ProMed
Molding for Life

THE CHALLENGES OF MANUFACTURING COMBINATION COMPONENTS

In this article Bob Parsons, Vice-President, Quality & Regulatory Affairs, and Jim Arps, PhD, Director, Business Development, both of ProMed Pharma, discuss three significant challenges faced by companies looking to manufacture components for combination products in the medical sector and how ProMed has risen to meet them.

This article is adapted from a set of ProMed Pharma LLC white papers: "The Challenges of Manufacturing Combination Components" Parts 1 & 2.

THE FIRST CHALLENGE – FACILITY DESIGN

In order to ensure that any new operation in a manufacturing facility will be sustainable, it is necessary to thoroughly evaluate and specify the intended production area's size, layout, equipment, utilities and safety precautions prior to bringing a new drug substance into the facility. Adequate space is required for receipt, segregation, handling, storage and testing of drug substances and other raw materials.

Drug substances must be received, quarantined, sampled, tested and released prior to use, all of which must then be documented. Each shipment is tested at a minimum for identity, however purity, strength and quality must also be confirmed, as later discussed. ProMed quarantines all incoming product in appropriate temperature, light and humidity conditions using monitored, temperature controlled cages, coolers and freezers. To help ensure released and unreleased materials are never mixed up, materials are labelled and their containers physically segregated.

The equipment, air handling, process flow, customer requirements, cleanroom layout and utilities must all also be considered during establishment of a new pharma production facility. For utilities, the actual daily consumption and demand are measured, and the quality reviewed. In cases where the utility has an impact upon product quality, directly or indirectly, validation testing is performed to verify quality. For example, ProMed uses compressed air to drive actuators and remove materials. In some cases, the compressed air is in contact with product and therefore needs to be validated to ensure that no oils, moisture or microbial contaminants are present.

To minimise mix-up and contamination, the equipment placement, processes, material and personnel flows are considered with respect to each new facility and appropriate process are implemented. Equipment and process requirements are evaluated for appropriate size, required utilities,

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construction materials and monitoring instrumentation. New equipment is qualified to ensure that it is suitable to meet process requirements and tolerance specifications. Measurement and testing equipment requirements are also evaluated and new test instrumentation is qualified for its intended use.

ProMed's typical pharma production facility is an ISO Class 7 cleanroom suite dedicated to a single customer (Figure 1). ProMed prefers to build its cleanroom suites with one or more air handler units, that serve the main manufacturing areas and the mixing rooms. The dedicated unit helps to ensure drug particulates generated during the mixing process are not recirculated into the main cleanroom. Additionally, the mix room is designed to have a negative pressure differential with respect to adjacent rooms, to further ensure that particulates don't escape.

As each new manufacturing facility is brought online, ProMed performs design qualification (DQ) to ensure the cleanroom suite has been built to both its and its customer's specifications. Once the facility has been initially qualified, an environmental monitoring programme is established. The new cleanroom suite is thoroughly cleaned, after which initial testing includes two three consecutive day periods, first with no operators present (static testing), second with operators present (dynamic testing). The airborne viable micro-organism, surface micro-organism and non-viable particulate

Figure 1: A ProMed Pharma production floor.

levels from this initial testing are used to establish a baseline and the initial alert and action levels. The facility is then added to ProMed's routine environmental monitoring (EM) programme and sampling is performed quarterly.

THE SECOND CHALLENGE – RESOURCES

Individual Component Versus Batch Processing

In much of the medical contract-manufacturing industry, the work order is the batch size, corresponding to a number of components processed through the manufacturing environment. As parts pass through a particular operation, data is recorded on the batch as a whole. However, in combination product component manufacturing, there are processing steps where some characteristics (e.g. weight, yield) of individual units are tracked. This is done to ensure that the correct amount of drug is incorporated into the manufactured component. ProMed uses a unit manufacturing process, however it also tracks individual components within each batch as necessary.

