogenization may create lumpiness or globules due to insufficient or incomplete mixing of oil and water phases. This reduces the patient experience with the product and can create significant challenges during product application. Finally, irregular amounts of the API will be distributed on affected areas producing less than optimal effectiveness.

Another significant problem area that occurs in the manufacturing process is flow restriction where material gathers together in a vessel and resists homogenization. This can be eliminated with proper equipment when correctly used.

Proper homogeneity produces even distribution of medication in ointments, gels and creams.

PARTICLE DISTRIBUTION – Proper distribution of molecules affects formulations in which material is not soluble including ointments and pastes.

Particle size, distribution and shape are important properties of the finished product and can significantly affect stability, appearance, usability and performance.

The need to consistently recreate uniform particle sizing techniques is growing to meet demand for newly developed active pharmaceutical ingredients with poor aqueous solubility well-suited for semi-solid dosage forms.

SPREADABILITY – The degree of spreadability is an important factor in determining therapeutic value of a semi-solid drug product. Spreadability for semi-solid dosage forms describes the action of a product as it is applied to the skin or other surfaces.

Product spreadability determines the proper distribution of the drug on the target area, plays a role in creating a positive patient experience with the product and affects how the product is removed from the primary package.

Factors known to determine desirable spreadability are temperature, particle distribution and rate of flow from the primary package.

When felt in hand, a quality spreadable product should have sufficient viscosity while enabling optimal spreadability. For example, a semi-solid product with the consistency of honey has viscosity however spreads too rapidly, producing undesirable dripping upon application. Similarly, wax when heated or cooled shows poor viscosity and produces optimal spreadability only under specific conditions.

A product with poor spreadability fails to provide proper distribution of active pharmaceutical ingredients and produces a negative patient reaction and has a high degree of application difficulty.

GRITTINESS – Grittiness is defined as having the characteristics of sand and is generally avoided in quality semi-solid manufacturing.

The potential for irritation of the affected area increases with particle size. As grittiness is directly related to particle size and shape, semi-solid products manufactured with high quality standards show little to no gritty appearance or texture.

SURFACTANTS – Integral to the formulation of quality semi-solid pharmaceutical drug products are inactive ingredients called surfactants that facilitate the combination of aqueous and oil phases during the manufacturing process for creams or wetting of particles in gels or ointments.

During manufacturing, procedures are followed to avoid bleeding, separation and other phase changes that

negatively affect the finished product.

Surfactants are an important factor for the production of stable semi solid dosage forms.

The amount of surfactant in every formulation affects many key quality factors including surface tension, the ability of water to penetrate the oil barrier, removal of contaminants (detergency) and conductivity.

When surfactants are not properly and carefully utilized, the entire manufacturing process is compromised. When the two miscible oil and water phases are improperly treated, visible characteristics of the product suffer, the breakdown of separate ingredients takes place and effectiveness and performance suffer.

MANUFACTURING PROCESSES AFFECTING QUALITY

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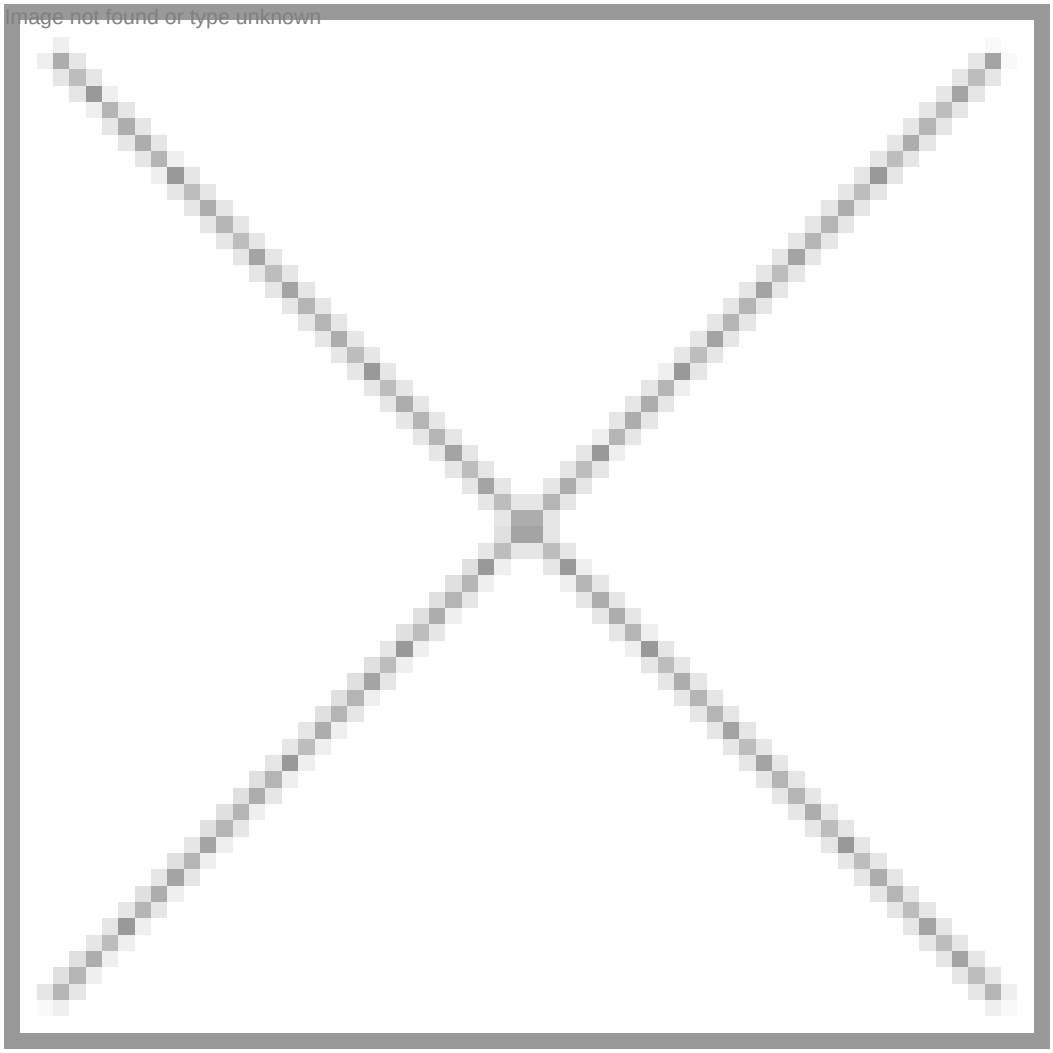

Proper temperature monitoring at every stage helps assure quality semi-solid product results. Photo credit: WDPrx

In real estate the key is location, location, location. In quality manufacturing of semi-solid products, the key is temperature, temperature, temperature.

The essence of quality semi-solid manufacturing is the proper treatment of oil and water phases to optimize effectiveness and produce desired physical qualities of homogeneity, particle distribution and spreadability.

Proper temperature monitoring helps assure successful results for production of creams, ointments and gels. Grittiness and poor spreadability are two symptoms of poor temperature regulation in low quality products.

