Rethinking Active Packaging
New Material Science Solution to Old Challenges

Aptar
CSP Technologies

Badre E. Hammond | VP Commercial Operations

About Aptar CSP Technologies

- Joined AptarGroup August 2018
- Material science specialist delivering innovative, highly-engineered, active packaging solutions
- Headquarters Auburn, Alabama, USA, with global footprint
- + 1 billion components manufactured annually, 4 manufacturing locations worldwide
- + 500 worldwide patents

Auburn, AL USA

Atlanta, GA USA

2018 Expansion - Auburn, AL USA

Niederbronn-Les-Bain, France

Guangzhou, China

3-Phase Activ-Polymer™ Material Science

3-Phase Activ-Polymer™ Material = Platform Material

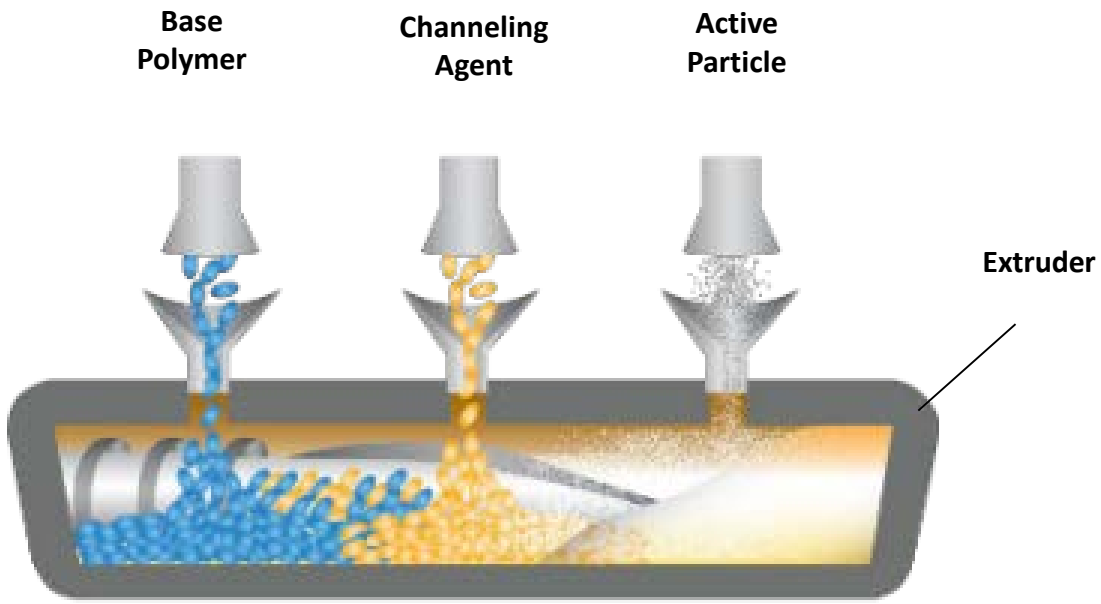
Material Science: Adding Chemistry to Polymers

3-Phase Polymers

1. **Majority Polymer**: Base structure component

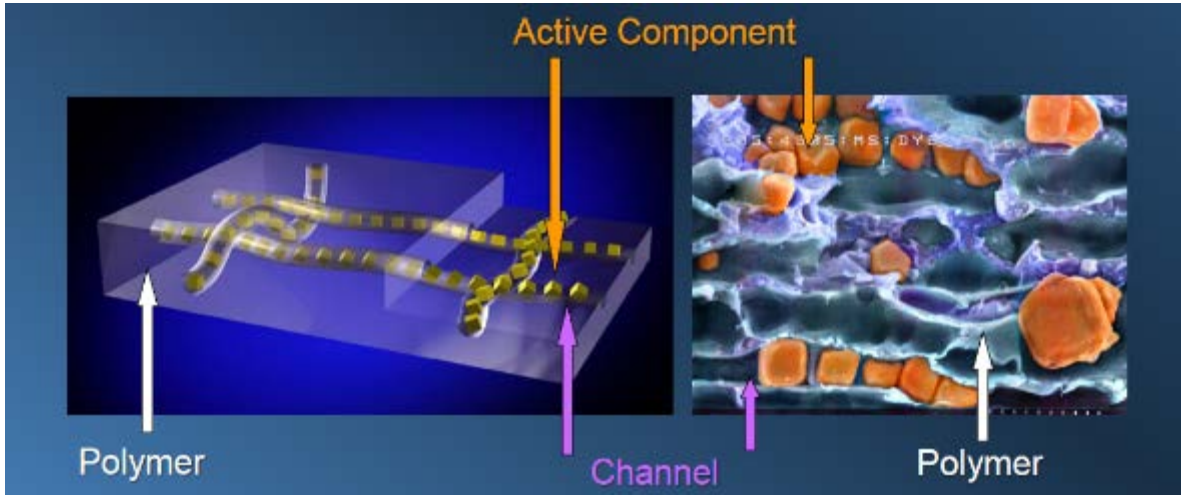
2. **Particle:** Adsorbing/absorbing – active component

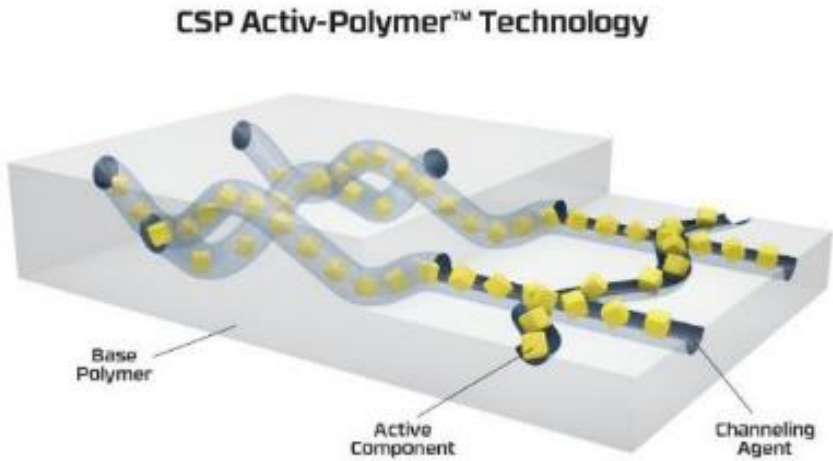
3. **Minority Polymer/Channeling Agent:** Immiscible in majority polymer



Material Science: Adding Chemistry to Polymers

- Channels created within a polymer allow movement of gases
- “Active” particles are added to the polymer in order to:
  - **Adsorb** or **Absorb** (moisture, gases, reactive impurities, odors, formaldehyde and other volatiles)
  - **Release** (aromas, biocides, nutrients, carbon dioxide)
- **Gas diffusion** is controlled through the channel composition



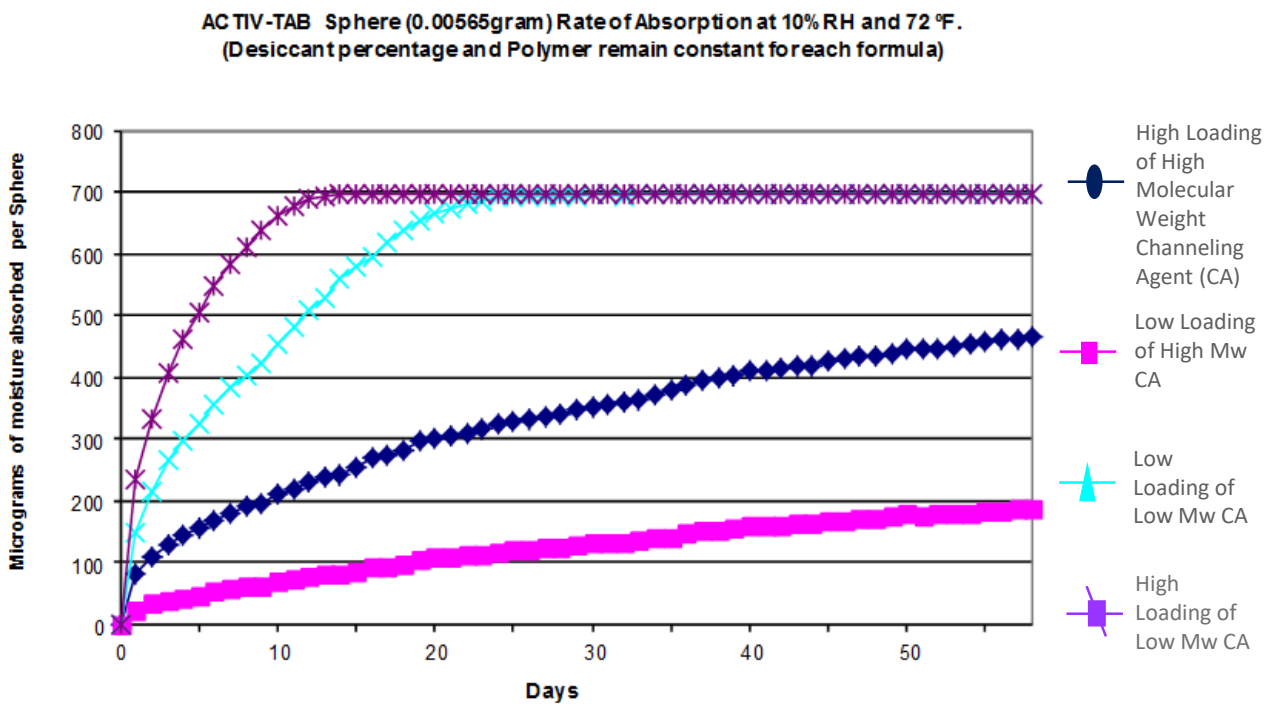


Heads Space Management

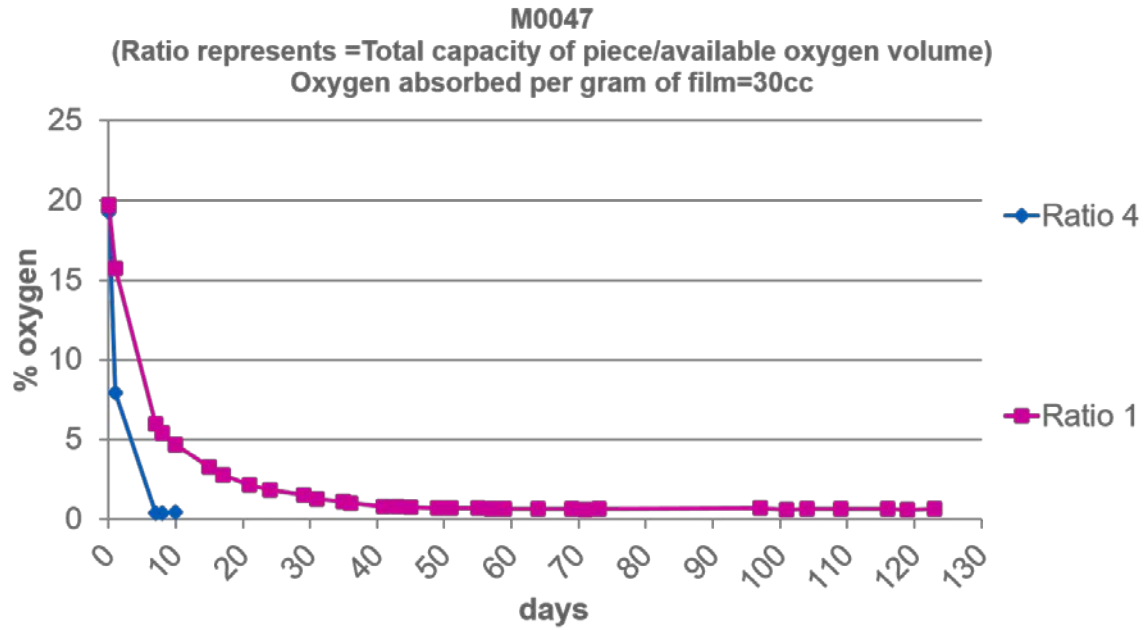
3-Phase Activ-Polymer™ material allows the **control of kinetics** based upon formulation

- Uptake rate can be increased or decreased
- Capacity can be increased or decreased