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Conveyance Methods

Maintaining a unique part identity through several processing steps requires a conveyance method that is easy to use and capable of maintaining said individual part identity. For example, if a step processes 8 parts, then the part trays need to have 8 columns. This can also involve the use of placeholders. Throughout the process, rejected parts lead to empty spaces in the conveyance, thus placeholders are needed to ensure another part is not inadvertently placed in this location. If an acceptable part is placed into the wrong conveyance location the data from previous processing steps proving the part meets specifications are lost and, as a result, an acceptable part would be rejected.

Required Paperwork

Everyone in the medical contract manufacturing industry understands the importance of accurate device history records and other processing paperwork. Combination products impose a further level of required diligence. There is more of it, at times it can seem to be more confusing, and it subject to a higher degree of scrutiny. Paperwork errors can result in significant unplanned financial and delivery issues.

It takes a certain type of operator to perform successfully in this environment, especially when compared with other, less risky, roles. Some organisations that are manufacturing combination products are actually moving towards performing personality profile testing on both existing and prospective employees to minimise turnover and error risk.

Understanding Value

Combination product components are of the highest value of any of the parts ProMed presently manufacture (Figure 2). The addition of the drug, the additional processing data (individual units) and the higher requirements of the quality system all add cost. Additional time was spent with the operators so that they properly understood the impact of their actions when operations were not correctly followed, leading to scrap. Additionally, scrap from this type of operation is considered a hazardous waste and must be treated as such, resulting in further additional cost.

THE THIRD CHALLENGE – REGULATION

Up until recently, companies manufacturing combination products were faced with the formidable task of deciding how to best comply with multiple, and sometimes overlapping, regulations for both devices and pharmaceutical products. When the US FDA issued the final rule for 21 CFR Part 4, cGMP Regulation of Combination Products, on January 22, 2013 and the Final Guidance for Industry on how to comply with these new requirements in January 2017, much of the grey and conflicting areas were resolved, making it apparent that a either a device-based quality system or a pharma-based quality system, enhanced with supplementary policies and procedures to cover the other, is the preferred route.

ProMed's combination products quality management system (QMS) was derived from the existing ISO 13485 certified and 21 CFR 820 compliant device quality system used in its moulded products area. The key provisions of the Pharma regulations in 21 CFR 210 and 211 that are needed for manufacturing devices with a drug constituent are identified in Table 1.

Drug Product Containers & Closures

To comply with the additional pharmaceutical requirements, ProMed enhanced its pharma QMS to ensure that drug components and drug product containers are received using approved in-house procedures. Where cleanliness is a requirement, ProMed ensures cleaning of the containers and components takes place and that containers are closed and only opened in environmentally controlled areas to prevent the introduction of contaminants into the products or components.

Figure 2: Combination product components, such as these various cardiac pacing components to be loaded with a steroid, are very high value products.

Section	Description
Section 211.84	Testing and approval or rejection of components, drug product containers, and closures.
Section 211.103	Calculation of Yield
Section 211.132	Tamper-evident packaging
Section 211.137	Expiration Dating
Section 211.165	Testing and Release for Distribution
Section 211.166	Stability Testing
Section 211.167	Special Testing Requirements
Section 211.170	Reserve Samples

Table 1: Further regulatory requirements for manufacturing medical combination products.