Creams – During the manufacturing process for most creams, for example, all oil phases and water phases are weighed before surfactants are added to the water phase. Temperature is generally raised to 70 degrees Celsius separately for each phase. When the correct temperature is reached, the phases are mixed together and the process of harmonization begins.

Ingredients are broken down during homogenization. In water-in-oil formulations, water is broken down and oil is broken down in oil-in-water formulations until an emulsion is formed.

Gels – Temperature is equally important for proper manufacture of gels. Hand soaps and other cold method gel formulations involve cooling water to a range of four degrees to ten degrees Celsius before adding to the mixing container. Gelling agent is added at the aqueous phase to increase viscosity and improve stability before medication is introduced. If the gelling agent mixes improperly with the dispersing medium, clumping may occur. During the 24-48 hour swelling period, the liquid permeates the gel and volume increases. Then, entrapped air is removed as needed by mixing and other techniques before the product is cooled.

Ointments – Ointments are translucent, viscous preparations formulated for topical or transdermal application. Common formulations involve bases of petrolatum and mineral oil. Ointments perform specialized functions because they act as the carrier of the medication and also control the rate of absorption upon application.

Temperature again figures prominently in the manufacture of quality ointments. Constant monitoring is required to regulate temperature of each ingredient. An ointment formulation with an oleaginous base containing four ingredients, for example, involves first heating to the highest melting point of all ingredients and then cooling as other elements are added to the mixture.

A process including four ingredients with melting points of 70 degrees Celsius, 40 degrees Celsius, 30 degrees Celsius and 80 degrees Celsius would begin by setting the highest melting point temperature. When added, the mixture is cooled to 70 degrees Celsius, when the ingredient with the next highest melting point temperature is introduced. The cooling process continues with additional stages added at 40 degrees and 30 degrees Celsius. Subsequent ingredients are then added and the product is cooled to room temperature.

Failure to adhere to quality manufacturing procedures for ointments will result in decomposition of raw materials and adverse patient experience.

EQUIPMENT

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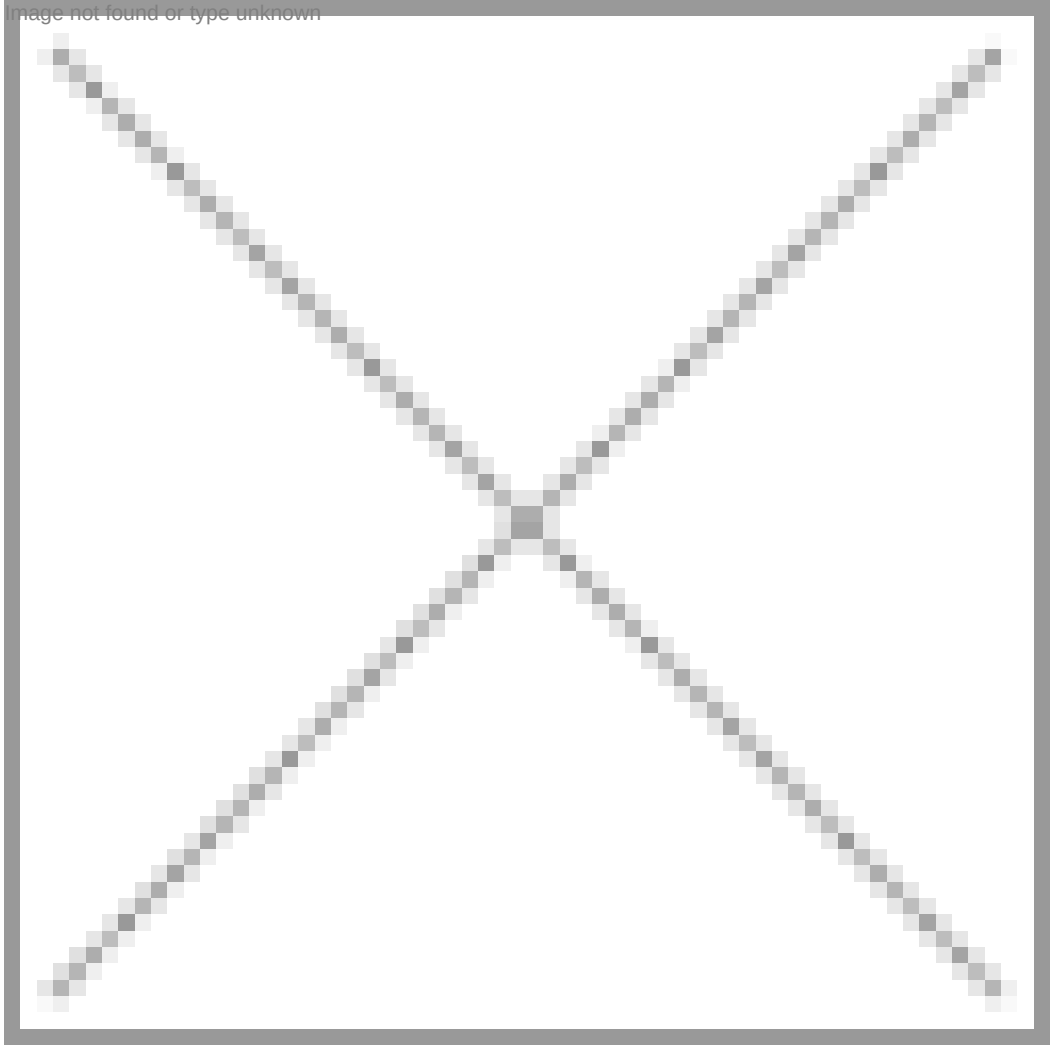

Bulk homogeneity for semi-solid ingredients is achieved with correct and appropriate use of tanks, agitators, scraper blades and other manufacturing equipment. Photo credit: WDPrx

Proper equipment is equally important as correct formulation in the manufacture of quality semi-solid pharmaceutical drug products.

Mixers, emulsifiers, jackets, tanks, agitators, mills and other equipment are integral to the manufacturing process and must function at high efficiency for desired results.

Tanks are the standard receptacles for storing and processing semi-solids. They must meet or exceed certification requirements of ASME and USDA. They may have pitched, dish or cone bottoms and come in a variety of capacities from 25 gallons to 2,000 gallons and greater.

Heating and cooling jackets are designed to provide temperature regulation with extreme responsiveness and exacting precision. When performing effectively, open, dimple and coil style jackets reduce batch processing time, increase production capacity and eliminate temperature variances.

Agitators, mixers, dispersers, mills and emulsifiers mix, blend, dissolve, disperse and emulsify ingredients across a range of viscosities. High quality equipment is made with heavy-duty gearboxes for durability and may also have variable-speed capabilities. Agitators may be fitted with bars and scrapers that work to

increase product uniformity. For example, scraper blades contact the walls of the tank for enhanced mixing, especially useful for higher viscosities up to and beyond 2,000,000 cps found in certain cream formulations.