Customized Absorption Rates



Oxygen Scavenging Customization



Active Packaging – Putting Chemistry into Polymers

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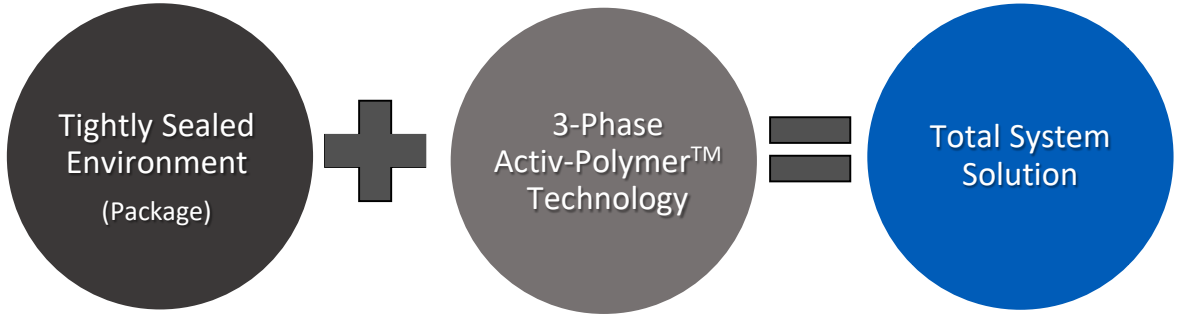
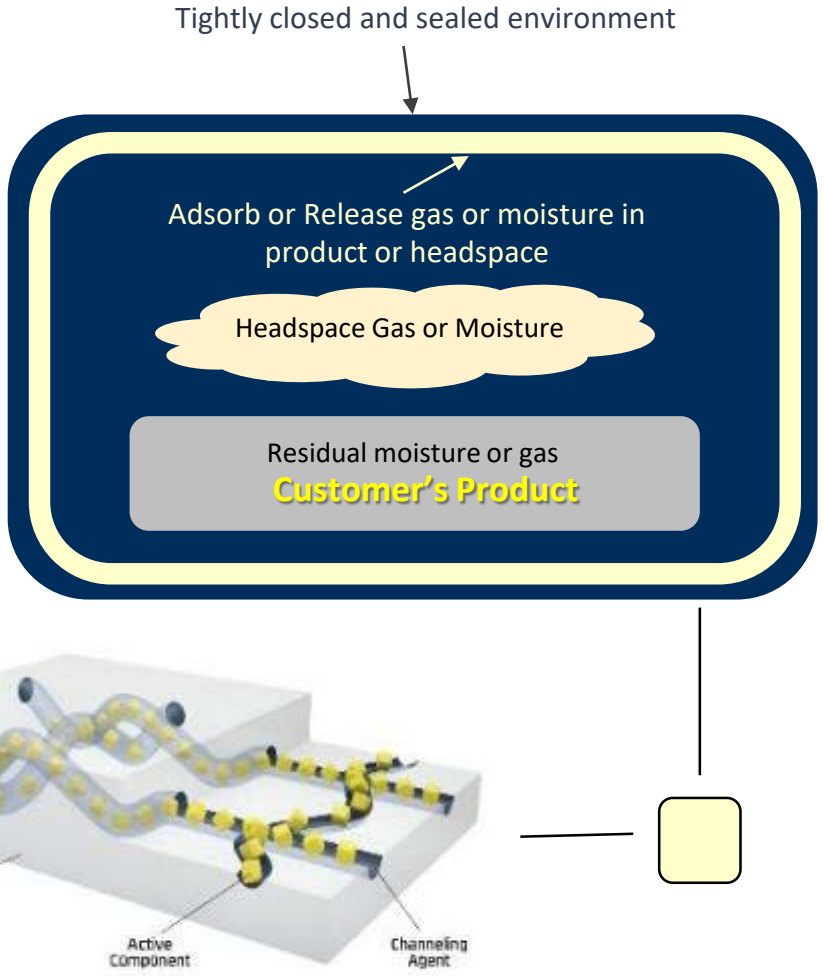
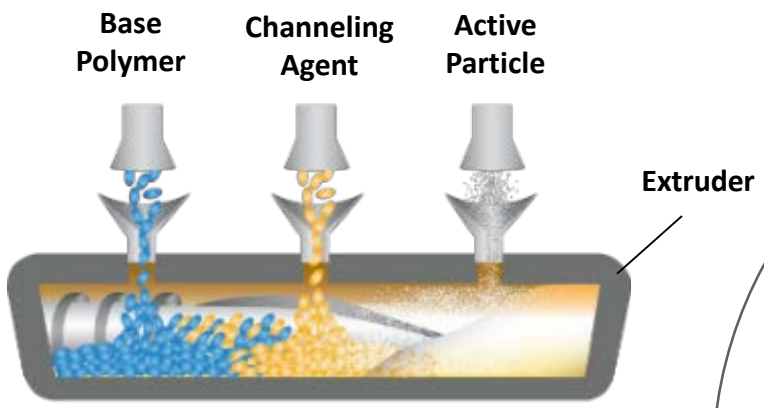
Utilizing 3-Phase Activ-Polymer™ technology requires a tightly sealed environment

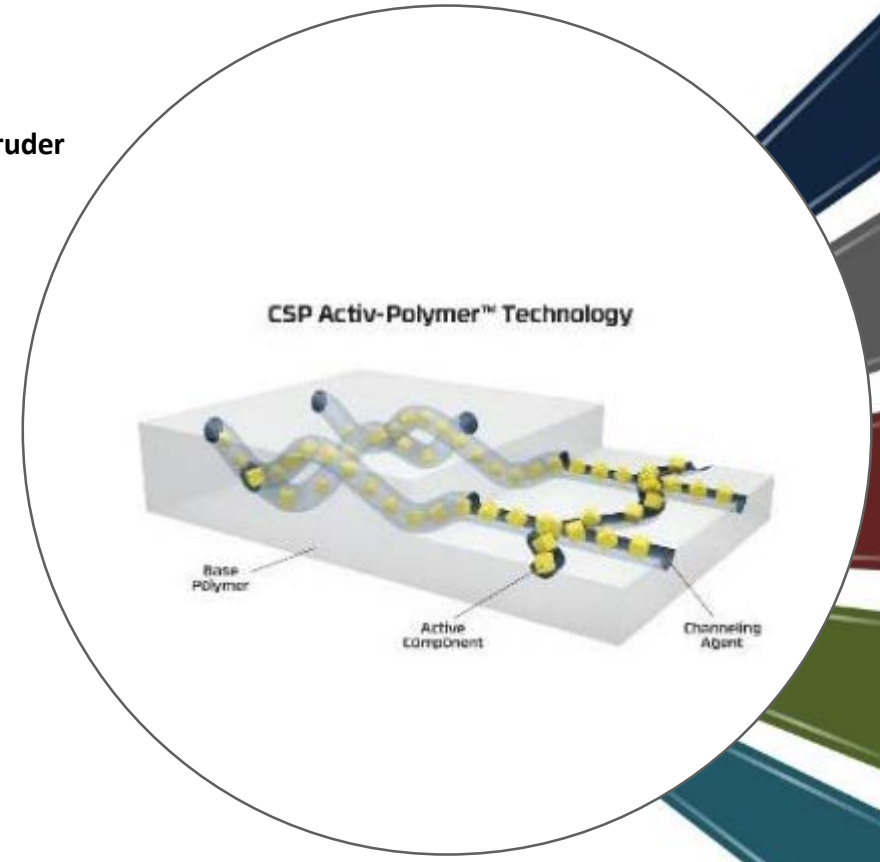
- Chemistry required determined
- Gas or moisture transmission rates are reviewed
- Focus on seals associated with package
- Amount of ***3-phase material*** required will depend on how ***tight*** of an ***environment*** it will be placed in





Three Phase Material = Platform Material





Active Packaging Management

- Moisture Control
- Scavenging
- Antimicrobial
- Emitters
- Odor removers

Injection molding

Thermoforming

Extrusion film

Extrusion blow molding

Hot melt

Platform Technology Serving Broad Therapeutic Areas

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Material science deployed in key therapeutic areas → **Activ-Vial™, Activ-Seal™, Pharmapuck™, and Activ-Film™**

Oral Solid Dose	Transdermal	Drug Delivery	Diagnostics	Probiotics	Medical Device
Immunodeficiency Treatment	Hormone Patch	Anti-Fungal	Blood Glucose Testing	Dietary Supplement	Implant Neurostimulator

Application Field: Oral Solid Dose

Protecting Oral Solid Doses from O_2 / Moisture

- **Secondary packaging with sachets**
  - Adds materials and size to packaging
  - Complexity for end-user

- **Fishbone designs**
  - Adds materials and size to packaging
  - Complexity for end-user

Protecting Oral Solid Doses from O_2 / Moisture

- **Cold form foil**
  - Excellent barrier protection
  - Does not address initial water content or headspace moisture/oxygen
  - Increased blister card size vs. thermoform
  - Compliance (tablet not visible)

- **Foils with integrated desiccants**
  - Mitigates ingress through edges
  - Fixed desiccant capacity per blister

Protecting Oral Solid Doses from O_2 / Moisture

- **Nitrogen Purging (reduce/eliminate oxygen)**
  - Difficult to validate; often a custom solution
  - Adds time to line stoppages
  - Operator safety – monitor room oxygen levels
  - Below 8 - 10% oxygen, can be difficult to achieve
  - Does not address oxygen ingress

Sources of Moisture and Oxygen in Blister Packaging

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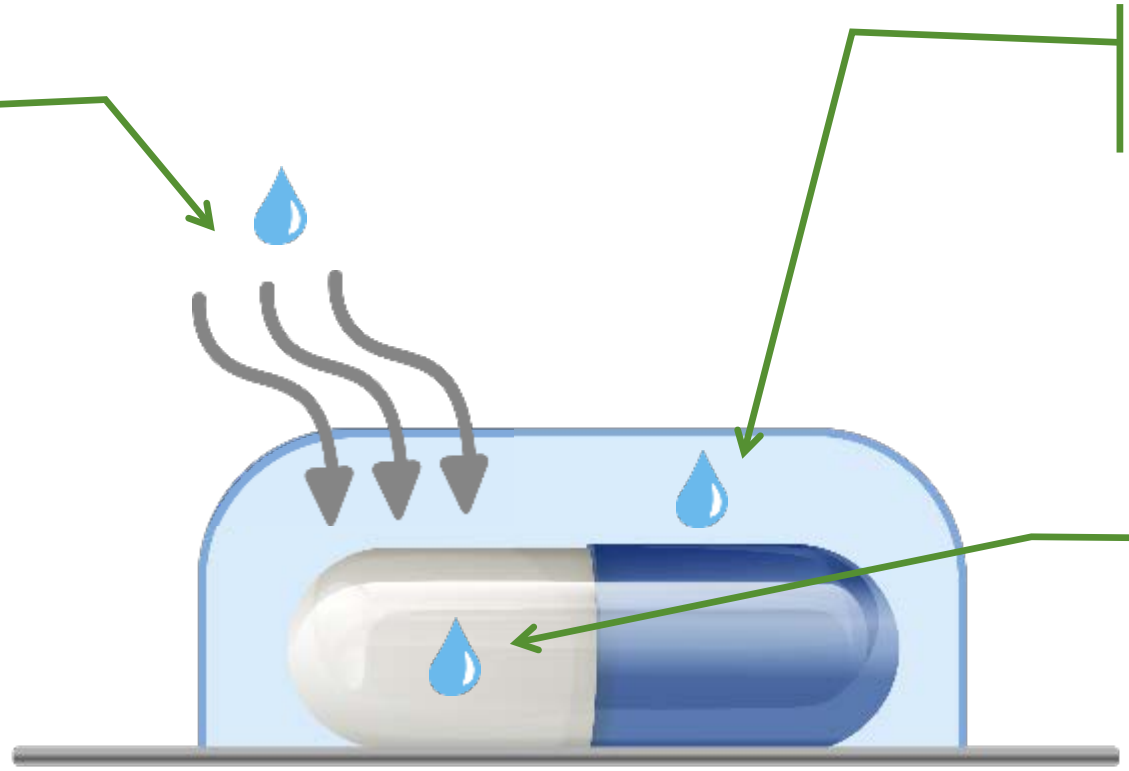
2. Ingress through the package over time

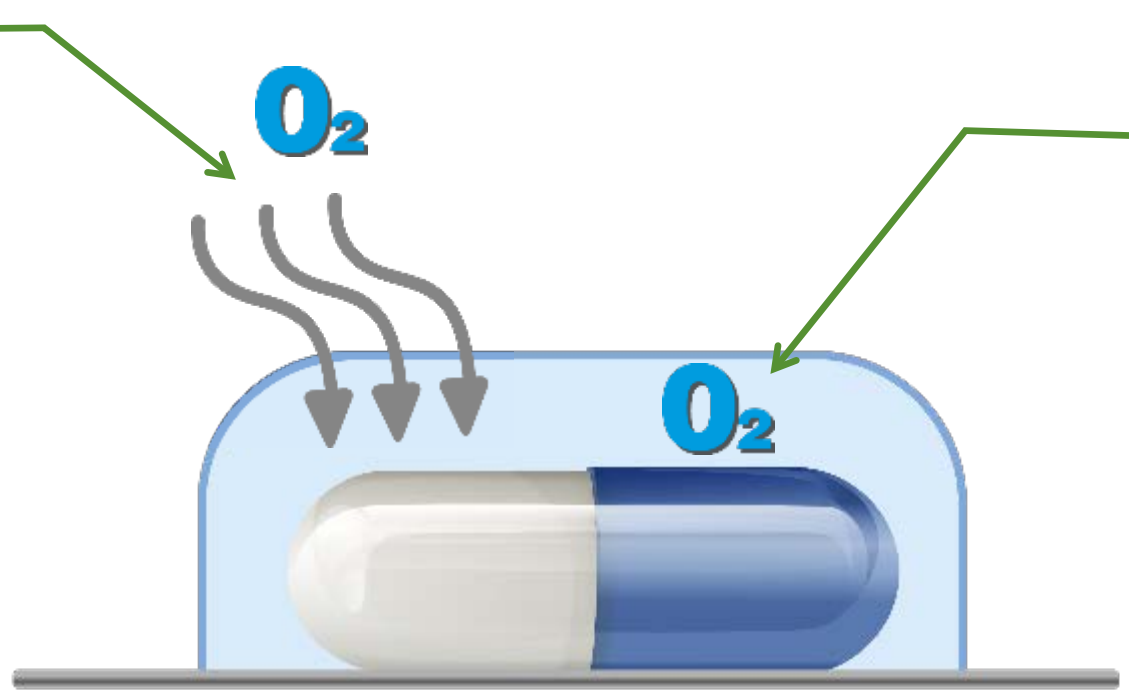
1. Within the initial headspace of the blister



3. Initial water content of the oral solid dose

Sources of Moisture and Oxygen in Blister Packaging

2. Ingress through the package over time



1. Within the initial headspace of the blister

Protecting Oral Solid Doses from O_2 / Moisture

Activ-Blister™ Solutions

- Management of all sources of moisture & oxygen
  - Silica Gel and Molecular Sieve desiccants
  - Combination options available (e.g. moisture + oxygen)
- Customized capacity and uptake rates
- Oxygen products do not require moisture to be active
- Integrate into existing and new packaging lines

