TAPEMARK®

FROM ONE TO ONE MILLION

Scaling transdermal patches from the lab to mass production

A Path to Production

> Producing a successful transdermal drug formulation is a major undertaking. It can take millions of dollars and years of development.

Completion of a formulation, however, only leads to your next big challenge: scaling from one lab patch to 1 million production patches. And it can be especially difficult if you lack experience in transdermal patches. Commercial production can bring a variety of complexities, ranging from perplexing quality issues and unexpected production delays to high waste.

All of this can slow your time to market, increase your production costs and result in products that don't deliver on your promise to patients.

By following a quality-by-design (QBD) approach, you can proactively address these issues and better ensure a successful product launch.

Four key elements of a QBD approach include:

1. Determine the requirements
2. Assess the risks
3. Define the design space
4. Optimize the control strategy

1. Determine the Requirements

Good process design works in reverse: It begins with your end product and finishes with the raw materials that will be used to produce it.

With this in mind, you should first determine the quality target product profile (QTPP) that you want to achieve in your final product. Key questions that will help determine your QTPP include:

- What dosage will the patch deliver?
- How long should it be adhered?
- What shape will it be?
- How will users know it's applied properly?

The QTPP will drive your specifications, beginning with your product's critical quality attributes (CQA) and critical process parameters (CPP). It's important to remember that not all attributes are CQAs. Focus on those that are essential, or detrimental, to your product's safety and efficacy.

With your CQAs and CPPs in place, you can then define the critical material attributes (CMA) that will be needed in your raw materials to achieve your QTPP.

"A CQA is a physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range or distribution to ensure the desired product quality."

Guidance for Industry: Q8(R2) Pharmaceutical Development, FDA

2. Assess the Risks

A failure modes and effects analysis (FMEA) can be a long and tedious process. But it's absolutely critical to understand your risks and create a robust process upfront so you can produce a quality product in the end.

The first step in a FMEA is to define all process-step failure modes. The severity, frequency and ease of detection for each of those failure modes is then evaluated on a scale of one to 10. Multiplying these three numbers together produces a risk priority number (RPN) for each failure mode. The higher the score, the greater the risk.

If the RPN score exceeds a defined acceptable range, it indicates that either the process must be revised or a mitigating action must be taken to lower it to an acceptable score.

"Failure modes and effects analysis provides a structured approach to identify, estimate, prioritize, and evaluate risk with the intention to prevent failures."

Process Robustness – A PQRI White Paper, Product Quality Research Institute

3. Define the Design Space

Defining your design space involves examining your operations to ensure they will produce a quality product. Key considerations at this stage include:

Design of experiments (DoE) tools should be used to evaluate the impact of CPPs on CQAs. It's important to not only understand each individual CPP, but also how they interact with each other. This will set up the process parameters that will enable you to achieve your desired product results.

For example, looking at the interactions between the CPPs of speed, temperature and pressure will help you determine the optimal ranges of each for heat sealing a pouch.

Raw materials selection is often overlooked during design. But raw material attributes (RMA) have acceptable ranges just like processes. If acceptable ranges are not defined and specified, the RMAs can vary from lot to lot. This can ultimately impact product performance.

Materials with large particles, for example, will perform differently than fine particles. This can impact a drug's bioavailability.

How do you determine an acceptable range for an RPN score?

There is no standard acceptable range. It varies in each situation based on a number of variables.

If needed, turn to a partner with transdermal production experience to help determine an acceptable range for your application.

3. Define the Design Space (continued)

In-process testing involves understanding how materials are impacted during manufacturing.
This can help you create a more robust production process and ensure the right controls are in place.

In-process testing can include methods to ensure your blending process has achieved a homogenous mix. It also can include measuring and quantifying adhesion characteristics throughout your manufacturing process.

Finished-product testing analyzes your final product's physical properties. This can help ensure your product is produced with the desired physical characteristics and performs as expected.

Adhesion and tack testing, for example, can help you determine if your product will adhere to a user's skin for a given period of time. This requires that you first define what levels of adhesion level and tack are required in a finished product, and then implement the methods or tools to measure for those levels.