Sigma blade mixers or shearers create minimum dead space during mixing and are particularly suited for wet granulation processes. Homogenizers force mixes through small ports at high pressure, reducing particle sizes to meet product specifications.

When these sophisticated machines complete their work, the mixture should achieve ‘bulk homogeneity,’ with uniform distribution of ingredients throughout the tank.

TESTING

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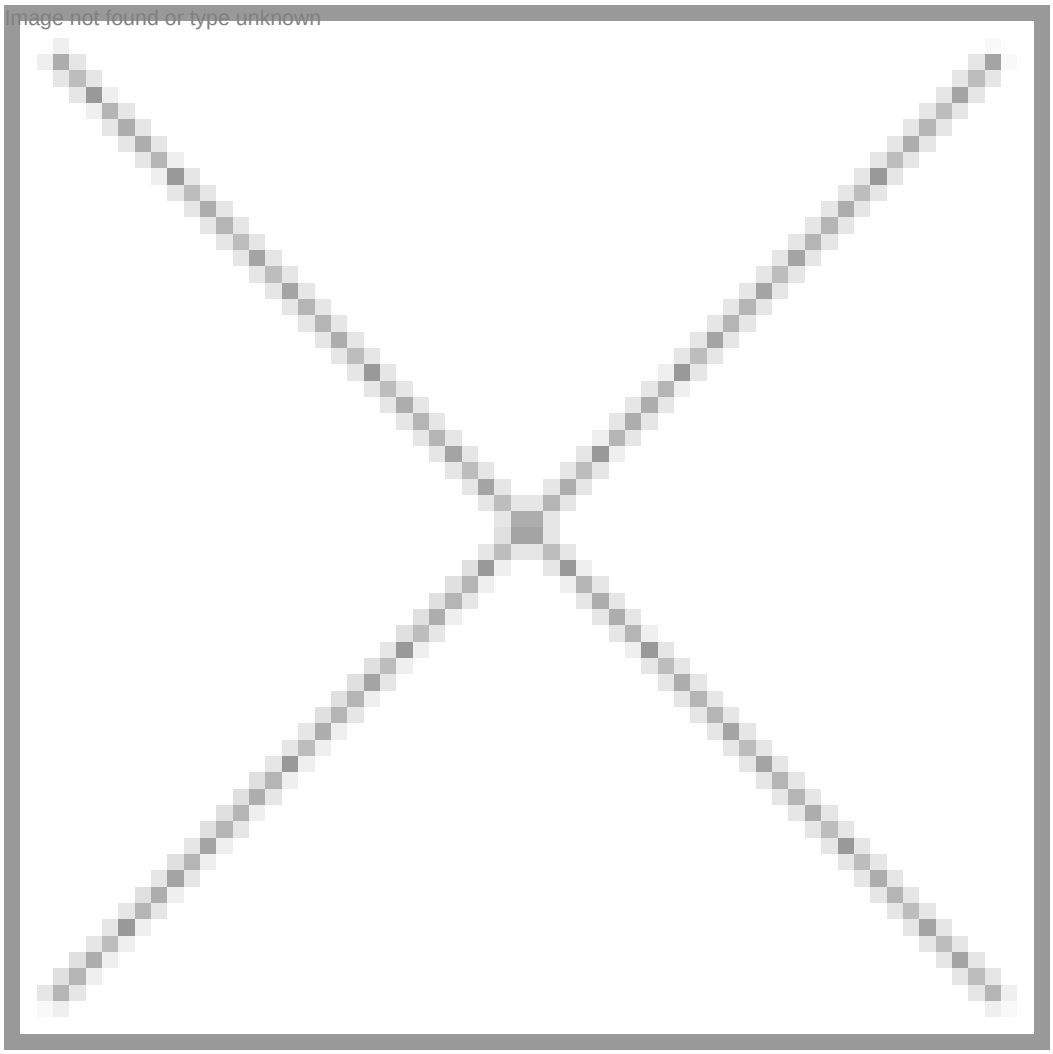


Microbiological testing performed with physical and chemical tests prevent unfavorable results during the manufacturing process. Photo credit: WDPrx

Monitoring the quality of drug products requires physical, microbiological and chemical testing throughout development and manufacturing.

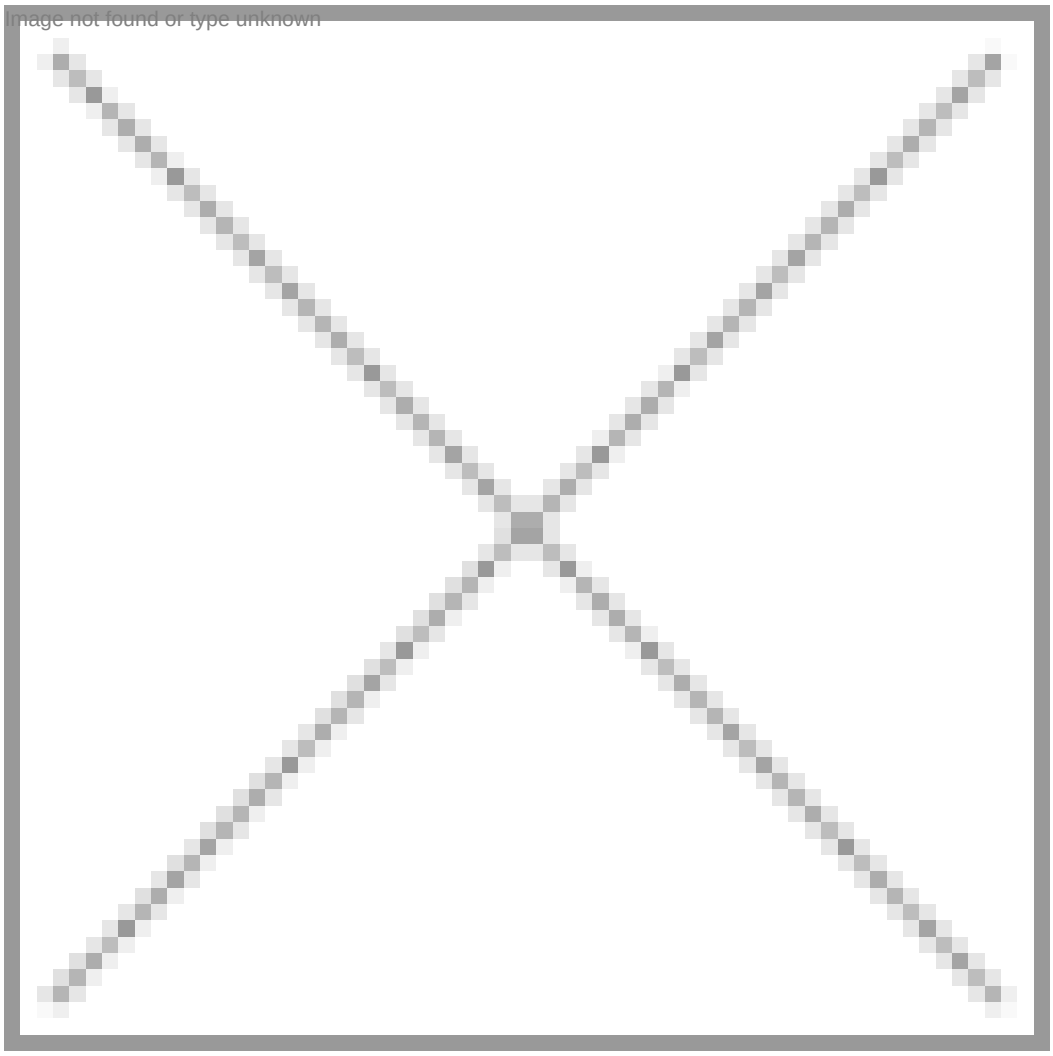
Specific testing of semi-solid formulations maintains quality control and prevents unfavorable results.