Proprietary Heat-Staking Process

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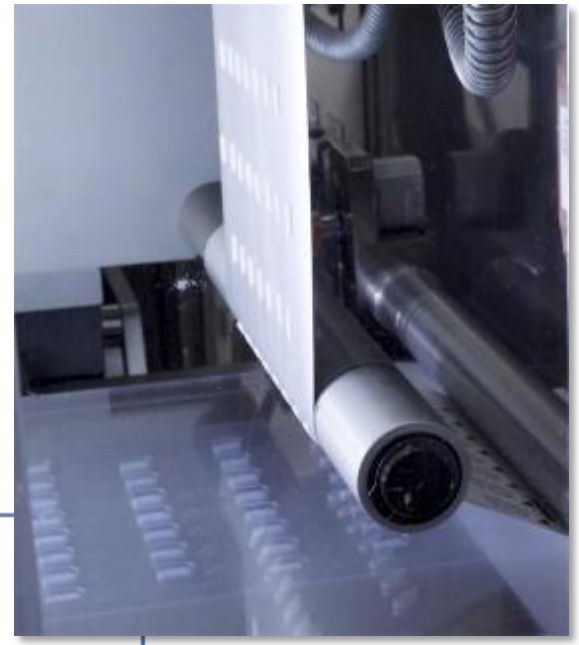
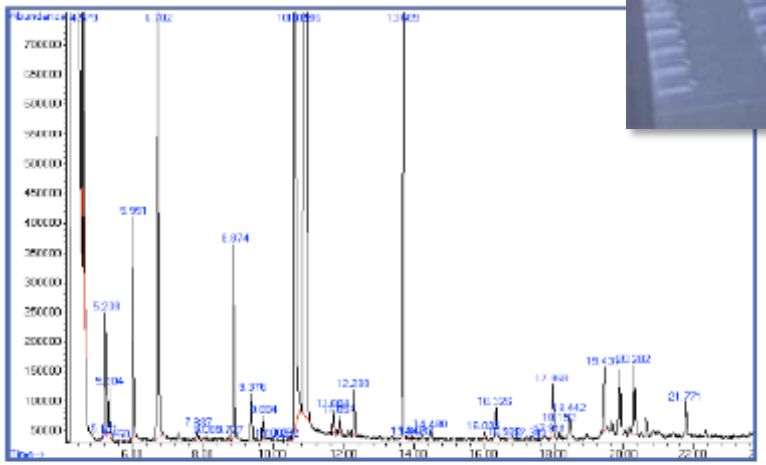
Heat-stake formulations provide adhesive-free attachment within blister

- No adhesive residual solvents
- Eliminates adhesive and backing material
- Helps to meet ICH guidelines for residual solvents



Adhesive residual solvents can:

- Migrate into package headspace or product
- Show up in analytical tests as impurities
- Adversely react with the drug product
- Create odors



Major solvent peaks: Ethyl alcohol (class 3), Isopropyl alcohol (class 3), Benzene (class 1) and Toulene (class 2)

Chart above shows a typical GC chromatogram of solvent outgassing from a medical grade adhesive.

Case Study

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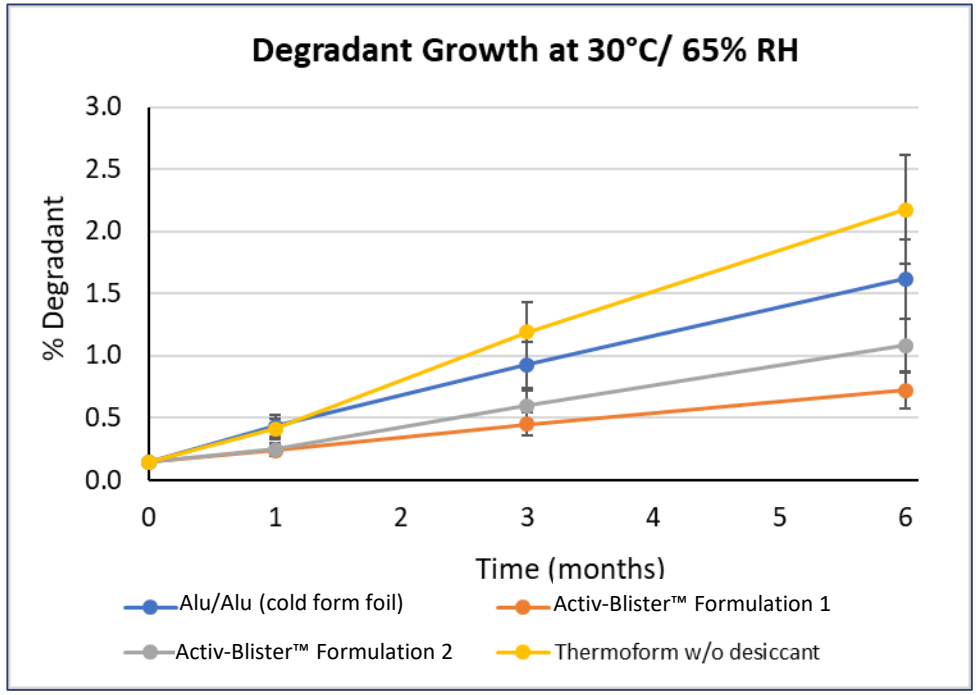
Objective: Compare efficacy of Activ-Blister™ packaging configurations with cold-form foil in maintaining the stability of a model tableted drug product.

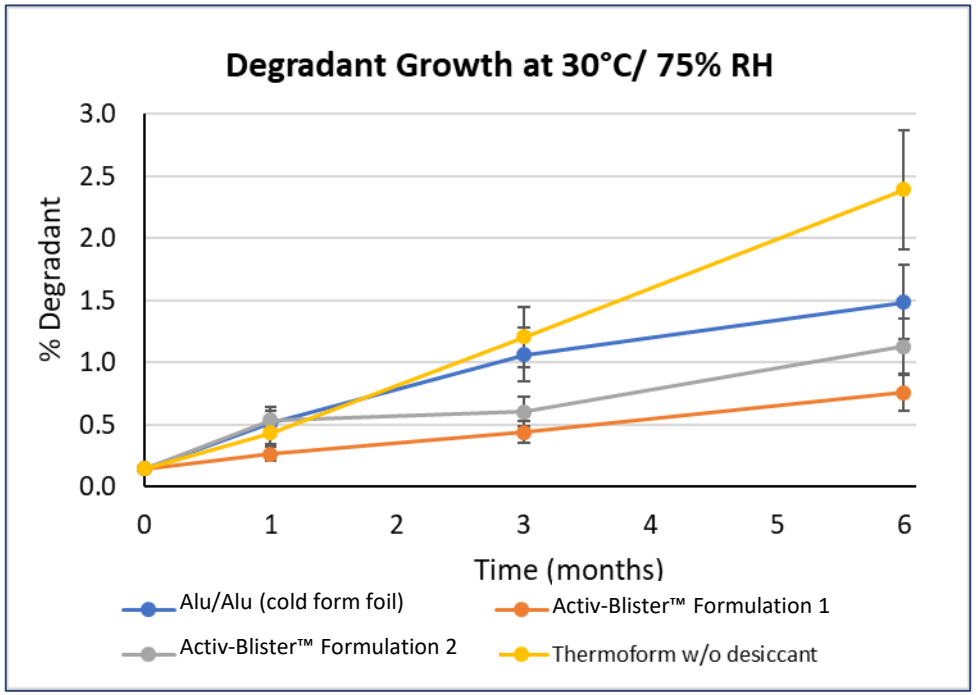
Blistering & Storage Conditions for Stability Study:

Packaging Configuration	Low Water Content, 25°C/60% RH	Low Water Content, 30°C/65% RH	Low Water Content, 30°C/75% RH	Low Water Content, 40°C/75% RH	High Water Content, 25°C, 60%RH
	1, 3, 6 months	1, 3, 6 months	1, 3, 6 months	1, 3, 6 months	1, 3, 6 months
Thermoform Activ-Film™ Formulation 1 (Activ-Blister™)	X	X	X	X	X
Thermoform Activ-Film™ Formulation 2 (Activ-Blister™)	X	X	X	X	X
Cold-form foil	X	X	X	X	X
Thermoform without Activ-Film™ (Activ-Blister™)	X	X	X	X	X

Case Study - Data

Growth of main degradant in tables stored under ICH stability conditions under different packaging configurations





Data courtesy of joint study with FreeThink Technologies and PCI Pharma Services

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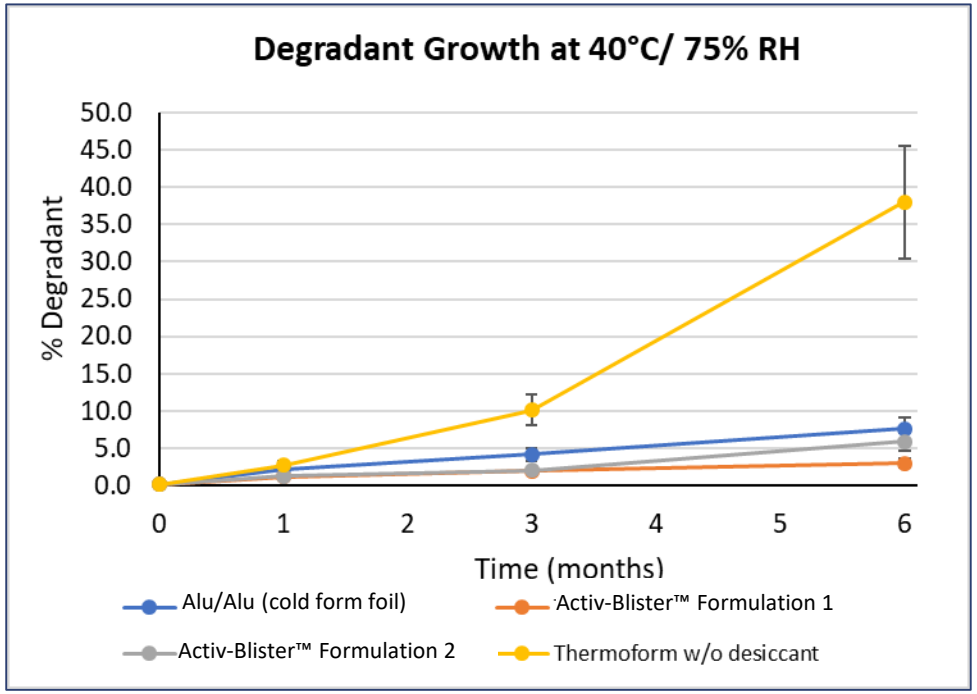

Data courtesy of joint study with FreeThink Technologies and PCI Pharma Services

Application Field: Probiotics

Major Customer Probiotic Brands Utilizing Aptar CSP Technologies' Active Packaging Solutions

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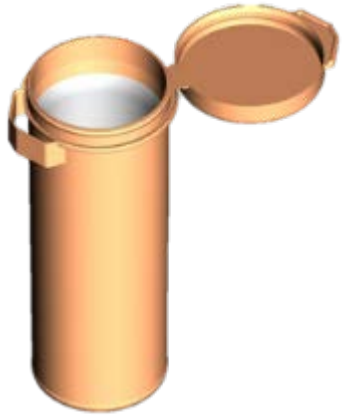
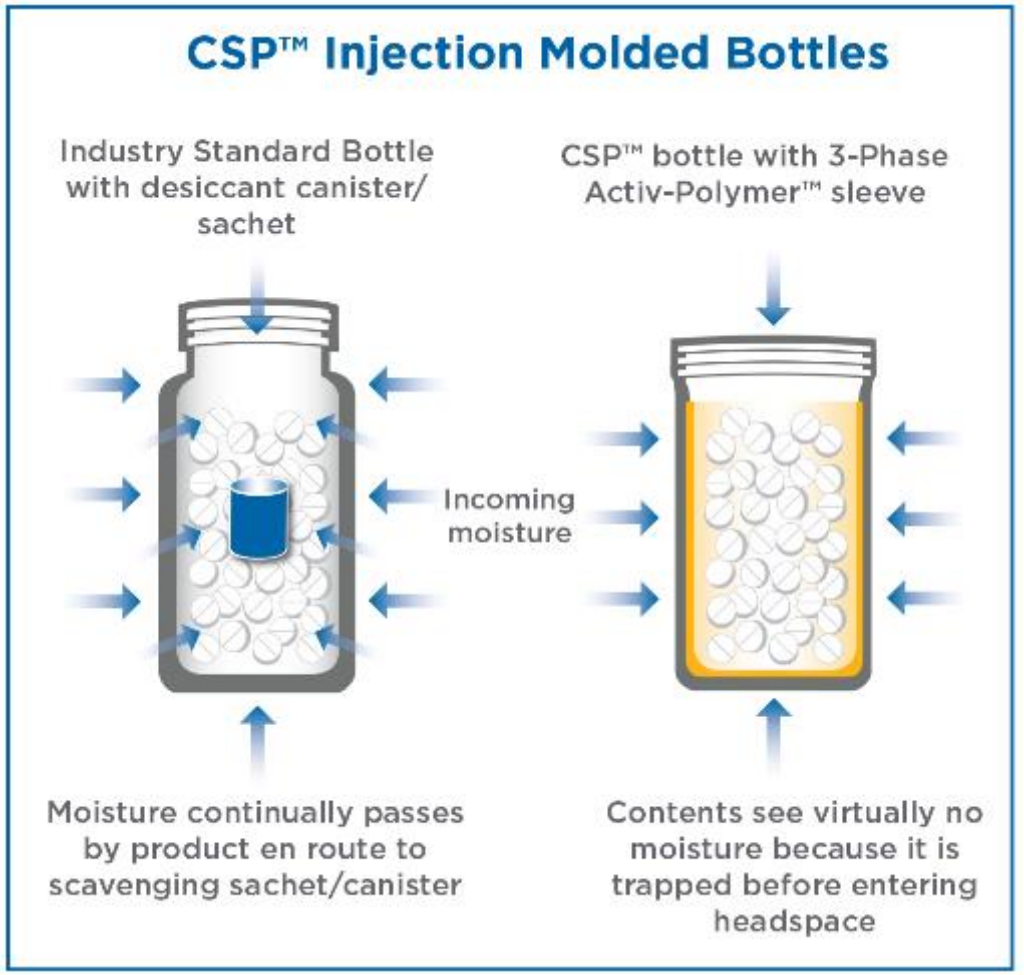
Advanced Tube Technology

- ✓ Greatest product stability
- ✓ Guaranteed potency and freshness until expiry
- ✓ Protection from moisture

Technology Applications

- **CSP™ Flip-Top Activ-Vial™** with integrated 3-Phase Activ-Polymer™ sleeve
- Patented “Close In The Mold” Technology Ensures **Moisture-Tight Seal**
- Maintains seal integrity throughout shelf life and consumer use life
- Child-Resistant/Senior-Friendly Closures



