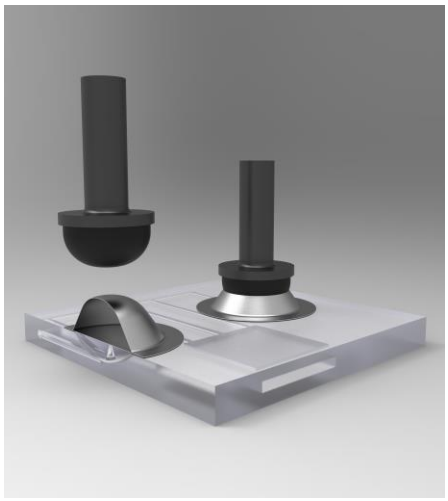
Design, development & validation of point-of-care reagent blisters: A process walkthrough

Designing, developing and validating point-of-care diagnostic reagent blisters is so complex because medical device manufacturers must have their sights set on several different targets at once.



They need to know:

- If their reagent is compatible with specified blister materials
- Whether the chosen actuation method is compatible with blister shape and seal characteristics
- Whether filled blisters will collapse and dispense the appropriate reagent volume to the test card reservoir
- Whether extant testing methodologies are adequate to assess the quality of new blisters or if new tests must be devised
- If their blister manufacturing and consumable assembly process is capable of ramping up from initial engineering builds through full-scale manufacturing runs to meet aggressive commercialization timelines

Owing to this complexity, medical device manufacturers risk underestimating or overlooking the critical technical aspects of delivering reagents to blisters and then attaching those blisters to test cartridges or other consumables.

The ways those complexities impact the onboarding of blisters to an associated consumable adds to the challenges.

These reagent-filled blisters must interact with the entire test system. They are a critical component to the efficacy and repeatable performance of a given point-of-care diagnostic test.

Use this white paper to learn:

603-692-9955 | somersworth@j-pacmedical.com

- Blister design, material selection and feasibility testing considerations
- More detail on the qualification and validation considerations related to diagnostic reagent blister development
- How program guidance from a turnkey point-of-care blister manufacturer can strengthen your processes and help commercialize your product faster

For a more concise summary of what to consider when designing reagent blisters, read this article.

Know what contributes to good blister design

Understanding the mechanics of a point-of-care test utilizing reagent blisters is essential to developing the most effective blister design.

The design of the consumable test card is contingent on test chemistry and defined instrument functionality that drives performance of the test. Developers must define reagent chemistries and know the associated dose volumes required to perform the test.

The instrument activates the test card in a manner that introduces the appropriate volume of reagent at the correct time and in a given order to drive a successful test. This activation method — along with the associated activation force — is a critical contributor to blister design.

Blister material selection

Blister material selection can begin once reagents and their formulations established. Selected materials should provide optimized chemical resistance to the contained reagent and display barrier performance characteristics to meet shelf life requirements.

A typical reagent blister is made from two unique foil laminates. The formed bottom stock is typically a heavier foil gauge that allows the blister reservoir to be cold-formed without fracturing the material and compromising barrier properties. The lidstock generally is a lighter and more flexible foil suitable for needed barrier properties but which also enables piercing — the most typical method to drive dispensing of the contained reagent.

These two substrates are heat sealed together to form the reagent blister.

Blister geometry

603-692-9955 | somersworth@j-pacmedical.com

Two variables impact the overall shape of a blister: the space available within both the instrument and on the microfluidics consumable and the desired overall volume of the blister reservoir.

Blisters can accommodate several shapes, but the most typical is a dome reservoir shape. These perform most reliably and are the most economical to manufacture. (In general, complex blister shapes should be avoided because it's more difficult to design a workable actuation method. This creates opportunities for leaks and increases overall costs.)

Blister volume includes a 20% headspace above the target reagent fill volume. This headspace provides some clearance for the placement of lidstock over the reagents. This minimizes the risk that reagents with varying meniscus types will interfere with heat sealing, ensuring more reliable, consistent heat sealing.

For any given blister bottom stock, the depth of draw that will be required to gain a needed volume within an available space must be carefully considered. As we noted above, formation of the reservoir must be accomplished without fracturing the foil or laminate layers to provide optimal stability performance.

A validated flat flange around the reservoir enables a high-quality barrier heat seal between the top and bottom blister stocks while also providing a flat surface to allow solid mounting of the blister to the microfluidics card via a two-sided pressure-sensitive adhesive.