Physical tests determine visual and chemical separation, color change, pH, crystallization and any degradation of appearance, viscosity or spreadability.

One of the key chemical tests determining high quality semi-solid products measures the degree that ingredients are uniformly distributed in the product. Assays for potency are conducted during bulk manufacture within mixing tanks and also throughout the packaging run within tubes and jars. Additional analytical tests are conducted during the manufacturing process to monitor for product degradation and any impurities.

Microbiological stability is assured by testing for microbial limits and preservative effectiveness.

PACKAGING AND STORAGE



Store products in a controlled area that avoids variances in temperature, humidity and light. Photo credit: WDPrx

The complexities involved in producing quality semi-solid pharmaceutical products require that attention be paid to packaging and storage procedures to maintain effectiveness.

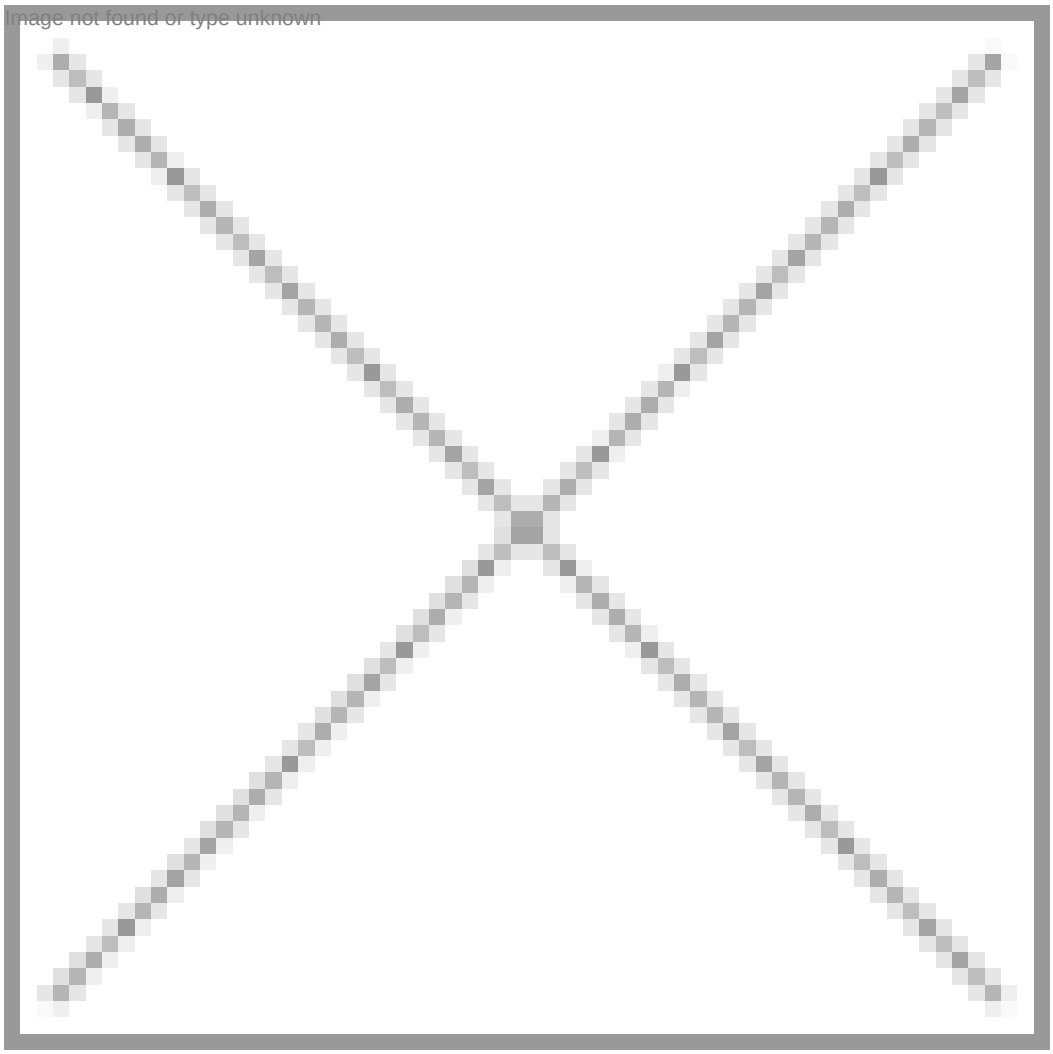
It is normal practice to store the product until all quality control tests are completed before packaging.

Storage location should avoid variations in light and temperature that may negatively affect product integrity.

The storage container must be checked for any indication of peeling and leakage, penetration, adherence and deformation.

Active ingredients may react with improper packaging. Vigilance is required to monitor migration and color change of ingredients as these are indications of product instability.

QUALITY PEOPLE MAKE QUALITY PRODUCTS



Highly trained scientists, technicians, project managers and other administrators focus on quality in processes and procedures that save time and avoid additional cost. Photo credit: WDPrx

The quality manufacturing of semi-solid dosage forms relies on a continuum of factors occurring consecutively, continuously and simultaneously to produce successful results.

The variety of dosage forms including ointments, gels, creams and pastes employ different production techniques but all rely on the correct functioning of human and machine elements from formulation, manufacturing and production to testing, storage, packaging and fulfillment.

With production lines becoming increasingly automated, the need is more acute than ever before for experienced technicians to guide semi-solid products along the path from development to commercial sale.

FUTURE OF SEMI-SOLID DOSAGE FORM

Personalized medicine is spurring interest in patient-centric treatment modalities. Oral solid dosage manufacturing is being transformed by 3-D printing technology that enables customized dosing. Similarly, semi-solids provide an ideal delivery method for customized doses of medications created on a patient-by-patient basis.

Different quantities of active ingredients incorporated into semi-solid dosage forms can be precisely delivered to specific patients for maximum effectiveness.

Growing interest in semi-solid products is based partly on the convergence of personalized medicine and specialty pharma distribution that are poised to become an ever-larger percentage of total volume of medications available on the market.

Another factor heightening interest in semi-solid dosage forms is the quantity of new active pharmaceutical ingredients (API) lacking aqueous solubility. Developments in various dispersion techniques are producing positive results that in certain cases may be incorporated into semi-solid products.