Typical finished-product testing examines:

- **Assay**
- **Impurities**
- **Content uniformity**
- **Related substances**
- **Residual solvents**
- **Drug release**
- **Microbial**
- **Critical excipient content**

4. Optimize the Control Strategy

By getting in front of challenges in your control strategy early on, you can help optimize your processes, avoid delays and compliance issues, and keep your costs down come production time. Top challenges to address include:

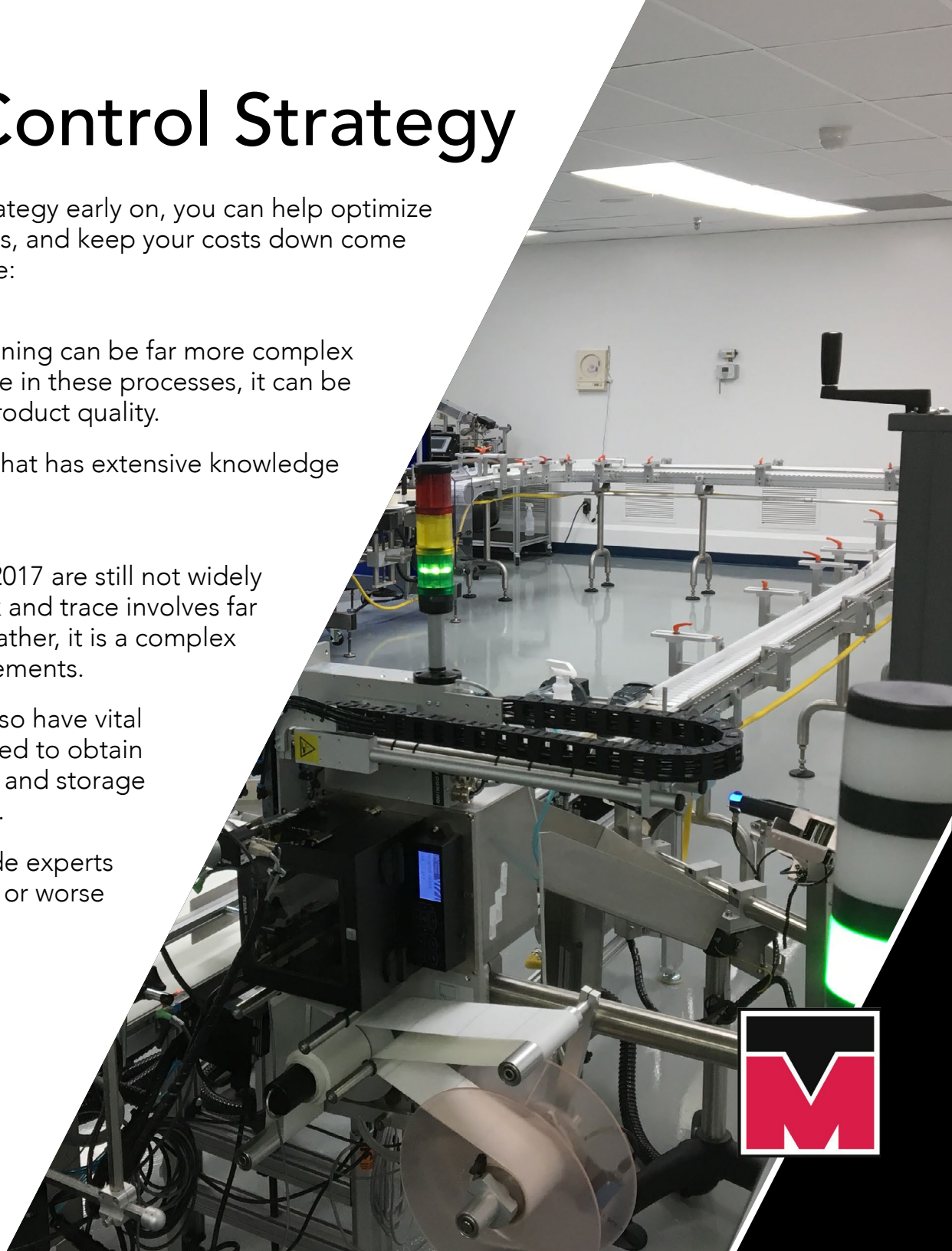
Process complexity
Processes such as converting, packaging and cartoning can be far more complex than many manufacturers expect. Without expertise in these processes, it can be difficult for you to achieve a consistent yield and product quality.

Consider partnering with a contract manufacturer that has extensive knowledge and experience in these processes.

Compliance
Track-and-trace requirements set to take effect in 2017 are still not widely understood in the industry. Keep in mind that track and trace involves far more than adhering serial numbers on products. Rather, it is a complex and far-reaching effort, with significant data requirements.