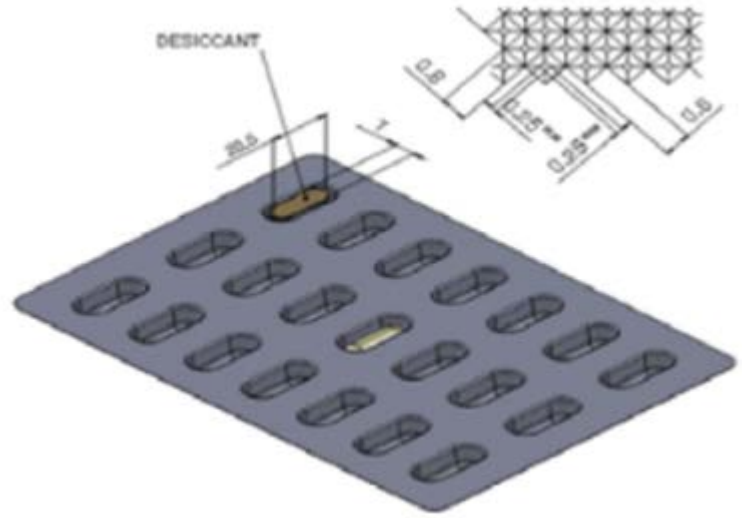


Activ-Blister™ Solutions

Results of Aclar-type thermoformed blisters + Activ-Film

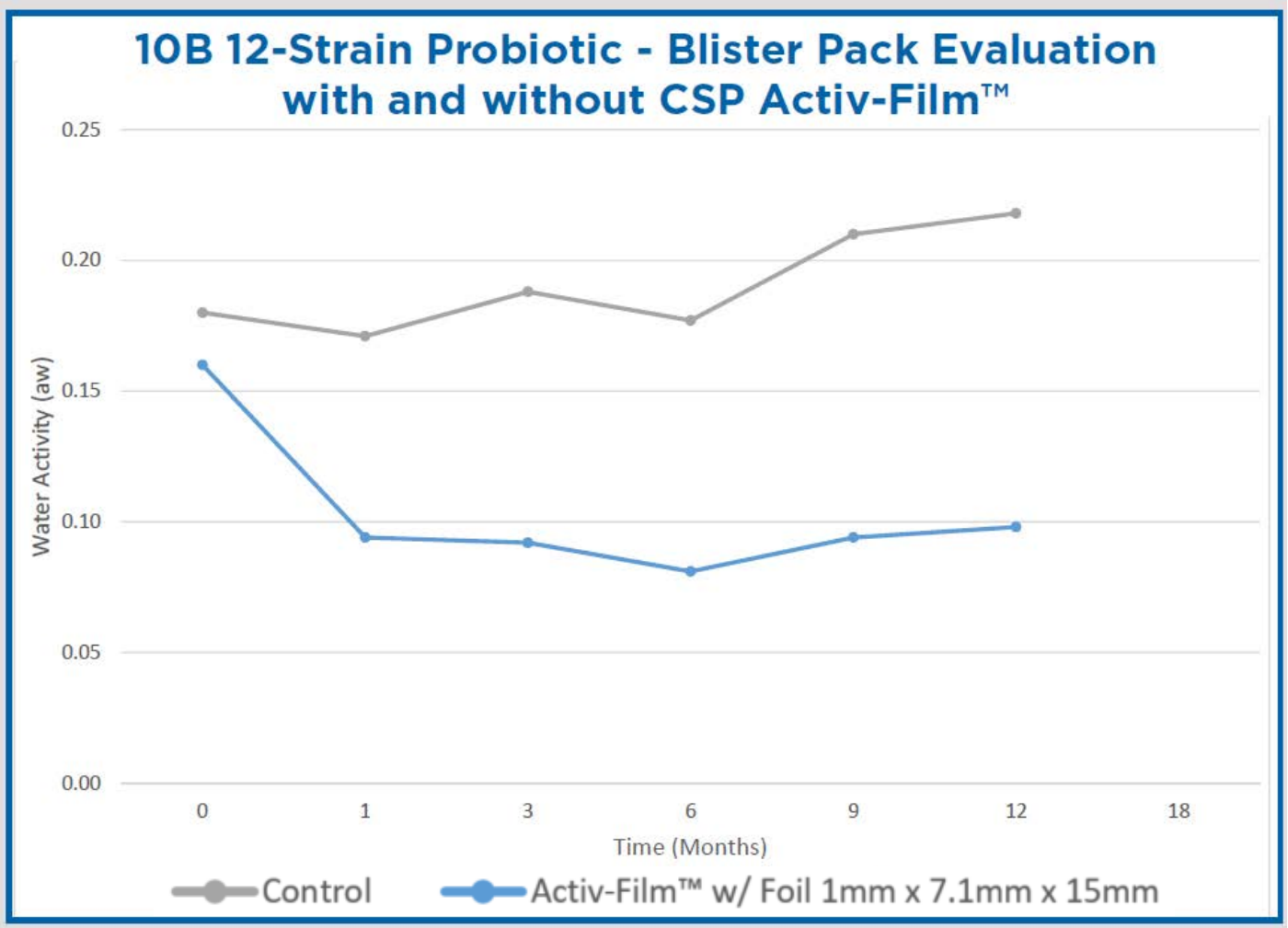
Aclar® type	Temp/RH (°C/%RH)	Days to saturation
Rx160	25/60	209
Rx160	30/65	71
Rx160	40/75	21
UltRx2000	25/60	370
UltRx2000	30/65	220
UltRx2000	40/75	71
UltRx6000	25/60	1036
UltRx6000	30/65	647
UltRx6000	40/75	209

Assume ~6.6mm x ~13mm x 1mm piece for
Size 0 capsule



Probiotic Capsule Water Activity

(Standard PVC.PvdC Blister Packaging vs. Activ-Blister™ Packaging with CSP Activ-Film™)

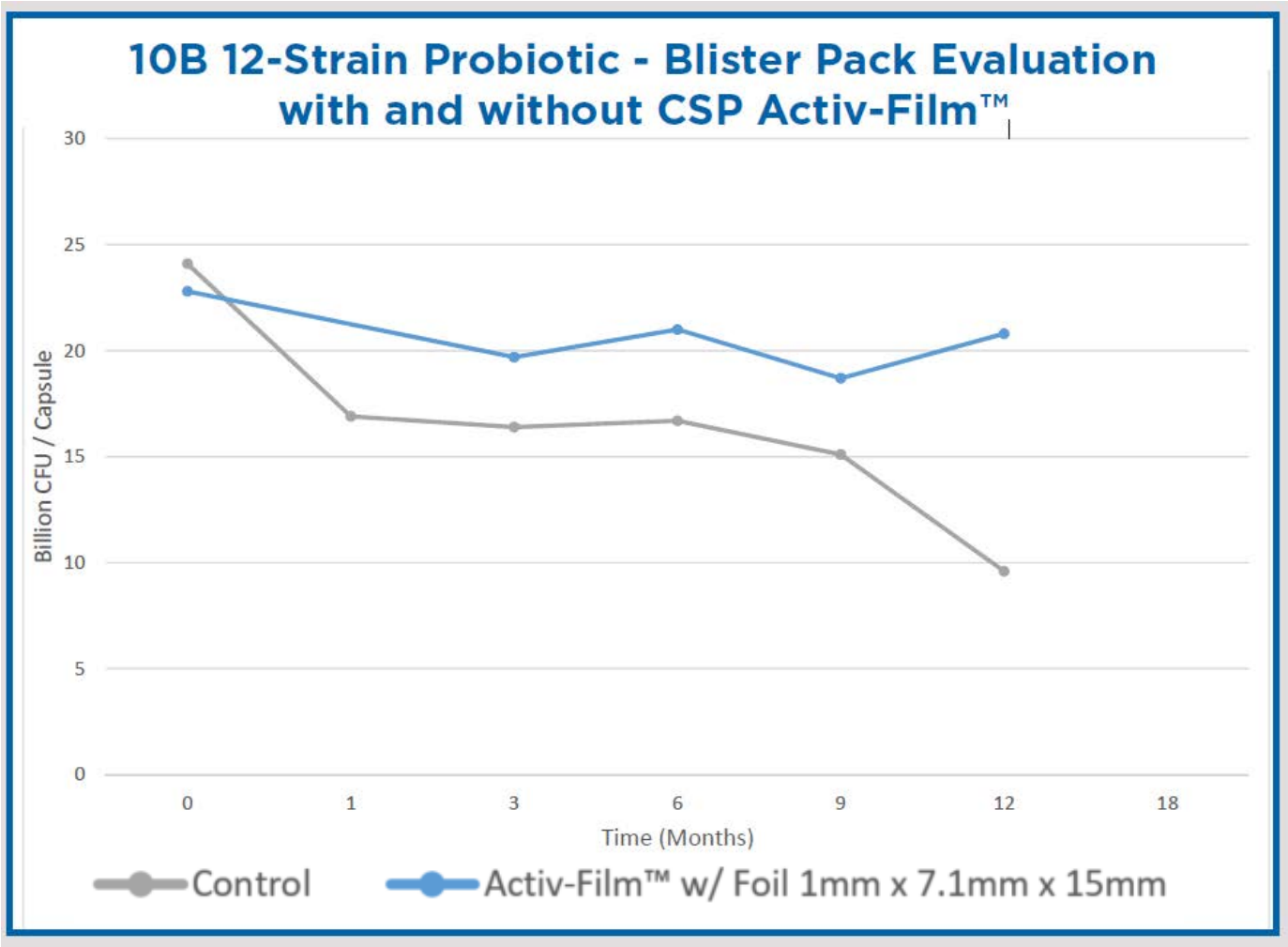


Storage Conditions:
22°C ± 2°C
40% ± 5% RH

Data courtesy of

Probiotic Capsule Potency

(Standard PVC.PvdC Blister Packaging vs. Activ-Blister™ Packaging with CSP Activ-Film™)



Storage Conditions:
22°C ± 2°C
40% ± 5% RH

Data courtesy of

Probiotic Stick Pack Water Activity

(CSP™ Activ-Film™ vs. No Activ-Film™, Ambient Conditions)

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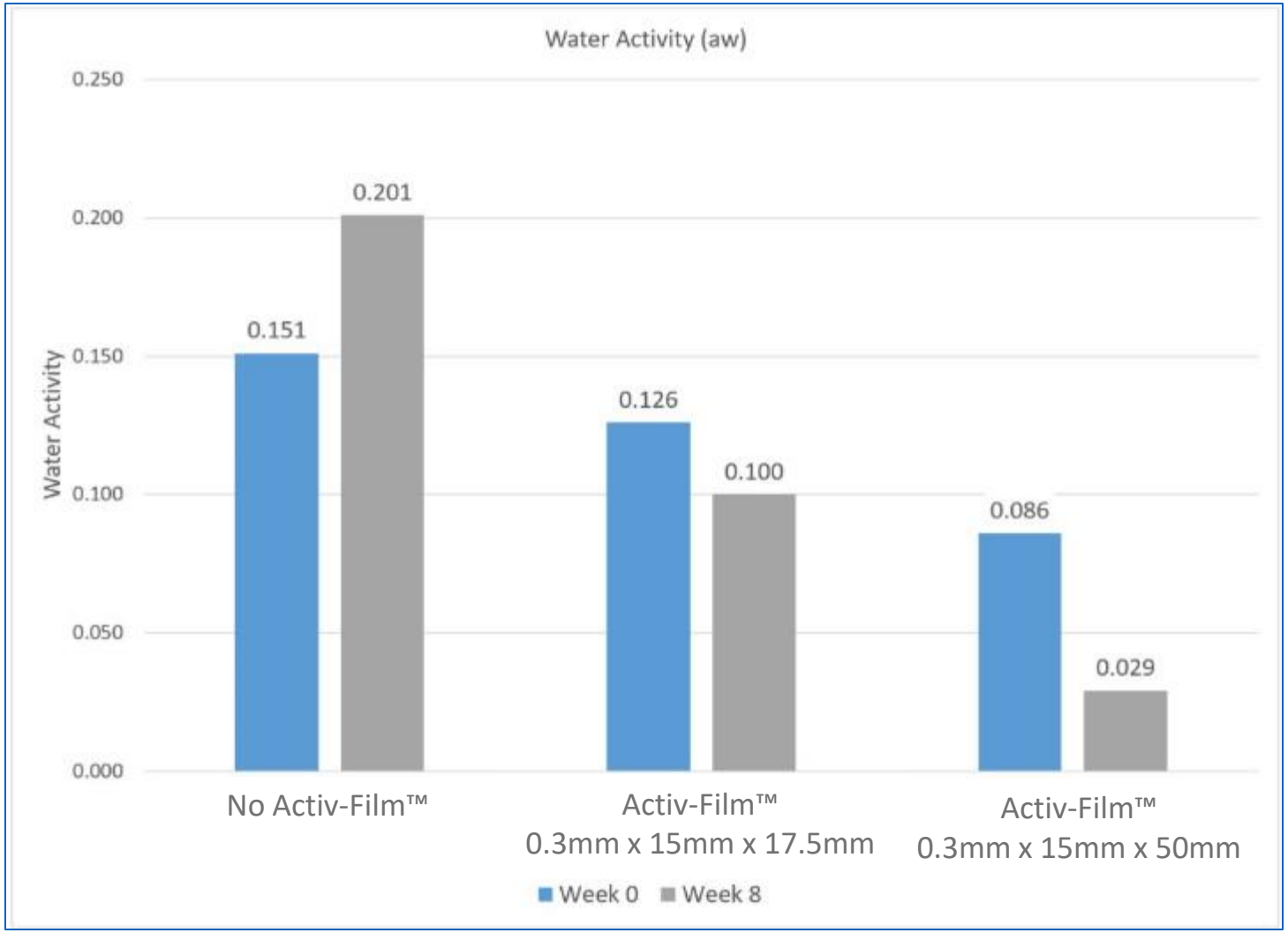
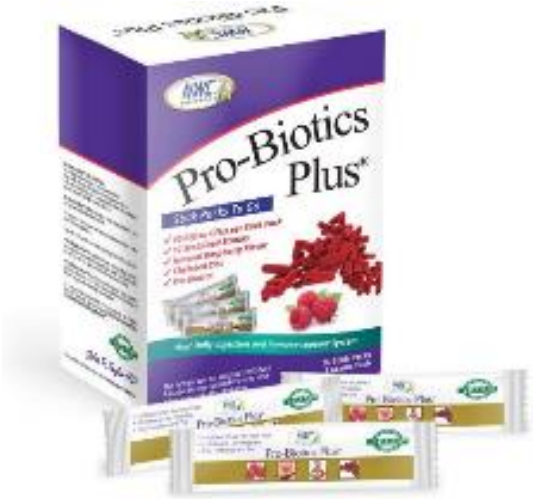