As their popularity grows, manufacturers of quality semi-solid medications must continue to maintain patient trust to assure their continued adoption in the market for the benefit of patients.

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About WDPrx – Woodfield Pharmaceutical, LLC

WDPrx – Woodfield Pharmaceutical, LLC is a proven and reliable CMO partner specializing in oral solutions, liquid solutions, suspensions and semi-solids. Our established record of commercialization success spans more than 30 years in continual operation built upon a strong foundation of financial strength and stability.

Our experienced team provides end-to-end pharmaceutical outsourcing services from Research and Development, Commercial Manufacturing, Regulatory Support, Primary and Secondary Packaging and Labeling.

The modern facility in Houston, TX is DSCSA compliant and Serialization-ready. WDPrx is cGMP compliant and utilizes advanced technology to support full Technology Transfer and System Integration for minimal production down-time. “Crafting Contract Manufacturing Solutions” is the WDPrx mission. We value our reputation earned over time as creative problem-solving specialists with flexible capabilities committed to client communication and success.

WDPrx extends client capabilities, efficiency and reach from development through production with the highest levels of quality pharmaceutical manufacturing.

WDPrx in Contract Pharma

The Psychology of DSCSA: Four Stages of Serialization

View the WDPrx article in Contract Pharma’s September 2017 Issue.

WDPrx Monthly Newsletter August 2017

WDPrx continues to expand business opportunities with industry outreach and news stories highlighting our full range of development, manufacturing and testing capabilities.

Click here to read the most recent update.

WDPrx Monthly Newsletter July 2017

WDPrx continues to expand business opportunities with industry outreach and news stories highlighting our full range of development, manufacturing and testing capabilities.

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WDPrx Monthly Newsletter June 2017

WDPrx continues to expand business opportunities with industry outreach and news stories highlighting our full range of development, manufacturing and testing capabilities.

Click here to read the most recent update.

The Single Skill That Makes Or Breaks Technology Transfer Projects For Contract Manufacturers

Relationships are difficult to navigate effectively. One party often feels the other is taking advantage of the situation. Things are left unsaid. Things that are said are often not meant. Disagreements may occur.

Such is the world of technology transfer for pharmaceutical contract manufacturers.

Encourage Communication

Technology transfer involves the efficient transition of technical and manufacturing capabilities between separate entities. Developing and manufacturing pharmaceuticals is an exacting process requiring scientific, regulatory and operational expertise within the manufacturing facility for successful commercialization. Transferring technology to another entity adds additional potential obstacles to be overcome.

technology transfer

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Process validation taking place during a technology transfer project at WDPrx – Woodfield Pharmaceutical, LLC.

WDPrx, a pharmaceutical contract manufacturer specializing in liquids including oral solutions, suspensions, syrups and semi-solids, involves a dedicated team of laboratory scientists, production technicians and regulatory experts for each tech transfer project. With different companies involved, each with their own culture and established procedures, detailed step-by-step responsibilities must be developed and agreed to avoid misinterpretation leading to delays.

Experience Counts

According to Adam Runsdorf, WDPrx President, “Over the course of 30 years of operation, WDPrx has established a reliable system for technology transfer. From initial contact progressing through large-scale manufacturing and pharmaceutical laboratory testing, our protocol stresses scientific requirements and positive personal interactions with all involved parties to assure successful outcomes.”

technology transfer

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Scale-up at WDPrx from small batch to commercial quantities during a technology transfer project.

The challenges when working with virtual manufacturers are often heightened because there may be a lack

of complete historical data about the product involved with the transfer. Some virtual manufacturers may rely on expertise from the contract manufacturer about scale-up and other pharmaceutical development and manufacturing areas to enable a streamlined transition to the production site.

Three Steps For Success

Although each transfer involves a unique set of circumstances, WDPrx follows three general guidelines that help assure a successful tech transfer relationship.

technology transfer

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Packaging and labeling should be considered at the beginning of the technology transfer process.

At each stage, the best commercial manufacturing organizations set themselves apart with high levels of communication, accountability, planning and experience.

1. **Get Acquainted** –

Define the elements of a successful project at the start and determine expected final outcomes; develop a checklist; examine original formulations, analytical methods and production methods; review original equipment to confirm whether modification in the new facility is required; examine training procedures to

assure clear understanding of individual and team responsibilities

2. **Develop Trust –**

Seek input from previous manufacturer if available to reduce cost and gain information helpful during the production process; analyze documentation for completeness and up-to-date production records; evaluate SOP protocols concerning processing, packaging and cleaning; confirm analytical testing methods meet SUPAC guidelines; conduct packaging line trials and a comprehensive health and safety review; check every process prior to preliminary engineering runs and scale-up

3. **Complete The Task** –

Confirm original success parameters are addressed and resolved; create a support team for manufacturing with direct access to all materials and notes pertaining to the technical transfer; implement a mutually agreed-upon statement of work; regularly consult with original team members to maintain course and keep lines of communication open.

technology transfer

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A WDPrx technician reviews data transmitted during a technology transfer project.

There are many challenges to organizations involved with technology transfer of complex documentation

and proprietary procedures. An important factor determining success relies on the ability of both parties to overcome practical and also the inter-relational elements of the project. Many contract manufacturing partners can handle the hard scientific challenges of tech transfer. The most overlooked ingredient to success is the attention paid to the soft emotional skills. Mastery of these soft skills including patience, motivation, empathy and self-awareness can make or break the relationship between technology transfer parties.

The science and the psychology of technology transfer are bridged by frequent and transparent communication throughout the project timeline. Adds Runsdorf, “Delays in the transfer process can occur due to lack of communication, misinterpretation and misperception. Most of these are avoidable with thoughtful and detailed consideration of all parties to overcome challenges and earn client satisfaction.”

technology transfer

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Communication is an important ingredient that must be added to every technology transfer project.

For further information about technology transfer at WDPrx – Woodfield Pharmaceutical, LLC, go to: https://www.wdprx.com/contract-manufacturing/development/

About WDPrx

WDPrx – Woodfield Pharmaceutical, LLC is a proven and reliable contract manufacturing specialist across a range of delivery methods including oral solutions, liquid solutions, suspensions and semi-solids. Capabilities include Research and Development, Material Procurement, Manufacturing, Process Optimization, Formulation, Pharmaceutical Validation, Pharmaceutical Laboratory Testing and Pharmaceutical Analytics Services.

Contract packaging operations handle liquid and solid-dose configurations.

The modern facility is dedicated to the highest levels of quality pharmaceutical manufacturing. Based in Houston, TX, WDPrx is cGMP compliant and utilizes advanced technology to support full Technology Transfer and System Integration for minimal production down-time.

Contract Packaging Operations At The Center Of Transition To Serialization

A version of this story appeared in the June 2017 issue of Contract Pharma Magazine under the title "Adapt Or Die."