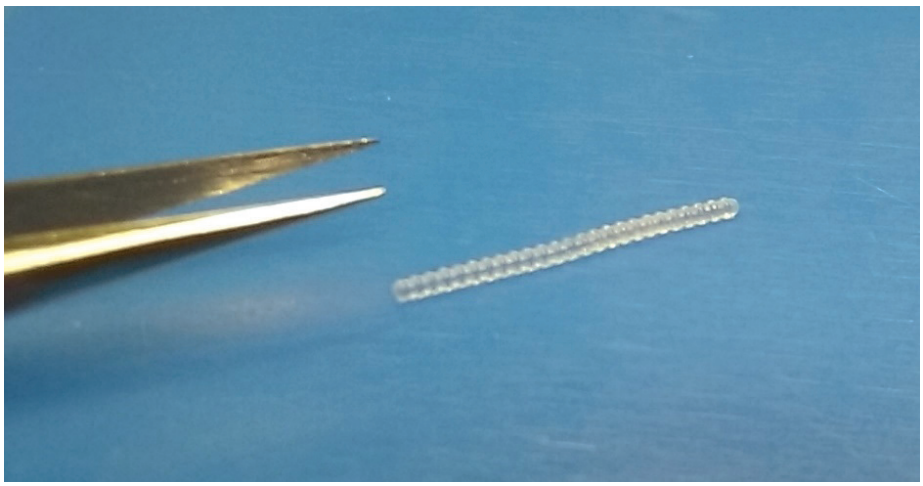

Figure 3: A moulded resorbable polymer implant for subcutaneous drug delivery.

Representative samples of each shipment of each lot are collected for testing. Certificates of analysis (CofA) are reviewed for compliance to pre-established materials specifications. If testing is required, the quantity of material and amount required for reserve samples is determined and sampled from incoming containers. Sampling is generally based upon the $\sqrt{N+1}$ rule for N number of containers unless a higher

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degree of scrutiny is required. Testing for compliance with specifications is performed by ProMed's in-house ISO 17025-accredited laboratory or an approved contract lab.

Calculation of Yield

Although many colourants and mix ratios of activators and resins are critical in silicone moulding processes, traditional device manufacturing processes do not require calculation of yield. To comply with the pharma calculation of yield requirements, ProMed implemented comprehensive batch records to calculate and document the theoretical yield and actual yield of drug in components that have a drug constituent. The batch records are predefined through process development and process validation to ensure that the specified loading and elution targets are achieved.

It is important to note that ProMed's combination products typically consist of a moulded silicone or resorbable polymer structure impregnated with the drug substance or API (Figure 3). Once an API is fully encapsulated within a polymer matrix through the moulding processes, the next step is to confirm the drug's elution profile and burst. In other words, to test and confirm how fast the drug substance elutes or discharges from the polymer. This complex analytical testing is performed in-house using validated methods or by an approved contract laboratory, as appropriate. The results are used to confirm actual yield and that the drug elution profile meets specifications. Conforming product is released for final packaging or further processing by quality assurance (QA).

Tamper-Evident Packaging

ProMed does not currently manufacture over-the-counter (OTC) drug products and, as such, tamper evident packaging is not a requirement. However, in its combination products area, it does use non-resealable pouches and labelling practices that comply with and constitute tamper-evident packaging. If breached or missing, a consumer can reasonably be expected to determine that tampering has occurred.

Expiration Dating

Expiration dates for combination products with a drug constituent are established through the product development process while working closely with the pharmaceutical customer. Expiration date testing and ageing studies are established in accordance with the requirements of 21 CFR 211.166 to meet customers' requirements, with the stability programme managed by ProMed, an approved lab or the customer. It is ensured that drug product meets applicable standards of identity, strength, quality and purity at the time of use and each individual unit is labelled for sale with an expiration date as determined by appropriate stability testing.

Testing and Release for Distribution

ProMed samples and tests each batch of drug product for conformance to specifications, including the identity and strength of each active ingredient, prior to release. Samples are collected according test plans defined in approved batch records, which include the method of sampling and the number of units per batch to be tested.

Once the samples are tested, the QA team verifies that the test results conform to predefined acceptance criteria and that the samples and results statistically represent the entire batch prior to approval and release. Any batch failing to meet established standards, specifications or any other relevant quality control criterion are rejected. Due to the nature of manufacturing moulded combination devices, reprocessing is not usually possible.

Special Testing Requirements

ProMed tests each batch of drug product purporting to be sterile and/or pyrogen-free using an approved contract laboratory to verify conformance to such requirements prior to product release. The test procedures are included in the approved batch records.