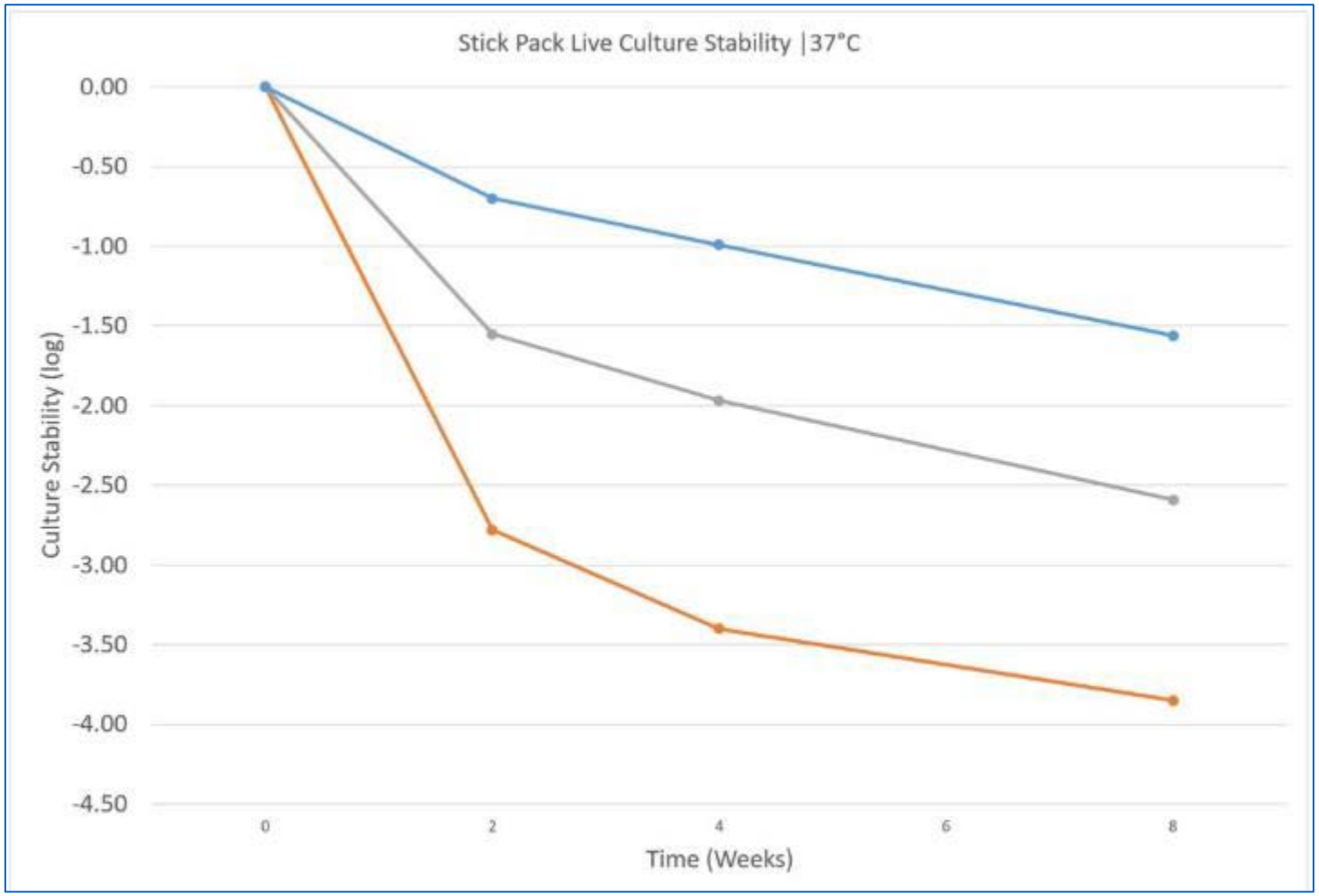


Data courtesy of

glac
good lac get good life

Probiotic Stick Pack Stability

(CSP™ Activ-Film™ vs. No Activ-Film™)



No Activ-Film™

Activ-Film™
0.3mm x 15mm x 17.5mm

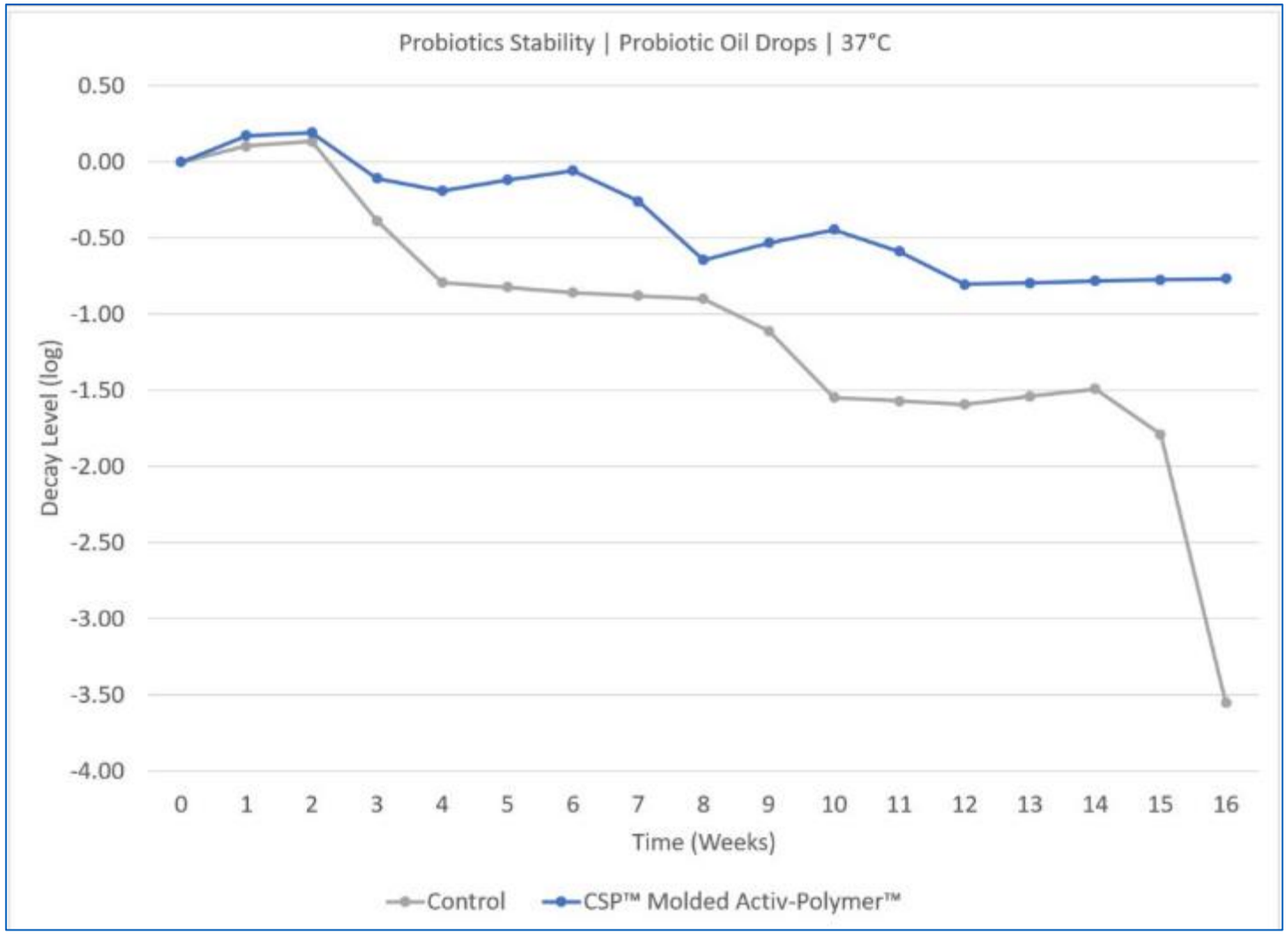
Activ-Film™
0.3mm x 15mm x 50mm

Data courtesy of

glac
good lac get good life

Probiotic Oil Drops Stability

(CSP™ Molded Activ-Polymer™ vs. Control)



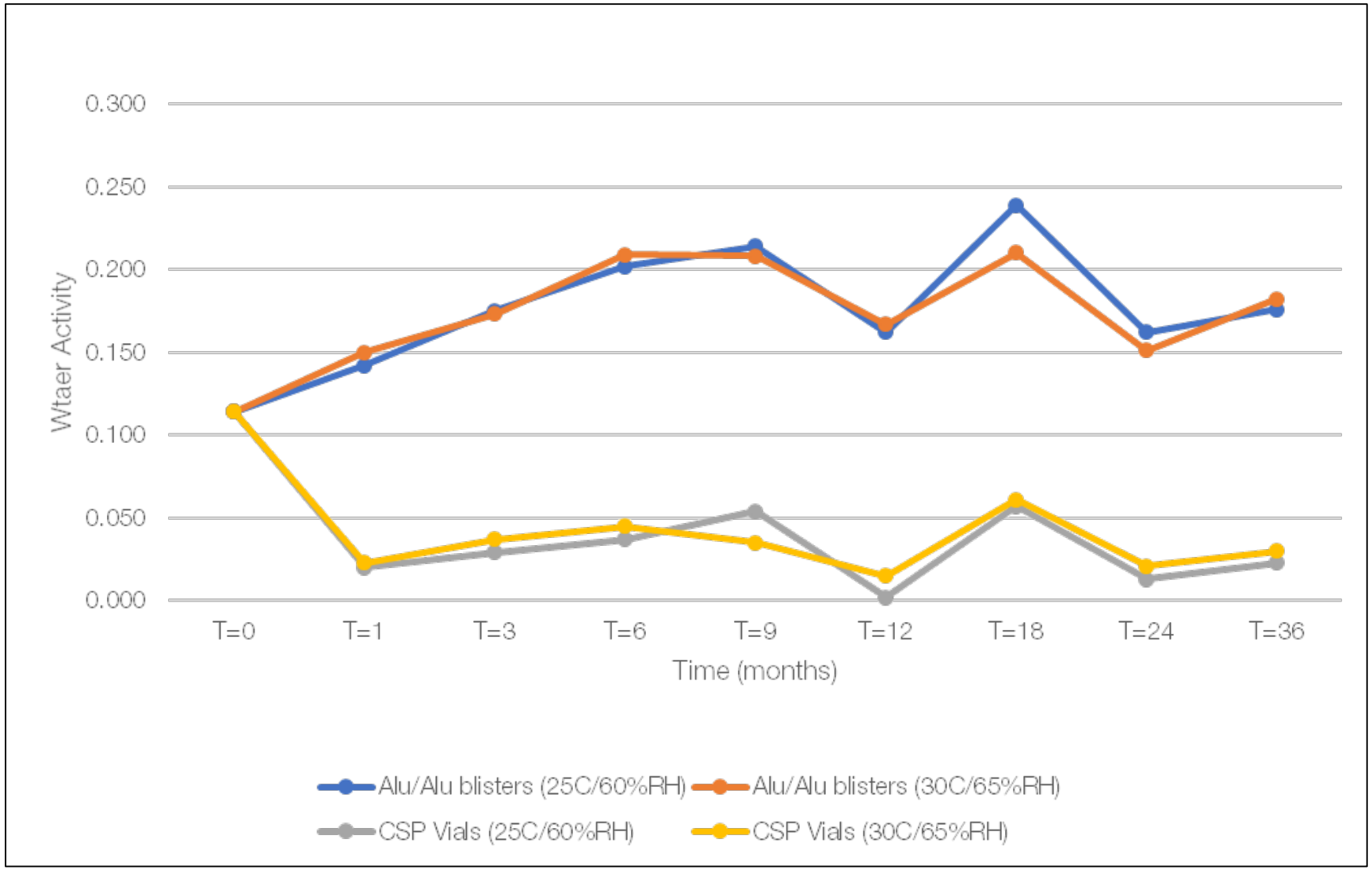
CSP™ Molded Activ-Polymer™ in graph uses 1 Tablet:

- 3mm thick x 8mm OD
- 0.2 gram

Data courtesy of

Probiotic Capsules – Water Activity

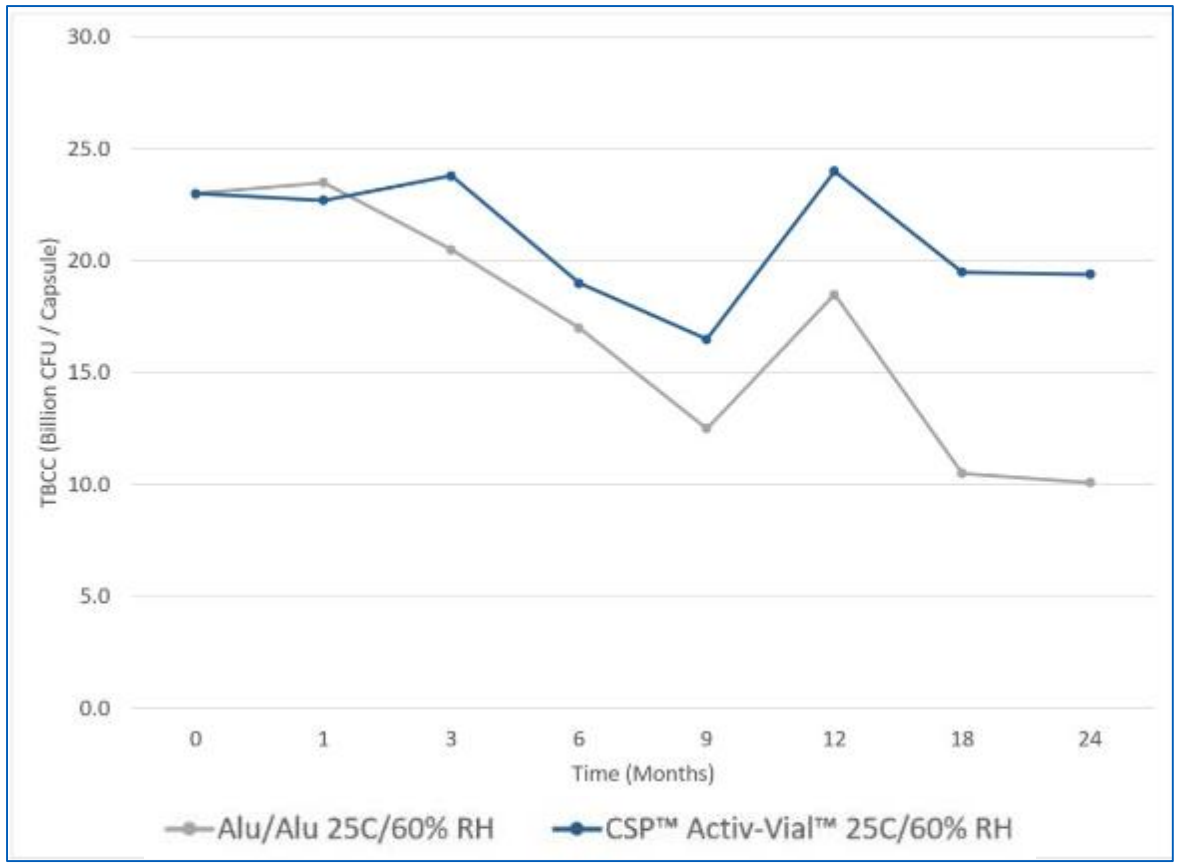
(CSP™ Activ-Vial™ vs Alu/Alu Blisters)

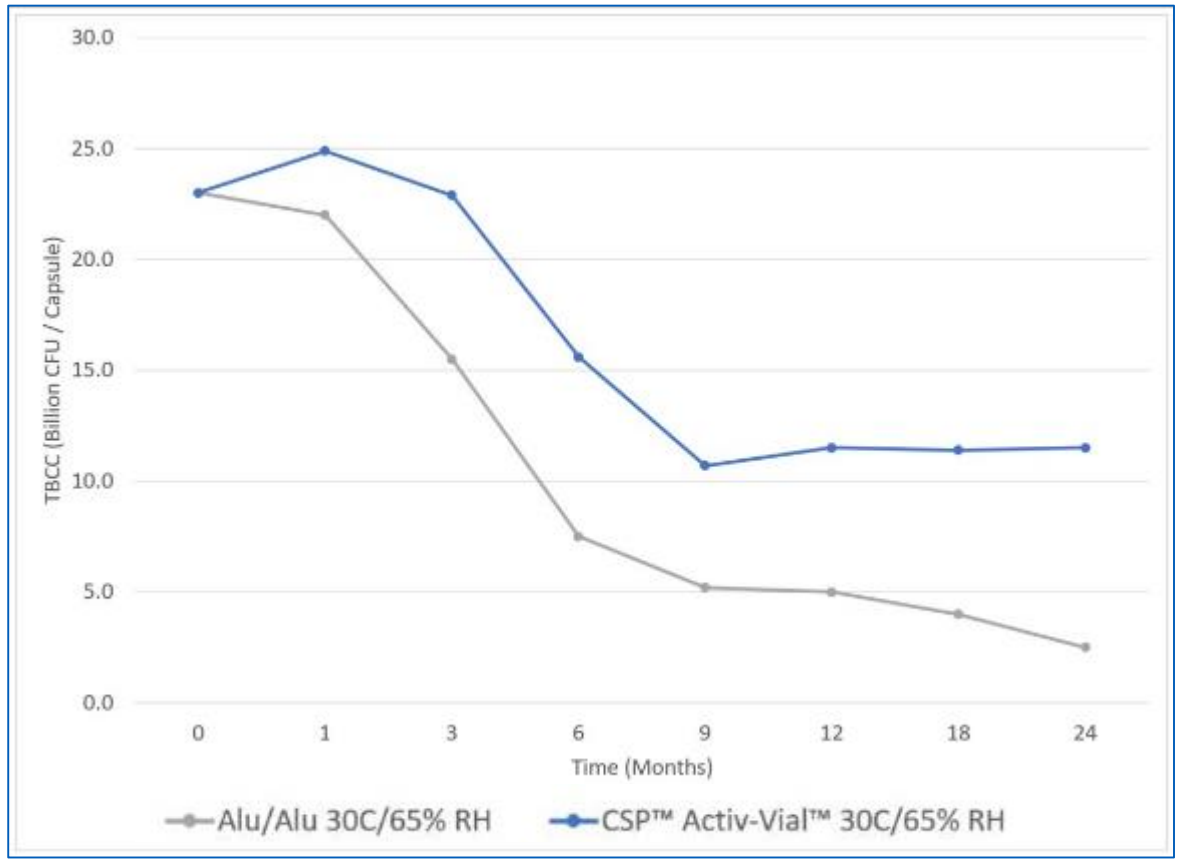


Study performed in partnership with UAS Labs, a leading probiotic manufacturer.

Probiotic Capsules – Strain Potency

(CSP™ Activ-Vial™ vs Alu/Alu Blisters)





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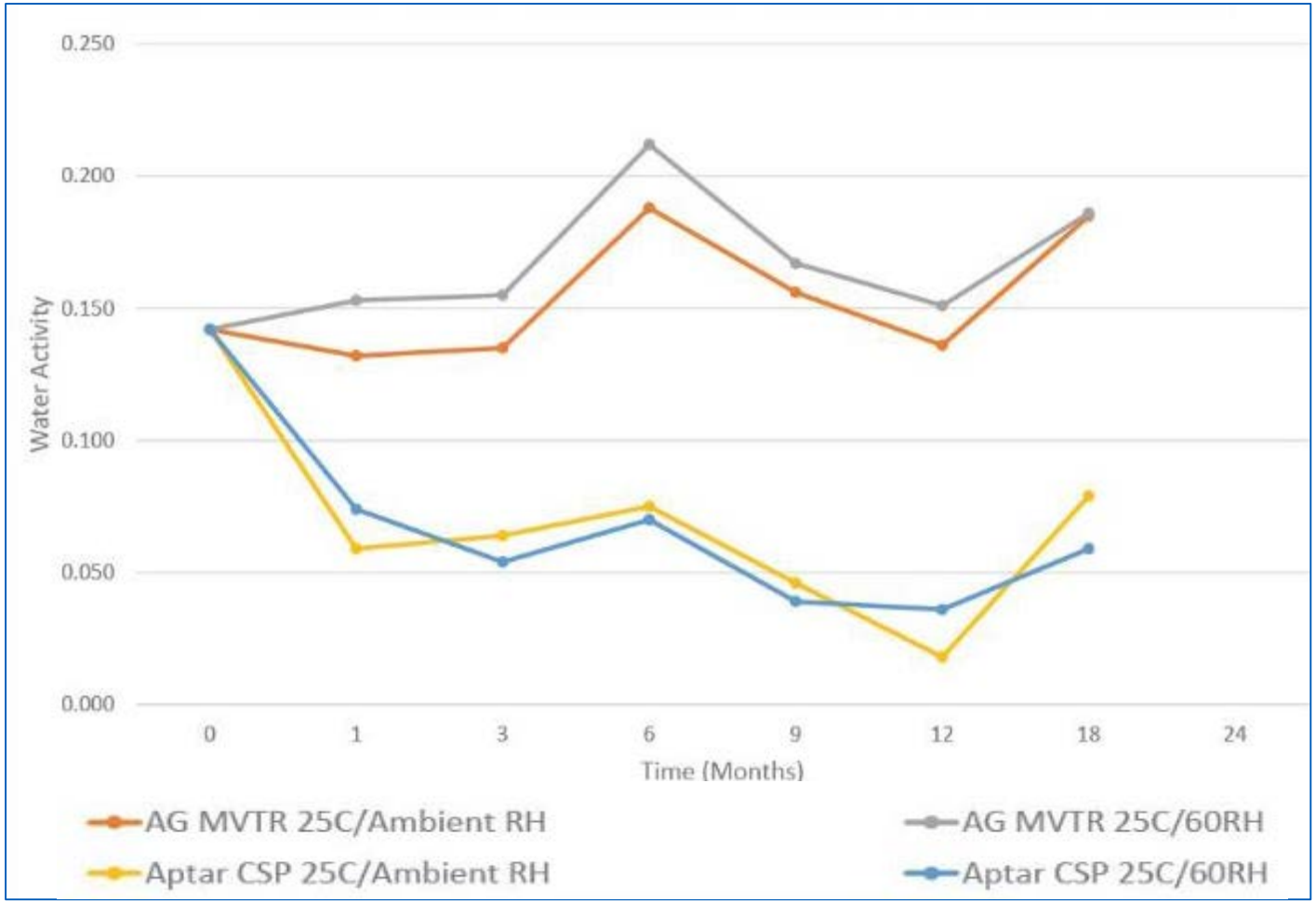
Water Activity in Probiotics + Cranberry

(CSP™ Activ-Vial™ vs. Amber Glass with Desiccant)



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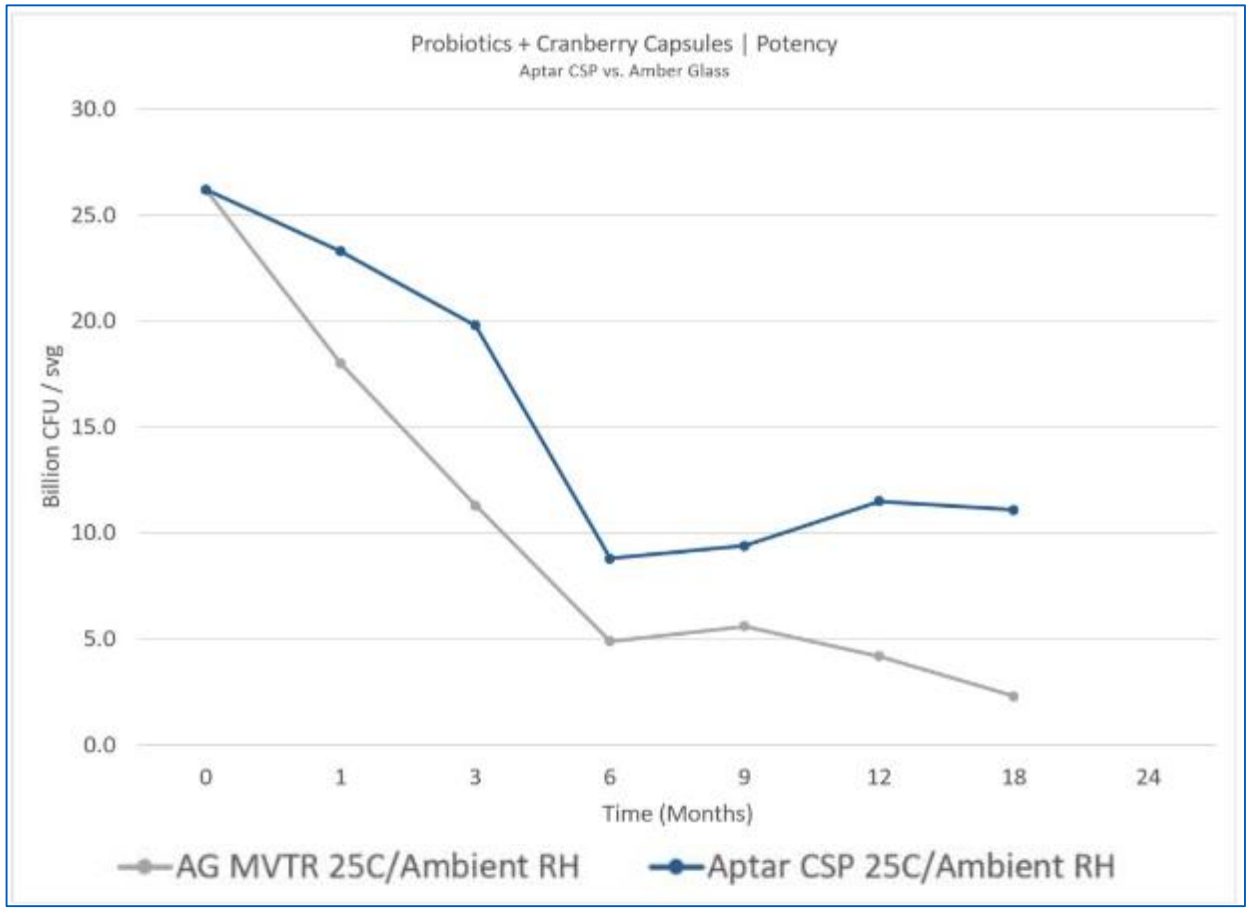
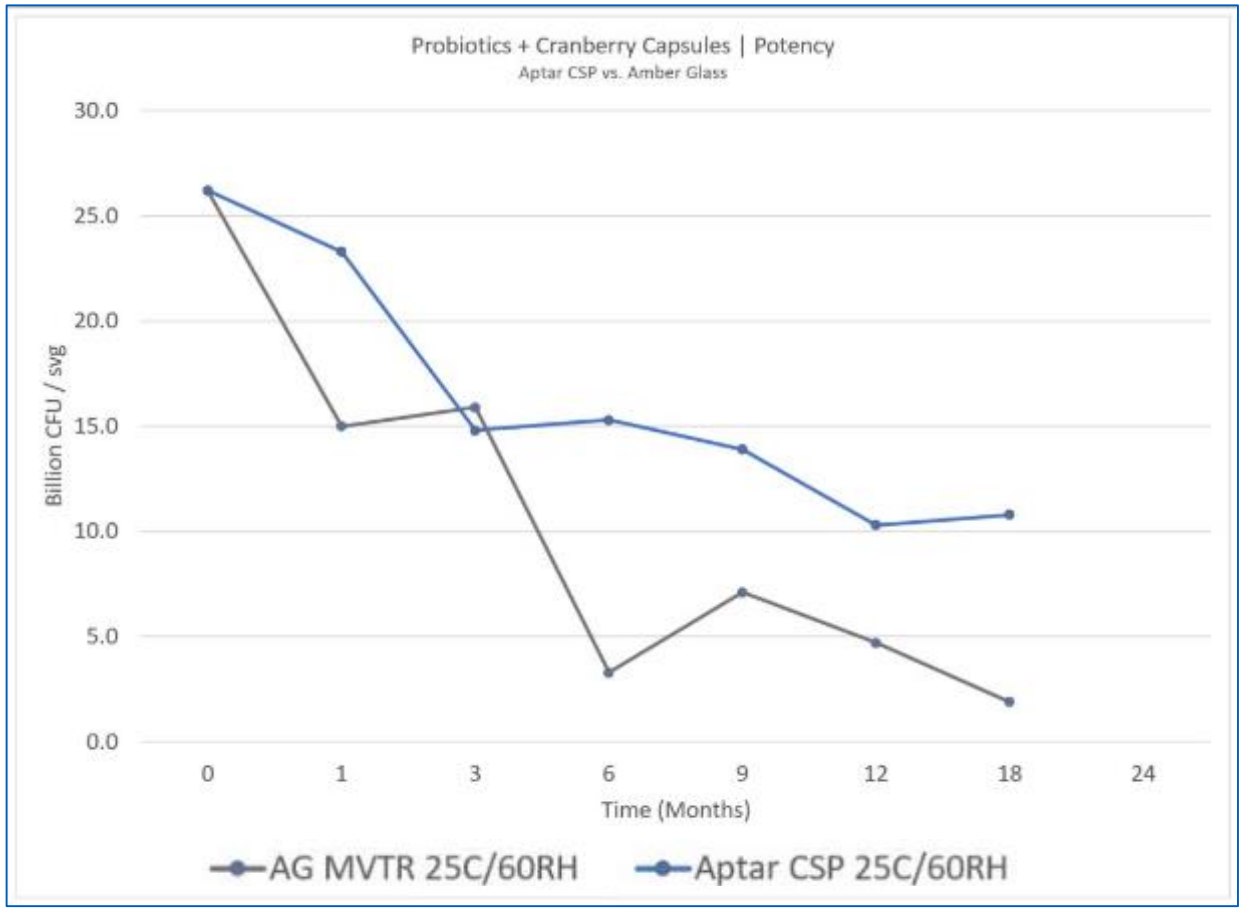
Potency of Probiotics + Cranberry Capsules