Adapt Or Die

As companies within the pharmaceutical supply chain near the November 27, 2017 deadline for the most recent phase of DSCSA compliance, contract packaging operations with comprehensive serialization implementation programs will see their business increase due to the new requirements.

A primary goal of the DSCSA is improving information transparency to minimize the market for counterfeit and diverted products. The Act states that the industry must build "an electronic, interoperable system to identify and trace certain prescription drugs as they are distributed in the United States." The Act does not specify a clear pathway to achieving this goal. This lack of direction frustrates many companies within the pharmaceutical supply chain. In an industry where any deviation from absolute precision can have dire consequences, instructions without detail are a cause for confusion.

For some contract packagers, the fuzzy wording of the DSCSA has become a reason to delay any decisive action until the government clarifies their position. For others, the situation is seen as an opportunity to develop a wide range of solutions without regulatory interference as long as the end result complies with the law. Companies with indecisive policies may find themselves at a disadvantage compared with others that began early and approved programs to support their clients along the path to serialization.

A Tale of Two Options

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Caption: Labeling on a production line at WDPrx – Woodfield Pharmaceutical, LLC in Houston, TX

Although all responsible parties within the pharmaceutical supply chain support the DSCSA, there are two differing viewpoints about the timeline to gain full compliance. The speed with which contract packagers embrace full serialization will impact their business operations and bottom lines.

The first strategy advocates adhering to the letter of the law which states that as of November 27, 2017, manufacturers must put a unique product identifier on certain prescription drug packages and must have a procedure for verification of the product at the package level including the standardized numerical identifier, or NDC. Re-packagers must comply with both mandates by November 27, 2018. This approach can be called the “Letter of the Law” strategy.

The alternative pathway might be called the “Spirit of the Law” strategy. This program is more aggressive and involves completing additional DSCSA requirements prior to their actual deadline. For example, product tracing by package level is a DSCSA provision required by 2023. However, several companies provide solutions today that satisfy the current understanding of this regulation.

A contract manufacturing firm with contract pharmaceutical packaging operations that is following the “Spirit

of the Law" strategy is WDPrx – Woodfield Pharmaceutical, LLC , based in Houston, TX. As the DSCSA was signed into law in 2013, WDPrx determined that the best way to assist their clients was to develop a comprehensive DSCSA compliance implementation program. According to WDPrx President Adam Runsdorf, "Our approach to DSCSA is that the law prompts the U.S. pharmaceutical industry to meet already-established heightened traceability regulations in other countries. We made the commitment early on to allocate resources and develop best practices for serialization to benefit our business and respond to future client needs."

This strategy enabled WDPrx to achieve several desired results:

1. **Industry Influencer**: Early adoption of serialization technology enabled WDPrx to be an 'early influencer' entering the new market ahead of competition. The management team evaluated numerous potential serialization vendors before the competition. This enabled WDPrx to take additional time to investigate solutions and negotiate from a position of strength because there was no time constraint. These discussions provided valuable insights that helped formulate the ideal serialization solution for WDPrx and their clients.
2. **Client Guidance:** Early adoption of advanced serialization equipment and technology provided a comprehensive knowledge base for the WDPrx management team to support and advise clients to streamline their own serialization programs
3. **Streamlined Onboarding:** By investing in a robust Information Technology infrastructure, WDPrx selected programs that offered increased flexibility to interact with multiple systems from external partners with minimal onboarding disruption
4. **Multiple Entry Points:** Creating a full suite of serialization services prior to deadline provides WDPrx with flexibility to offer a wide range of serialization-ready solutions to manufacturers and their CMO partners regardless of their own implementation status.

Solutions By Delivery Method

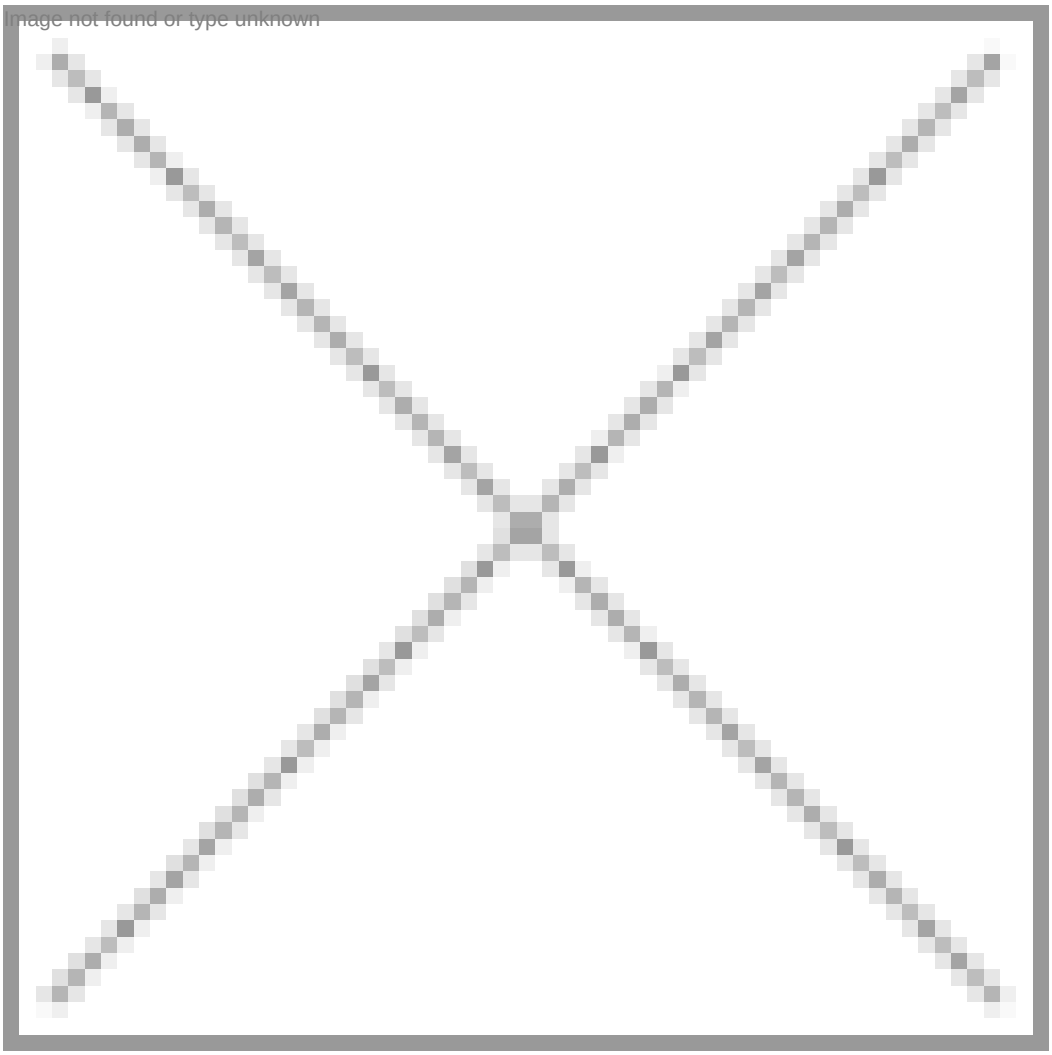
A selective history of track and trace begins with consumer products. Many of us remember the rainbow-hued stickers on the packaging of computer software office productivity CDs. A license number appeared on each sticker that activated the software when the characters were entered into the computer. The automobile parts industry and other industries developed their own systems. The international pharmaceutical industry adopted track and trace systems several years before the U.S. Turkey, for example, manages a national track and trace system that already functions in a similar fashion to the program envisioned by the DSCSA to be operational in the United States by the year 2023.

