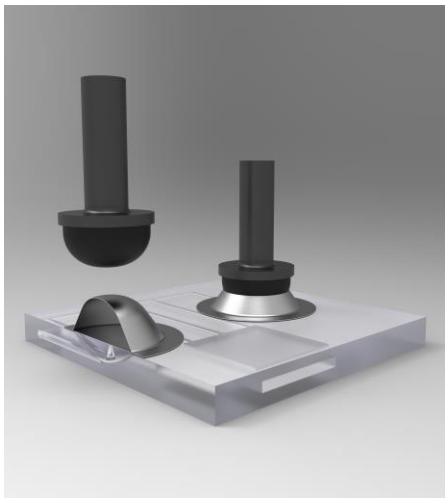
Design, Development, and Validation of Point-of-Care Reagent Blisters

Overview

Within the design and development activities for a Point-of-Care Diagnostic Test and the associated microfluidic consumable, the complexities related to on-boarding the needed reagents are often underestimated or overlooked. These reagent filled blisters are required to interact with the entire test system, and are a critical component to efficacy and repeatable performance of a given point-of-care diagnostic test. This white paper is intended to provide an overview of the design, qualification, and validation considerations related to these reagent blisters.



Blister Design

The design of the consumable test card is contingent on an established test chemistry and a defined hardware/console that will drive performance of the test. Reagent chemistries will be defined, and appropriate number of reagents and associated dose volumes required to perform the test will be known. The console will activate 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 method of activation, and the associated force of activation, will be a critical inputs to blister design. The ultimate volume of the blister reservoir will be driven primarily by reagent volume requirements to support a test, but must also include some assessment of reagent recovery efficiency that will be linked to the activation and piercing methodology incorporated in the test. Ultimate shape will be predicated on available space within the test console and on the test card.

Feasibility Testing

Blister Designs will iterate with development experience. Samples of these designs can be made using 1-Up tools and laboratory methods to support forming, filling, sealing, and die cutting of needed blister samples.

Blister Materials

With reagents and their formulations established, blister material selection can be undertaken. Selected materials should provide optimized chemical resistance to the contained reagent, and also provide required barrier performance 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 such that the reservoir of the blister can be cold-formed without fracturing or compromising the barrier properties. The lid stock is typically a lighter more flexible foil that provides needed barrier, but also enables piercing, the typical method to drive dispensing of the contained reagent. These two substrates are heat sealed together to form the reagent blister.

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Blister Geometry

The overall shape of the blister will be largely determined by the space that is available within the test console and on the microfluidics test card, and also the desired overall volume of the blister reservoir. Blisters can be any shape, but most typical and most consistent performing are typically a dome reservoir shape and a round die cut. Reservoir size is typically calculated with a 20% head space above the target reagent fill volume. This headspace provides some clearance for the placement of lidstock above filled reagents that exhibit various meniscus types that can interfere with heat sealing. For any given blister "bottom" stock, the depth of draw that will be required to gain a given volume within an available space will be carefully considered. Forming of the reservoir must be accomplished without fracturing the foil or laminate layers in order to provide optimal stability performance. A 3mm flat flange around the reservoir is typical to enable a high quality, barrier heat seal between the top and bottom blister stocks, and also provide a flat surface to enable solid mounting to the microfluidics card. A two-sided pressure sensitive adhesive is typically used to adhere the reagent blisters to microfluidic test cards.

Fill Volume

As mentioned previously, the blister design will include a reservoir volume calculation based on best available target fill volume and related headspace. Data needs to be established that demonstrates this reagent as filled will provide the necessary reagent dose to the microfluidic card when activated and pierced using the intended system methods. It is typical that the reservoir volume and/or reagent fill volume will require adjustment to ensure repeatable reagent delivery to ensure a successful test. Reagent recovery from the activated blister is key to setting a meaningful target fill volume.

Headspace Management

While the blister reservoir size is established assuming headspace over the filled reagent, various headspace management methods are available to reduce or eliminate ambient gases in this headspace that may negatively affect test performance. Ambient gases can be replaced with inert gases (N2 for instance) through gas-flushing, or the gas and headspace can be eliminated entirely using a vacuum sealing process. Reagent and process sensitivities to gases present in the blister headspace must be thoroughly assessed to ensure appropriate steps are incorporated in the reagent blister production flow.