Transdermals that contain controlled substances also have vital compliance requirements. They can include the need to obtain a quota from the DEA, implement secure handling and storage systems, and use abuse-deterring product designs.

Whatever your compliance challenge, utilize outside experts during the design stage to help avoid fines, recalls or worse once your product goes to market.



4. Optimize the Control Strategy (continued)

Cost of Goods Sold (COGS)
Process waste is the biggest cost driver in transdermals. Typical transdermal patch yields are anywhere from 50 to 80 percent – far lower than other dosage forms. This is why process design is so critical. It can have a 60 percent cost impact on your final product.

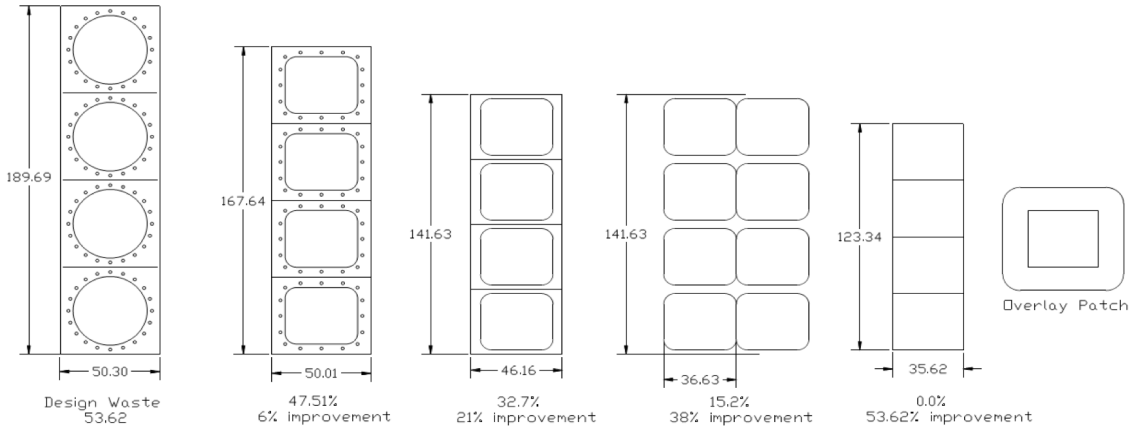
Your final yield is the result of multiplying six separate process yield factors together:

- Mixing yield
- Coating yield
- First trim slit yield
- Rounded corners (RCR) yield
- Die cut side or ladder yield
- Converting reject or centering yield

This means you could have five process yields above 90 percent but one at 75 percent, and you will end up with an overall yield of around 60 percent.

Design waste should also be targeted early on to help minimize your COGS.

For example, a circular patch cut from a square could generate 54 percent design waste. But by optimizing the patch's shape to the material it's cut from – such as a square patch cut from square material – you can significantly reduce or even eliminate this waste.



Additional Considerations

Beyond adhering to the four key elements of QBD, there are some additional considerations worth keeping in mind as you scale up to production:

- Break your process development into phase gates with defined end points. This will force you to complete each phase before moving on to the next. It also helps ensure that robust processes are in place by the time you get to full-scale production.
- Make process development a continuous cycle. Key learnings can come late in the development process or even after production begins. For example, CQAs and CPPs may be discovered long after the requirements stage.Still, this information should be captured and driven back into your requirements.
- When using a contract manufacturing organization (CMO), ensure it has strong in-house analytical capabilities and transdermal expertise. Transdermals have many subtleties that are not initially obvious to companies that are only familiar with other dosage forms.
- Remember that FDA guidance documents can be subject to interpretation. Having expertise in place, whether in-house or through a partner, can help you interpret these documents as they relate to your unique situation.

A Clear Path to Success

Many small startups and major pharmaceutical companies are similar in that they lack experience in bringing transdermals to market. A learn-as-you-go approach can be fraught with risk, from launch delays and cost overruns to inconsistent product performance.

Following the tenants of a QBD approach will help reduce these risks and help clearly define success from the start.

For more information or for a CMO to help take your patch from one to 1 million, contact one of Tapemark's transdermal experts at 800-535-1998. Or visit the Tapemark transdermal patches webpage to learn how the company can help you.

The global transdermal drug-delivery market is projected to exceed $95 billion by 2025.