When the DSCSA became law, the pharmaceutical industry in the United States experienced a rush to market from several solutions providers. After witnessing some industry consolidation, there remain many approaches to achieve serialization compliance for pharmaceutical packaging lines.

Contract packaging operations must select solutions from among the many companies and options based on the delivery method handled by their equipment. The hardware required for compliance on an oral solid-dose packaging line may be a different solution on a liquid-dose line. Different providers may specialize in

specific delivery methods. Decision-makers at contract packagers must analyze whether to rely on a single vendor or diversify potential risk across multiple suppliers.

An Implementation Experience – WDPrx



The Optel Vision exhibit at Interphex in March, 2017 displaying serialization equipment.

WDPrx – Woodfield Pharmaceutical, LLC is a CMO specializing in non-sterile liquid and semi-solid manufacturing. Packaging and labeling capabilities include semi-solid, liquid, gels, suspensions and solid-dose delivery methods. After a thorough evaluation process, the company selected Optel Vision, headquartered in Quebec, Canada to upgrade all packaging lines with DSCSA compliant optical and labeling systems.

Optel Vision offered a range of products for WDPrx that accounted for variations in packaging volume and level of automation required for each active line. Linear barcode scanners are being upgraded to 2D scanners. Labeling equipment is also being replaced or enhanced on all lines to meet DSCSA compliance. The level of automation integrated into each line is dependent upon packaging volume. Optel Vision is fully automating certain lines and is installing semi-automated solutions on other lines to better match variations in production quantities. “Optel Vision’s Fast Series products are preconfigured to enable existing

pharmaceutical packaging lines to meet compliance, quickly. And they are scalable to meet increased serialization needs in future," states Optel Vision Account Director Chris Collins.

Systems to integrate equipment and information technology assets with product tracing, verification and end-to-end serialization, also known as Level IV enterprise compliance, are being provided by TraceLink, creator of the TraceLink Life Sciences Cloud, the world's largest pharmaceutical track and trace network.

According to Brian Daleiden, TraceLink Co-Founder and VP of Industry Marketing, "Requirements for DSCSA compliance mandate a flexible track and trace system that can handle complex data management and compliance processing for information on lot-level and serialized products that is generated and exchanged among parties that manufacture, distribute or dispense pharmaceutical products in the United States. The integration of business systems, operational processes, transactional compliance data and crucial company/product master data are critical for secure, efficient DSCSA compliance in today's diverse supply network, and with over 265,000 trade partners on TraceLink's purpose-built network, companies only have to integrate once in order to interoperate with all of their trade partners. This instant network connectivity, coupled with an end-to-end track and trace compliance solution on a highly scalable cloud platform, enables our customers and partners to be DSCSA compliant while ensuring the flow of their products throughout the supply chain."

The TraceLink Life Sciences Cloud supports serialization programs by catching serial number generation requests from packaging line systems, generating DSCSA-compliant serial numbers and related data based on pre-defined profiles for specific product types and packaging hierarchies.

Resultant serialization data, aggregation information, commissioning events, shipment events and other operational events are exchanged between the TraceLink system and various packaging line and distribution systems using standard GS1 EPCIS and other data exchange methods depending on the data exchanged and the capabilities of the target systems.

Lot-level compliance data is exchanged today and archived in the Life Sciences Cloud to document products as they are bought and sold across the pharmaceutical supply chain. As serialized products start to become available across the supply chain to meet the 2017 – 2020 DSCSA regulatory deadlines, many companies are now starting to gear up for serialization data exchange between upstream and downstream parties on the Life Sciences Cloud platform to support efficient business operations, when required for verification of saleable returns or suspect products, or for further review or examination to help minimize product diversion and counterfeiting.

Solutions for Several Levels of DSCSA Readiness

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Proper packaging serialization promotes efficiency within the pharmaceutical supply chain.

Pursuing a program to implement comprehensive DSCSA serialization capabilities prior to FDA deadlines provides CPOs with additional new business opportunities. The CPO that is the furthest along with the most comprehensive DSCSA-compliant solutions is in the best position to address the specific needs of all participants at both ends of the pharmaceutical supply chain.

Packaging and labeling operations fulfil a key role within the pharmaceutical supply chain. Contract packagers manage relationships with multiple parties along the supply chain including pharmaceutical manufacturers, contract manufacturing organizations, third party logistics providers, distributors, wholesalers and dispensers.

It is likely that all parties are at different stages of DSCSA compliance. For example, some manufacturers may have equipment installed however it may not be validated. A CMO might have Level IV integration completed however installation of 2D readers on their equipment may be delayed. Smaller suppliers may not have any serialization plan in place.

There is a strong possibility that orders fulfilled by the CPO will be shipped to wholesalers, distributors and

healthcare providers that also are in various states of readiness to accept serialized product.

In these cases and in other similar scenarios, the serialization-ready CPO is able to respond to clients with customized solutions and is positioned to attract additional business based on the flexibility of their capabilities.

Amatheon Pharmaceuticals is a leading veterinary supplier of 'cross-over' medications and a client at WDSrx – Woodfield Distribution, LLC, a third party logistics provider for the healthcare industry. Amatheon distributes human-grade pharmaceutical drug products to the veterinary industry. "Our mission is to utilize the most innovate technological solutions to provide the best customer service experience," according to Robert DiCrisci, Amatheon President and CEO. The serialization expertise of the Woodfield team enables Amatheon to uphold their mission with the correct serialization solution for their product offerings to enable them to concentrate on their core business priorities.

A Word Of Warning

Two strategies predominate in the industry regarding serialization. One position advocates completing the minimum requirements of the law prior to the deadline and takes a "wait and see" attitude, not committing additional resources until further clarification and guidance is issued by the FDA about future implementation.

This argument, expressed by some large pharmaceutical contract manufacturers, holds that major wholesalers will not halt the flow of pharmaceutical drug products after the deadline if compliance standards are not met by what is essentially an arbitrarily selected deadline date.

The alternative strategy emphasizes early adoption of comprehensive serialization solutions. Many responsible CPO firms including WDPrx have made significant investments to achieve serialization in advance of FDA deadlines. Positioned between manufacturer and dispenser, the CPO and third party logistics providers work with large clients. They also work with many mid-size and small clients that have little to no leverage in their dealings with national wholesalers.