Although ProMed does not manufacture ophthalmic ointments, the company does manufacture implantable, drug eluting ophthalmic devices. ProMed ensures that these products have predefined requirements regarding the presence of foreign particles and harsh or abrasive substances, and that each

ABOUT THE AUTHORS

Bob Parsons has over 28 years of experience in quality systems, regulatory compliance, programme management and product development within the FDA regulated medical device, pharmaceutical and biotechnology industries. His quality assurance expertise includes certification as a lead auditor, performance of quality system gap assessments, system enhancements, alignment and implementation of all quality elements including design controls, risk management, purchasing controls, change control and post-market surveillance. Regulatory experience includes; ISO 13485, 9001 and 14971 certifications, providing guidance for FDA and CE clearance and a designated management representative as well as company representative and lead interface during FDA and ISO audits. He has extensive experience in 483 and warning letter resolution and working within consent-decree environments.

Dr James Arps has over 20 years of experience managing product development and commercialisation of medical devices, advanced coatings and drug delivery technology. He has worked with both industry and academic partners, guiding products through all stages of development from conceptualisation through to customer release. At ProMed Pharma, he oversees programme development activities for polymer-based drug releasing implants and combination device components. He works with a team of engineers to develop new drug delivery vehicles as well as robust manufacturing processes and platforms for controlled release of drugs from a variety of materials for applications in cardiovascular, women's health, ophthalmology and otolaryngology. He has a PhD in Applied Physics from Vanderbilt University (Nashville, TN, US) and an MS in Management of Technology from the University of Texas at San Antonio (TX, US).

batch of product is tested and confirmed to meet these specifications.

Because many moulded combination devices are formulated for controlled or extended release, drug burst and elution profiles are critical to product performance. To confirm how fast the drug substance elutes or discharges from the silicone matrix, analytical methods for dissolution and quantification are validated and performed in-house or by an approved contract laboratory.

Reserve Samples

ProMed retains an appropriately identified reserve sample from each lot in each shipment of active ingredient or released product. The reserve sample consists of at least twice the quantity necessary for all tests required to determine whether it meets established specifications, except for sterility and pyrogen testing. Reserve samples are retained for all drug product samples and excipients for one year after the drug product expiration dates at ProMed Pharma or at the customer's site.

Reserve samples are stored in a product-suitable environment in a closed container. The reserve samples are scheduled through ProMed's PM system for visual examination at least once a year to ensure that the sample integrity is maintained.

Other Requirements

ProMed has a formal procedure for performing annual product quality reviews (APQRs) for each drug product at the end of the first year of a product's commercial manufacturing and every year thereafter. All manufacturing process parameters, failed batches, OOS, non-conformances, complaints or other quality related events are evaluated for trends, systemic issues and opportunities for improvement. As a contract manufacturer, the report is shared with the customer and any changes are evaluated, validated, and approved by the customer prior to implementation.

Drug products in high concentration areas may pose a threat to employee health and safety. ProMed also has a programme for assessing overall personnel health and the protection and safety features required to keep them safe. To prevent exposure, a risk analysis is performed for each API and appropriate containment is specified.

CONCLUSION

In summary, with a dedicated quality system and proper cleanroom facilities and resources, ProMed Pharma has conquered the challenges associated with manufacturing combination products and is able to consistently supply quality drug products to pharmaceutical and device manufacturers. ProMed's expertise and experience in combination products, including drug eluting vaginal rings, glaucoma treatments and diabetes monitoring systems, has added great value to customers, from the planning stages through regulatory submissions and sustainable manufacturing.

ABOUT THE COMPANY

ProMed is an industry-leading supplier of small silicone components for Class III long term implants. Founded in 1989, ProMed has been successful in combining state-of-the-art equipment and tooling to produce tightly toleranced parts for medical devices that are sold in the US, Europe and Asia. ProMed began moulding silicone parts with a pharmaceutical constituent in 2005 and is headquartered in Plymouth (MN, US), with manufacturing facilities in Plymouth, Maple Grove (MN, US) and Puerto Rico.