Different sizes of flanges may be necessary depending on space restrictions on the card. If this is the case, consider:

- Some additional engineering and process tweaks might be needed to ensure the sealed barrier is sufficient and provide for adequate adhesion to the card
- Alternatively, you may decide the effort of redesigning the card itself to accommodate a more typical flange size outweighs the difficulties of sticking to a more unconventional shape

If you feel you may confront these alternatives and aren't sure which makes the most sense, engage a blister manufacturing and assembly provider as soon as you can.

It's an exercise in trade-offs. Engineers at J-Pac Medical excel in pointing medical device developers toward blister designs that (a) will result in the most consistent performance and (b) are the simplest and most effective to manufacture.

603-692-9955 | somersworth@j-pacmedical.com

Blister fill volume

As mentioned previously, the blister design must include a reservoir volume calculation based on the available target fill volume and related headspace. Developers need to establish via testing that a given reagent volume within the reservoir will provide the necessary dose to the microfluidic card when activated and pierced.

Typically, the blister and/or reagent volume will require some adjusting to ensure repeatable reagent delivery. There will be some loss as reagents travel from their blister reservoirs through microfluidic channels and ultimately to the testing site.

The amount of reagent lost will depend on:

- The console's activation and piercing methodology including actuation force
- The crush characteristics of the blister materials
- The design characteristics of the microfluidic channels

It's essential that blister design is not finalized until a blister fill volume reliably delivers enough reagent for a test to be successful.

Headspace management

While the blister reservoir size is established assuming headspace over the filled reagent, various headspace management methods can eliminate ambient gases in this headspace that may negatively affect test performance.

Developers must thoroughly assess reagent and process sensitivities to gases present in the blister headspace to determine what (if any) mitigating steps must be incorporated in the blister production flow.

One option is to replace ambient gases with inert gases. Alternatively, the gas and headspace can be eliminated entirely via vacuum sealing. Bear in mind that vacuum sealing is a more intensive process requiring advanced equipment. Consult a blister manufacturing provider to determine whether this is necessary or if the requirement can be side-stepped by changing other aspects of your product.

Preliminary shelf life study

603-692-9955 | somersworth@j-pacmedical.com

At this point, developers should perform an initial shelf life evaluation to gain additional confidence that the chosen blister materials and format will accommodate reagents for the targeted shelf life duration.

This preliminary stability study is meant only to provide an early indicator of blister performance. If quality inconsistencies are observed, adjustments to blister design, materials or manufacturing processes may be necessary.

Even though it "doesn't count," don't skip performing a stability study early! In our experience, medical device developers who overlook a preliminary investigation learn of quality problems upon formal testing which occurs much later in the development process.

This can cause significant, costly delays.

Blister design freeze and initiating process development

With feasibility testing completed, developers can claim a blister design freeze and initiate process development.

To support these activities, developers must fabricate production tooling and then develop the process the tooling will execute. To validate the processes, the typical IQ (installation qualification), OQ (operational qualification) and PQ (production qualification) methodologies must be employed.

Test runs conducted during process validation will yield usable blister samples you can use to validate your blisters and the diagnostic test.

The ultimate test for any reagent blister is the demonstrated integration to the test card, so buildouts and test performance of assembled consumables are always a concluding step in the various development phases.

Blister design is an iterative process sometimes requiring sample runs to determine the ideal design, material, forming, filling, sealing and die cutting specifications. Learn more or order blister samples from J-Pac Medical here.

603-692-9955 | somersworth@j-pacmedical.com

Blister forming method

By this stage, developers should have concluded the design activities that establish final blister format. Now, they must analyze the chosen forming tools to ensure that formed blisters will meet all specified dimensional requirements. This step must be performed for each tool and each blister geometry that is incorporated to the test consumable.

Test runs demonstrate the capability of new tooling. Once those are complete, teams conduct visual assessments and take measurements to assess the quality of formed test blisters. These data must be documented.

As a turnkey contract manufacturing partner, J-Pac Medical supports in-house development of custom tooling. The process of designing and integrating custom tooling, verifying that it will perform to your requirements and ensuring it is adequately documented contributes to a faster overall development timeline.

Reagent dispensing method

Reagent filling is typically accomplished using a multi-up array of fill stations. Developers must qualify and validate each position.

A design of experiments (DOE) and a subsequent short sample run are critical to determining pump settings for each position. Through DOE and sample runs, you'll be able to establish minimum and maximum fill volumes that will inform the ultimate target fill volume required for a successful test.