(CSP™ Activ-Vial™ vs. Amber Glass with Desiccant)



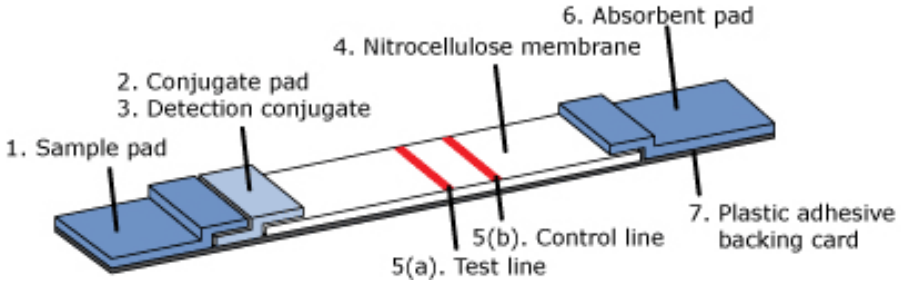


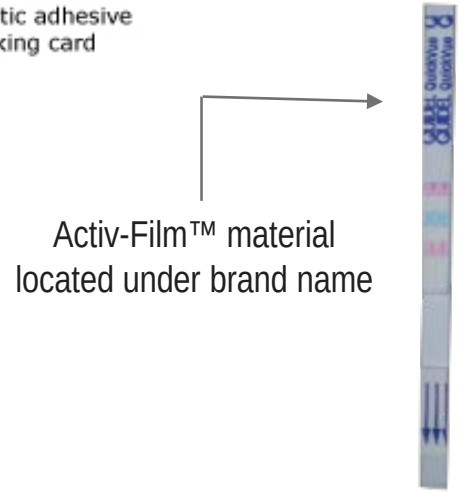
Study performed in partnership with UAS Labs, a leading probiotic manufacturer.

Application Field: Diagnostics

Lateral Flow Test Strips

- Activ-Film™ material applied to top of the test strip without adhesive
- Method relevant to test strips with excess length
- Utilizes adhesive present on existing card stock
- Activ-Film™ material added like other test strip components

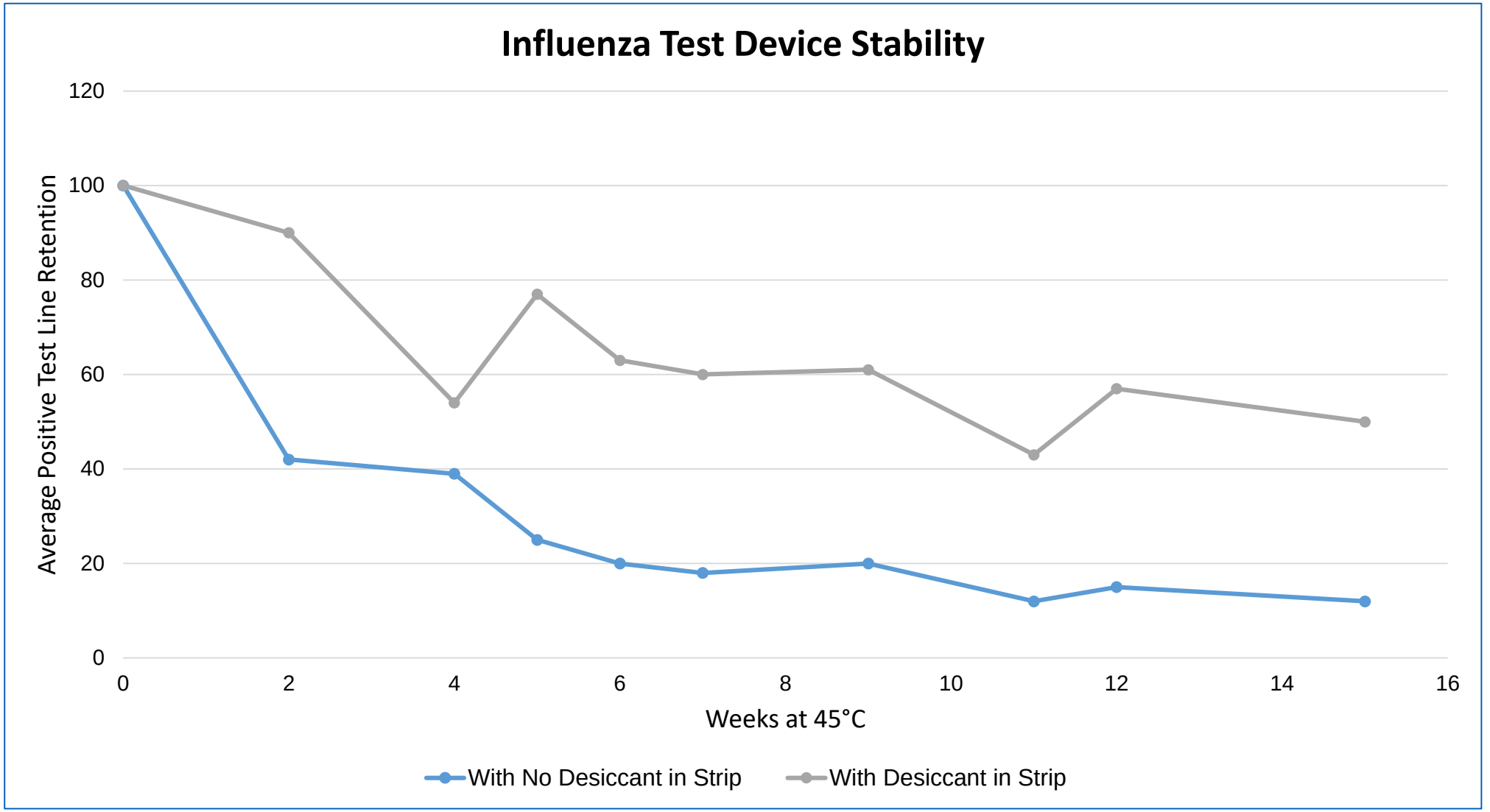




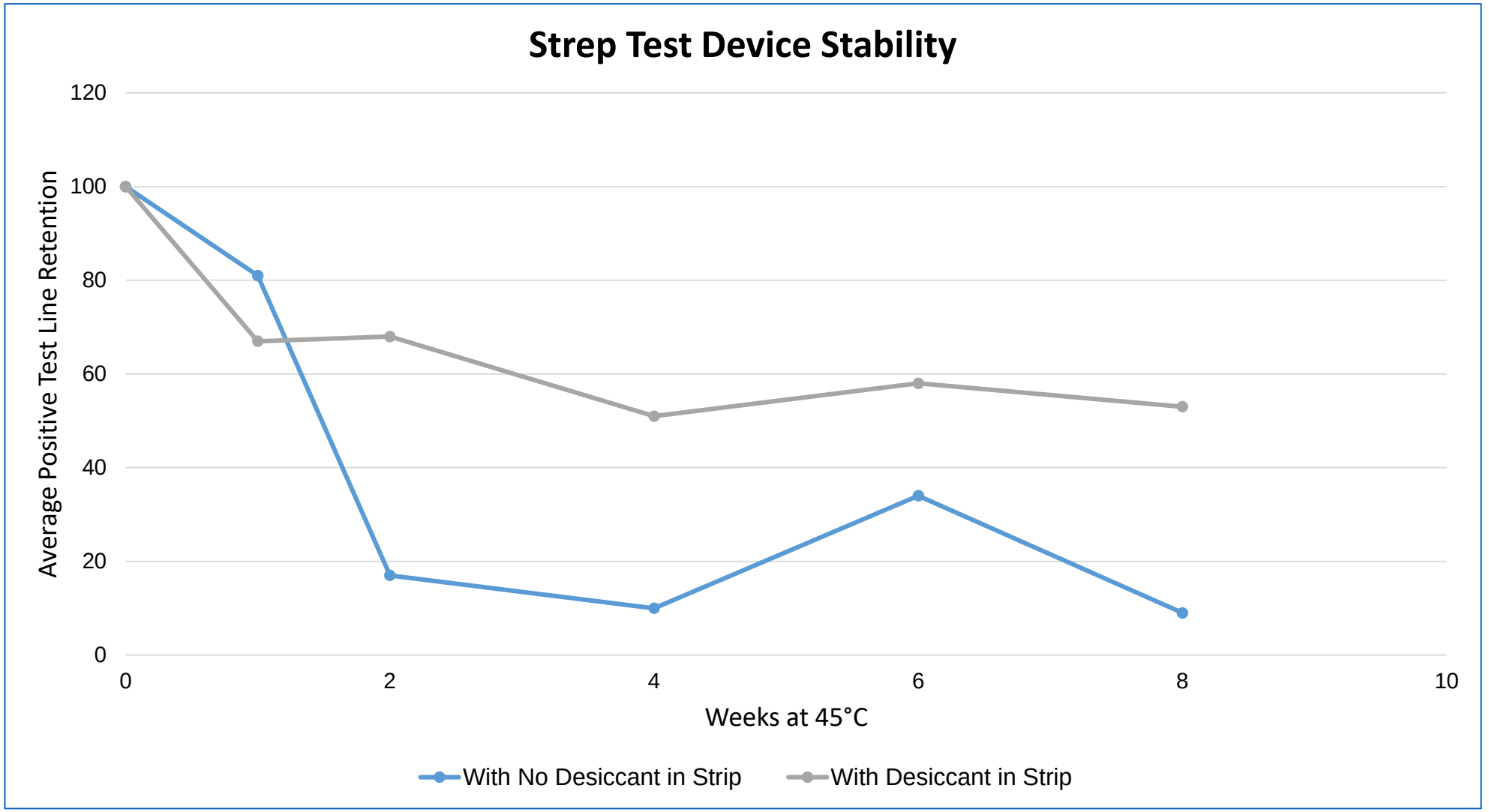
QUIDEL

"The device is manufactured to include an integrated desiccant within at least a test strip of the device. Addition of an integrated desiccant within the device improves signal to noise ratio, eases the manufacturing process, and saves in cost of production of the device."