Preliminary Shelf Life Study: At this point, a preliminary shelf life evaluation may be performed to gain additional confidence that blister materials and format will accommodate reagents for targeted shelf life duration. This is typically an accelerated study only to provide an early indicator of blister performance.

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Blister Design Freeze

With testing of feasibility quality blisters completed, blister design freeze can be claimed. With this key milestone attained, Process Development can be initiated. To support these activities, production tooling should be fabricated and processes developed on these tools. Blister production processes are validated using typical IQ, OQ and PQ validation methodologies, and blister and diagnostic test validation are accomplished using samples from the various development runs. 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.

Process Development & Validation:

Blister Forming Method

The final blister format is established from completed design activities. Each cavity of the multi-cavity production forming tool will be analyzed to ensure that formed blisters dimensionally meet all requirements as specified. This step will be performed for each tool for each blister geometry that is incorporated to the test consumable. Quality of the formed blister will be determined through visual assessment and measurements. Tooling capability will be demonstrated and documented.

Reagent Dispense Method

Target fill volume is established from the completed design activities. This fill volume takes into consideration the learnings of the reagent recovery activity described above. Reagent filling is typically accomplished using a multi-up array of fill stations, and each position will be individually qualified and validated. Pump settings for each position will be developed through the performance of a Design of Experiments (DOE) and a subsequent short sample run. Parameters will be established for low fill and high fill volumes that meet specification. This step will be performed for each reagent and fill volume that will be incorporated to the test consumable. Quality of the filled blisters is typically demonstrated through weight checks of filled blisters.

Heat Sealing Method

The blister materials discussed in this white paper are typically heat sealed to form a permanent bond. The heat seal process is characterized through the performance of a DOE, and parameters are established for heat seal tool temperature, nip pressure and contact time. Parameter sets will be determined for the low burst strength that meets specification, and also a high parameter set that meets specification. Quality of the sealed blisters is typically determined through visual assessment and burst testing.

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Prototype Build

With processes developed for the form, fill and seal components of the overall production flow, samples can be generated that can be used for benchtop testing to demonstrate performance feasibility. The data generated is not submission quality, rather usable as supporting information for process refinement and verification.

Test Methods

For a given blister and associated POC Diagnostic Test, customized test methods may be established to assess in-process components or finished goods. If the method is new, test method development and validation is required such that the method can be utilized to support the upcoming OQ's, PQ's and ongoing production. New test methods will be needed only if existing test methods are not able to adequately measure critical to quality attributes or performance.

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 performed under protocol and is typically completed as a single end-to-end process challenge that will include blister forming, blister filling and blister sealing. An end-to-end assessment is recommended such that interactions between each of these processes at their process extremes will be captured. Runs are typically 30 blisters per blister size/reagent combination from each tooling position. For all processes, process capability will be determined and documented with testing of critical to quality attributes as discussed previously.

Engineering Build

An engineering build is typically performed using OQ Nominal Parameters. Data gained from blister samples run at these parameters applies 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

Process PQ

This is the process validation and will include three (3) Lots of blisters that are ultimately saleable. These runs are performed under protocol by production associates using multiple crews and raw material lots to ensure the process is capable. A PQ will be run for each reagent/fill volume/blister geometry combination incorporated in the test consumable. These PQ blisters are typically passed on to be included in the fabrication of consumables that will be used to validate the performance of the overall diagnostic test. Successful completion of this step as measured by standalone data extracted from fabricated blisters, and blister performance in the Overall System Validation, establishes that the blister processes can formally transfer to manufacturing.

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About the Author

Rick Crane has more than 30 years of experience in the healthcare products industry. He brings strong general management skills demonstrated across operations, R&D, program management, technical sales, and marketing organizations. Crane is an Ameristar Packaging Competition Gold Star Award Winner for Medical Device Package of the Year, and is a patent holder. He has a Bachelor of Science from Ursinus College.

About J-Pac Medical

J-Pac Medical is a manufacturing outsourcing partner to medical device OEM's seeking a faster time-to-market and dependable long-term supply. We specialize in single-use medical devices, biomaterial implants, and lab-on-chip diagnostic consumables. J-Pac delivers a validated end-of-line solution for package design, cleanroom assembly, sterilization, and supply chain management. We are FDA registered and certified to ISO 13485:2016.

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