You must perform this step for each reagent and fill volume that will be incorporated to the test consumable. To assure quality, conduct weight checks of filled blisters and compare observed weights to the weight associated with minimum and maximum volumes.

Heat sealing method

The blister materials discussed in this white paper are typically heat sealed to form a permanent bond. Again, performing a DOE will provide critical data you'll need to establish:

- Heat seal tool temperature
- Nip pressure

603-692-9955 | somersworth@j-pacmedical.com

- Contact time

Start by determining the parameter sets for the low and high burst strengths that meet specification. Visual assessments and burst tests will show whether those parameter sets will work.

Be aware of the following potential complication: Developers might not always know how much force a specified burst-type testing console can deliver. Or, if they are aware, they may yet assume that the blister materials and heat sealing methods they've specified are capable of achieving seal characteristics necessary to work reliably with that chosen console.

It's not always a given, especially when blisters feature uncommon cross sections or flange sizes. In these cases, manufacturers must take special care to develop heat sealing methods and process parameters that create adequate seals without corrupting the reagents inside the blisters.

Uncertainty here may lead to product quality, shelf life and end use challenges that force developers back to the drawing board. For more, read about how contract manufacturing partners can help develop blister seal strength specifications.

Prototype build

With processes developed for the form, fill and seal components of the overall production flow, you can generate samples to use for benchtop testing that demonstrates performance feasibility.

As with the preliminary shelf life testing, these data are not submission quality but nonetheless are essential supporting information for process refinement and verification.

Test methods

The testing conducted to show whether a diagnostic reagent blister process will result in reliable quality manufacturing is one of the most crucial stages in program development.

Depending on the nature of the blister you've designed or the manufacturing process chosen to produce it, you may need to establish new testing methods to assess in-process or finished components.

603-692-9955 | somersworth@j-pacmedical.com

If a new method is needed, test method development and validation is required such that the method can be utilized to support the upcoming OQs, PQs and ongoing production. However, note that new test methods are required *only if existing test methods are not able to adequately measure critical-to-quality attributes or performance*.

Obviously, using existing test methods is preferable to inventing new ones if the option is available. A blister manufacturing partner familiar with testing methods can help you quickly determine whether new methods are required or not.

J-Pac Medical's extensive experience developing new testing methods (and our library of available existing testing methods we can pull from) is another contributing factor to an overall speedier product launch.

Process OQ

Process OQ is an overall process challenge that demonstrates the low and high parameter sets that result in blisters that will meet specification. This run is performed under protocol and is typically completed as a single end-to-end process challenge that will include forming, filling and sealing. An end-to-end assessment is recommended to capture the interactions between each of these processes at their process extremes.

Runs typically consist of 30 blisters per blister size/reagent combination from each tooling position. As above, you'll need to test the critical-to-quality attributes (and document the results) of the sample runs to determine whether your process is capable of achieving in practice its intended performance in theory.

Engineering Build

Next, developers perform an engineering build using OQ nominal parameters. Data generated from blister samples run at these parameters apply to downstream PQ blisters so long as the OQ parameters used for the run remain within the validated parameters that are established through PQ.

Samples from this run can be used for activities that include:

- Transit testing
- Formal shelf life studies to establish expiry claims for the consumable (typically includes both accelerated and real-time studies)
- Clinical trials

603-692-9955 | somersworth@j-pacmedical.com

Process PQ

This is the process validation which consists of three lots of blisters that are ultimately saleable. Associates execute these runs under protocol using multiple crews and raw material lots to ensure the process as designed is capable in real-world production.

Developers must run PQs for each reagent/fill volume/blister geometry combination incorporated in the test consumable.

From there, developers can use these PQ blisters to aid the fabrication of consumables that will be used to validate the performance of the overall diagnostic test.

Provided that standalone blister performance data gathered during overall system validation was satisfactory, "development" is complete and commercial production can launch.

Good guidance can make the difference

If the process described in this white paper is any indication, point-of-care test developers have their work cut out for them.

It doesn't help that developers face the added pressure to meet key development milestones and stay on-track under aggressive launch timelines.

If this is the case and you feel you need a partner who can provide critical technical guidance, reduce project risk and ultimately help launch your point-of-care test faster, contact the team at J-Pac Medical today.

603-692-9955 | somersworth@j-pacmedical.com