Lateral Flow Test Strips



Lateral Flow Test Strips

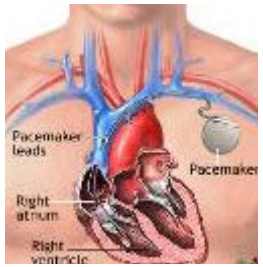


Application Field: Medical Device

Application Field – *A*ctive *I*mplantable *M*edical *D*evices

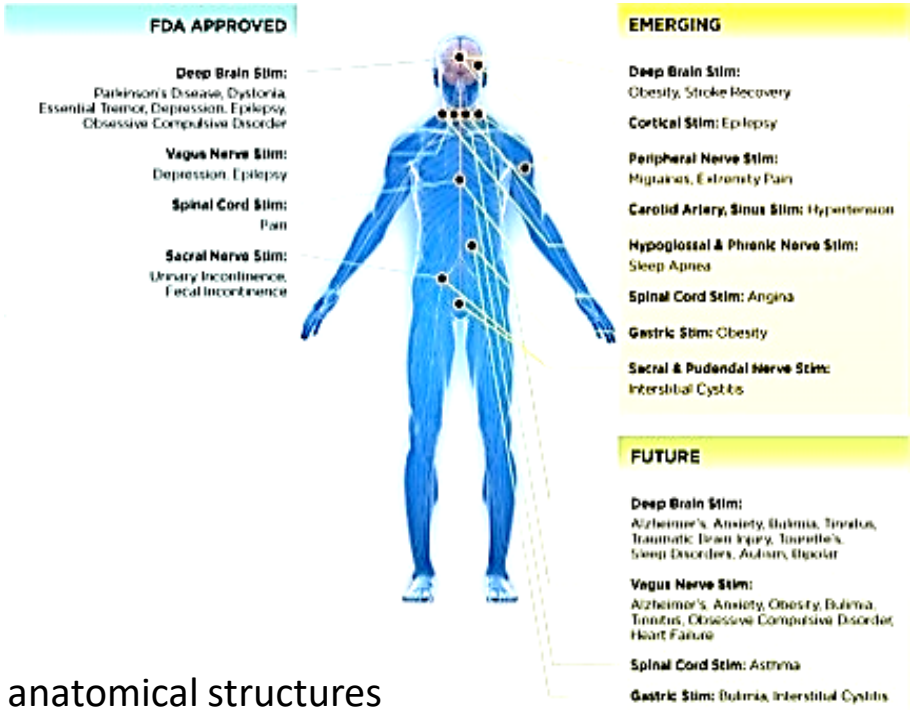
Pacemakers: Treat patients with hearts that beat too slowly; bradycardia

- Monitor heart rate and deliver low-voltage electrical impulses to stimulate heartbeat



ICD's: Implantable Cardioverter Defibrillators. Treat patients with hearts that beat too fast; tachycardia

- Monitor heartbeats and deliver high-energy electrical impulses, or "shocks," to treat potentially lethal, abnormally fast heart rhythms



CRT / CRTD's: Cardio Resynchronization Therapy. Resynchronizes beating of ventricles, which can beat out of sync in heart failure patients

- Can provide defibrillation (CRTD); cardiac arrest is a risk factor for some types of heart failure
- CRT/CRTD's cleared by FDA, 2002

Neuromodulation: Implantable device delivers electrical current to targeted anatomical structures

- Therapies include spinal cord stimulation (SCS) for chronic pain, deep brain stimulation (DBS) for symptoms of Parkinson's disease, tremor and primary and secondary dystonia

Application Field – *A*ctive *I*mplantable *M*edical *D*evices

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Value Proposition

- Devices are often purged with inert gas/hermetically sealed as plastics in devices act as insulators but can emit moisture, as do PCB's
- Extends battery life by minimizing circuitry corrosion

Features

- High Capacity
  - Controlled / Slow Uptake
- Precision die-cut film and molded parts
  - Thin film option: 0.2 mm
  - Thin film tolerance: +/- 0.05 mm
  - Die cut tolerance: +/- 0.01 mm
- Electrical Insulation – low dielectric constant

Application Field: Dermal Drug Delivery

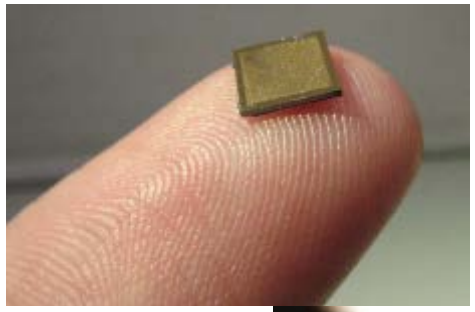
Application Field – Dermal Drug Delivery

Microarray Patches (MAP)

Active delivery system

Vaxxas Nanopatch™ is a novel, cost effective and safe vaccine delivery system

3-Phase Activ-Polymer™ technology incorporated into device with 2-shot component



Application Field – Dermal Drug Delivery

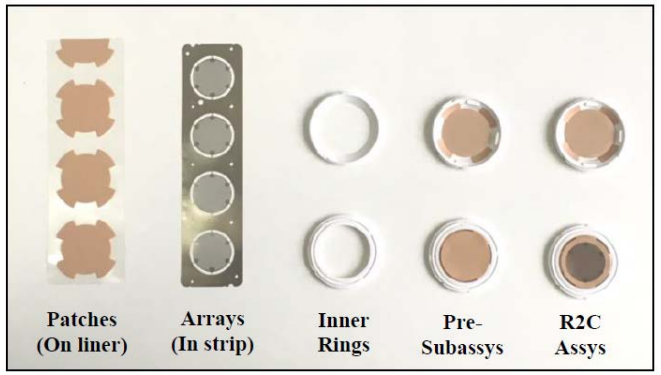
Adhesive Dermally Applied Microarray (ADAM)

Active delivery system

Zosano Pharma's investigational migraine treatment, ADAM Zolmitriptan Qtrypta (M207), is a novel formulation of zolmitriptan, a drug used orally and nasally to effectively and safely treat migraines.

ADAM RING ASSEMBLY ATTACHED TO APPLICATOR

APPLICATION TO THE SKIN



3-Phase Activ-Polymer™ technology incorporated into ring assembly with 2-shot ring

Application Field – Dermal Drug Delivery

Adhesive Dermally Applied Microarray (ADAM)

- Passive delivery system
- Estradiol estrogen hormone patch
- Hormone replacement therapy
- 3-Phase Activ-Film™ material affixed inside secondary packaging foil pouch

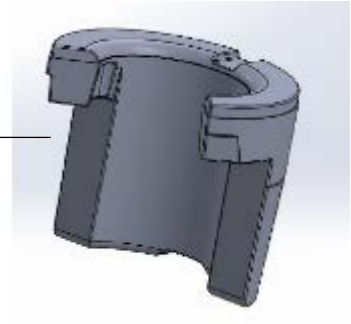
3-Phase Activ-Film™ material

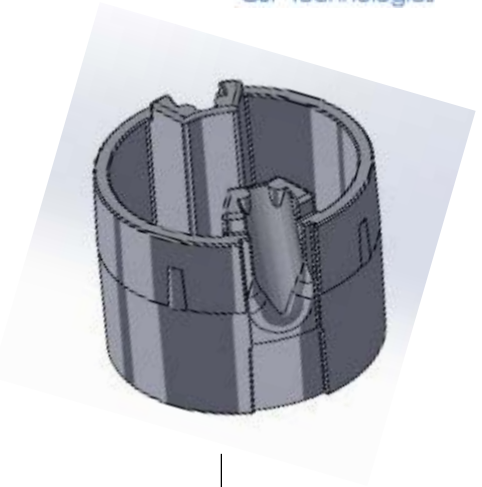
Application Field: Inhaled Drug Delivery

Application Field – Inhalation

Aptar
CSP Technologies

Metered dose inhaler component



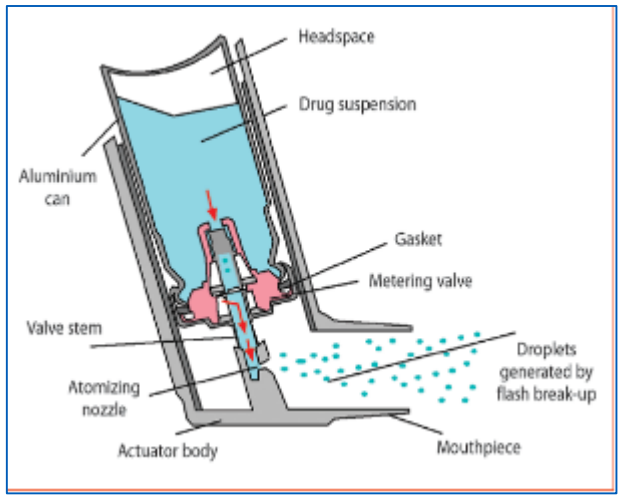


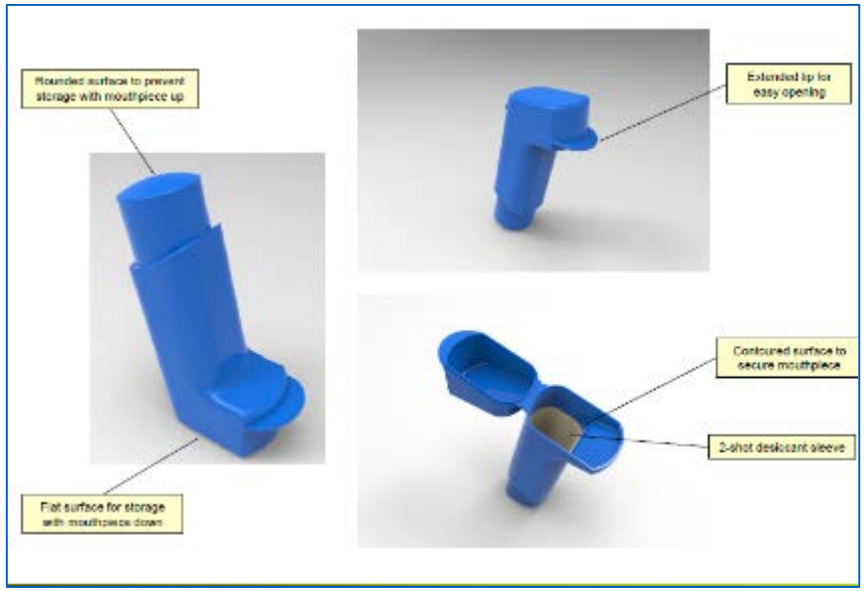
- Xhaler - Development with India Pharma company
- Breath Actuated Inhaler

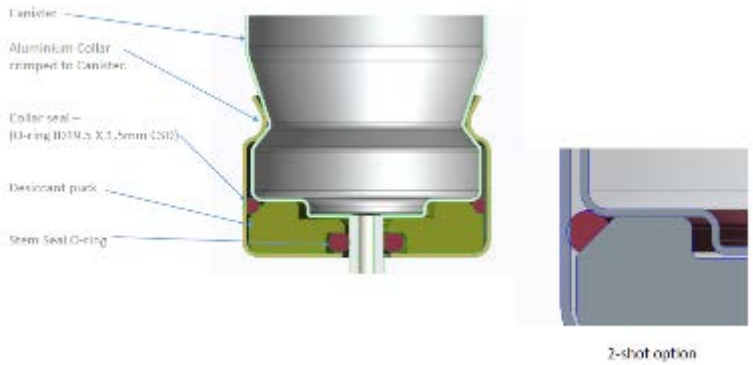
3-Phase Activ-Polymer™ material

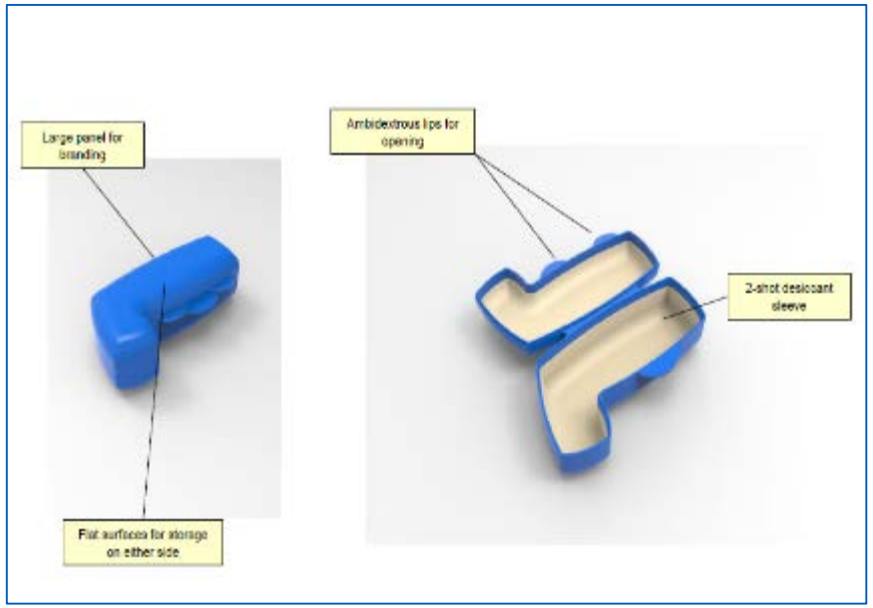
Internal component for reservoir-based dry powder inhaler

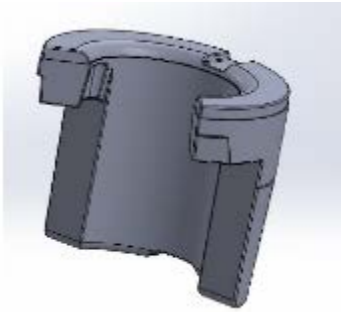
Pressurized Metered Dose Inhaler









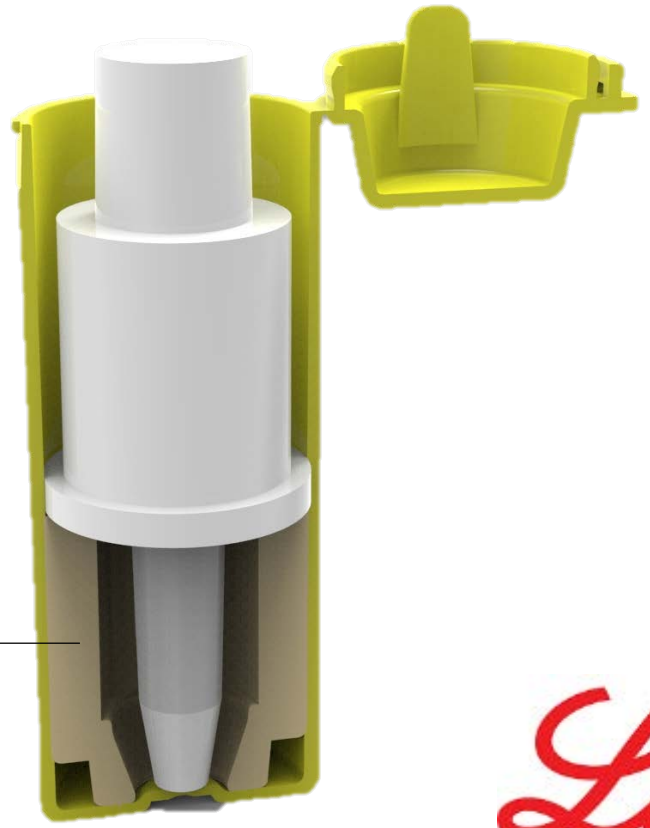


pMDI dose inhaler component

Nasal Drug Delivery

Aptar CSP Technologies

- Glucagon to treat severe hypoglycemia
- Internal features to prevent premature actuation
- Solid relationship with customer and CMO



3-Phase Activ-Polymer™ molded plug component inserted into flip top container

Lilly