Smaller manufacturers and brand owners are concerned that orders may be delayed or rejected by wholesalers if their shipments are not fully serialized by the deadline. The transition to full serialization will be challenging and wholesalers willing to work through the transition with larger partners may not extend the same consideration to smaller players.

Therefore, responsible contract packagers and third party logistics providers that are serialization-ready are able to offer serialization options to all clients that enable them to continue operations post-deadline and minimize the possibility of disruption further along the supply chain due to potential DSCSA compliance issues.

A Significant Commitment

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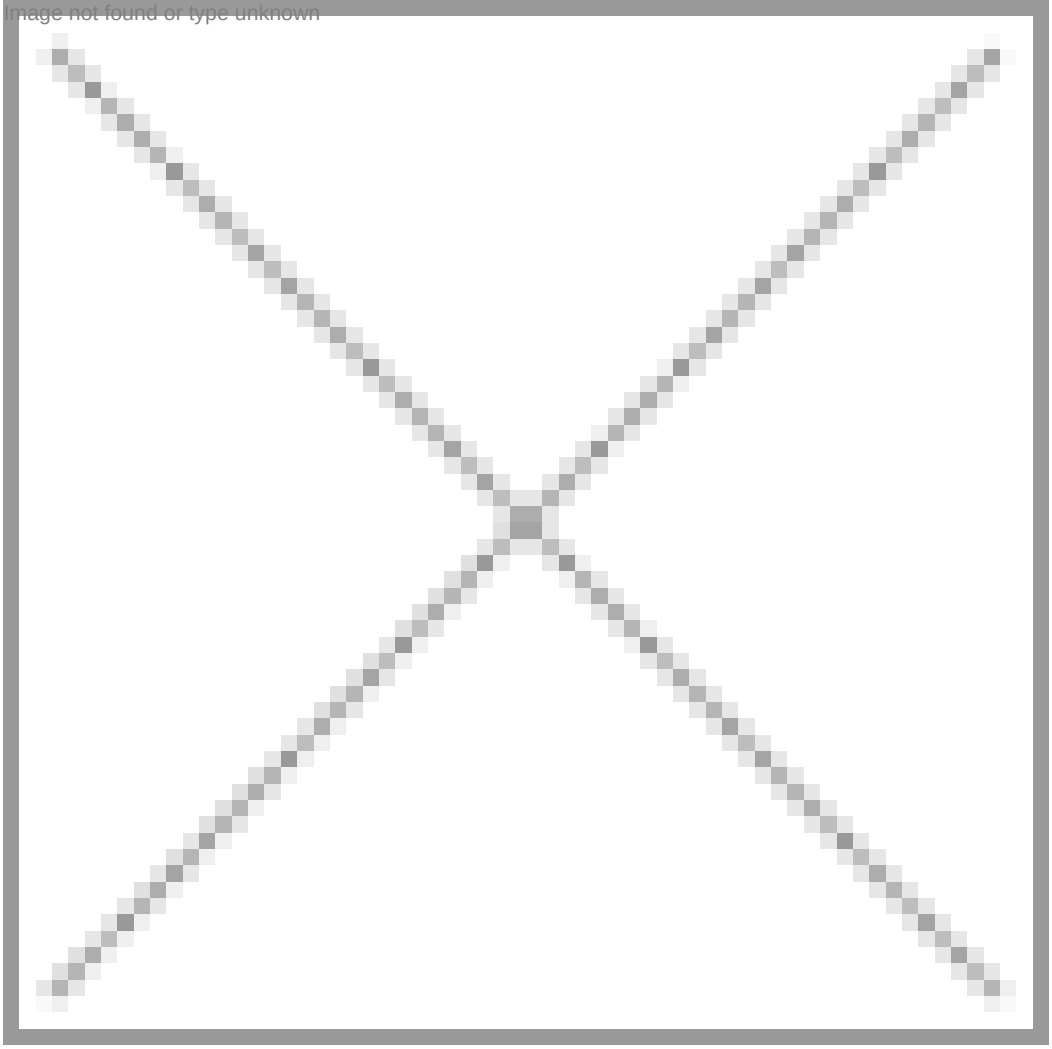

The transition to DSCSA compliance goes beyond hardware and software to include new training protocols and SOP guidelines.

Upgrading packaging and labeling equipment to conform to DSCSA regulations is an important priority affecting many departments within contract packaging operations and third party logistics providers including Warehousing and Distribution, Reverse Logistics, Transportation Management, Information Technology, Quality Assurance and Regulatory Affairs.

Item serialization requires specialized hardware and software to serialize drug products with the Unique Product Identifier (UPI) compliant with the GS1 Global Standard. The UPI contains vital tracking information including serial number, lot number, expiration date and other pertinent data.

In most cases, new printers, scanners, cameras, desktop devices and other hardware must be installed on each line and throughout the facility to read, store, print and process the UPI and additional data requirements for DSCSA compliance.

Line management software must be operational to manage serial number allocation and aggregation on each packaging line. To coordinate individual lines, additional technology is layered onto the system enabling communication between software programs and Warehouse Management System (WMS).

The fundamental objective for item-level traceability is achieved through a cloud-based repository to generate serial numbers and gain access to data for supply chain partners to establish full chain of possession.

Although this comprehensive solution is not required by the November 27, 2017 deadline, contract packagers and third party logistics firms that committed early to complete serialization programs can offer more options to clients requiring DSCSA compliance assistance. Many contract packagers and manufacturers are choosing to wait to implement change or their serialization timetable may be delayed due to lack of outside resources. Each situation may be slightly different. The prepared third party logistics provider and contract packager is in a strong position to bridge the gap for most clients to keep their businesses running smoothly leading up to and beyond the upcoming deadline regardless of their compliance status.

Choose Wisely

DSCSA compliance has fostered an entire industry dedicated to developing strategy, hardware and software for companies operating within the pharmaceutical supply chain. Multiple solutions are offered by different companies that each promote their own products and services. The crowded marketplace contrasts with the objective of the DSCSA to increase transparency in the marketplace to authenticate the passage of prescription medications from manufacturer to final dispenser and in the reverse logistics channel.

Contract packagers and third party logistics providers occupy an important place at the nexus of the supply chain between manufacturers and patients. Early implementation of DSCSA requirements prior to FDA deadlines benefits responsible 3PL and CPO firms and their small and mid-size clients including manufacturers and contract manufacturers.

Many manufacturers are delaying implementation until the FDA provides further clarification about the law. However, FDA public statements are always related to the phraseology of the law itself with little or no interpretation or guidance. This same situation is the reason responsible third party logistics providers and contract packagers offer clients several levels of serialization assistance. With correctly serialized products, all parties along the supply chain must accept and process inbound shipments.

Uncertainty is the enemy of pharmaceutical logistics. Proper planning with reputable pharmaceutical contract manufacturers, packagers and third party logistics providers increases confidence for manufacturers navigating through the transition to DSCSA compliance.

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WDPrx News Update for May 2017

Read about recent developments at WDPrx contributing to client satisfaction and increasing team motivation. View the WDPrx May News Update.