


Optimizing Probiotic Formulations:

Use of Active Packaging to Minimize Overages, Reduce Costs, and Improve Margins

Billy Abrams – Sr. VP, Business Development

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CSP Technologies

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About Aptar CSP Technologies

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

CERTIFIED
ISO
9001:2015
COMPANY

2018 Expansion - Auburn, AL USA

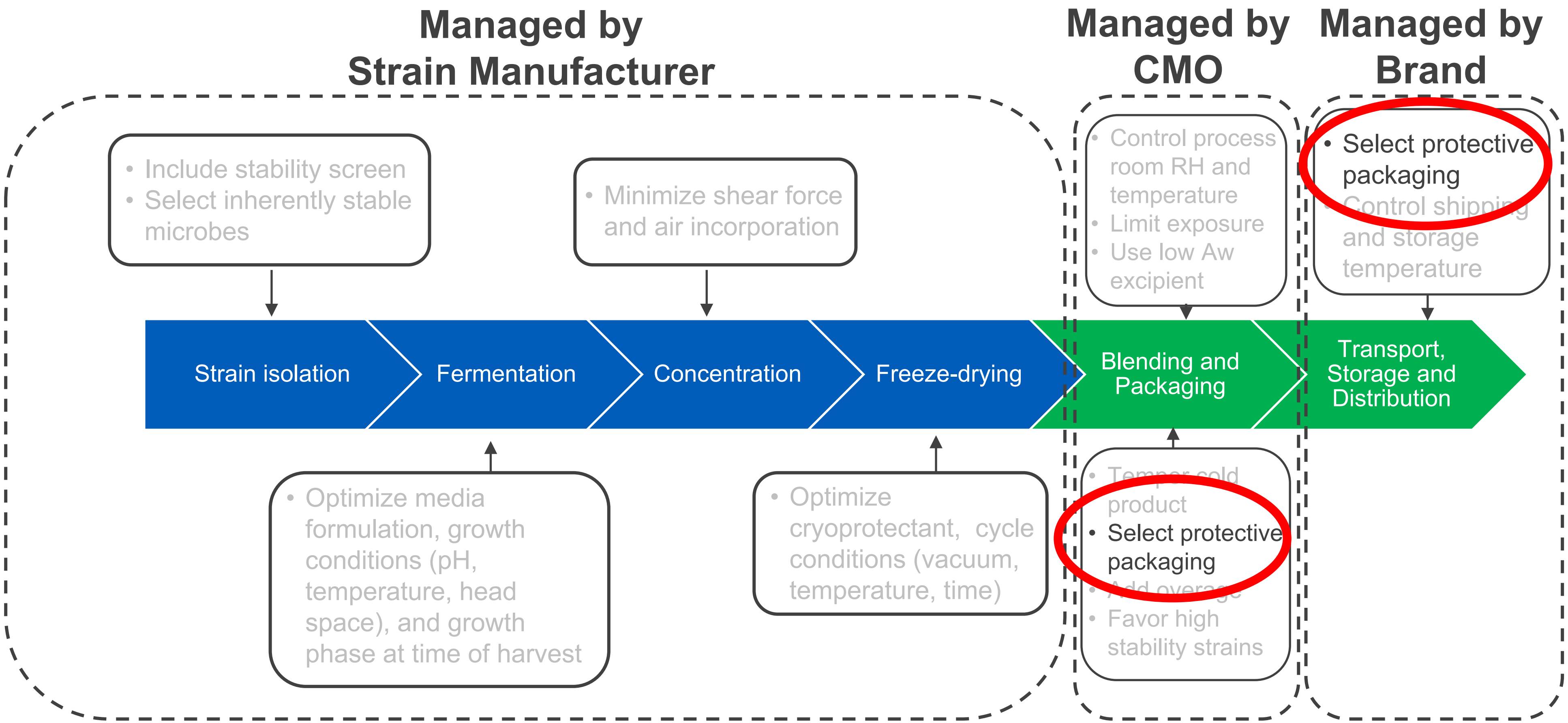
Niederbronn-Les-Bain, France

Guangzhou, China

Agenda

- Who is responsible for strain stability
- The critical role of water activity (Aw) in probiotic stability
- Negative consequences for failing to meet label claim potency
- Real-life studies of the impact of packaging and desiccant selection on water activity, stability and cost
- Conclusions

Strain producers, CMOs and Brands each have control over factors impacting probiotic stability



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- Real-life studies of the impact of packaging and desiccant selection on water activity, stability and cost
- The challenge for the Strain Manufacturer, CMO and Brand

Excellent article discussing probiotic production, processing and delivery with sections addressing stability.

microorganisms

MDPI

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Review

The Production and Delivery of Probiotics: A Review of a Practical Approach

Kurt Fenster [1], Barbara Freeburg [1], Chris Hollard [1], Connie Wong [1], Rune Rønhave Laursen [2] and Arthur C. Ouwehand [3,*]

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check for updates

Abstract: To successfully deliver probiotic benefits to the consumer, several criteria must be met. Here, we discuss the often-forgotten challenges in manufacturing the strains and incorporating them in consumer products that provide the required dose at the end of shelf life. For manufacturing, an intricate production process is required that ensures both high yield and stability and must also be able to meet requirements such as the absence of specific allergens, which precludes some obvious culture media ingredients. Reproducibility is important to ensure constant high performance and quality. To ensure this, quality control throughout the whole production process, from raw materials to the final product, is essential, as is the documentation of this quality control. Consumer product formulation requires extensive skill and experience. Traditionally, probiotic lactic acid bacteria and bifidobacteria have been incorporated in fermented dairy products, with limited shelf life and refrigerated storage. Currently, probiotics may be incorporated in dietary supplements and other "dry" food matrices which are expected to have up to 24 months of stability at ambient temperature and humidity. With the right choice of production process, product formulation, and strains, high-quality probiotics can be successfully included in a wide variety of delivery formats to suit consumer requirements

The inclusion of probiotics in dietary supplements primarily utilizes probiotics in the freeze-dried powder format. Capsules, tablets, and powder in stick packaging or sachets are the most commonly found formats on store shelves and are usually stored at ambient conditions.

Dietary supplement products should deliver the probiotic count declared on the label throughout the shelf life of the product. This ensures that the consumer receives the adequate dose of probiotics to affect the targeted structure function health claim or the otherwise suggested health benefit.

Dietary supplement formats typically have shelf lives measured in years, so a great deal of care must be taken to make sure that the proper probiotic cell count is maintained. Because probiotics, even in the freeze-dried state, are live microorganisms, more consideration must be given to their handling and storage than for other dietary supplements and food ingredients [16,31].

Water activity, followed closely by storage temperature, is the main factor impacting probiotic stability over the shelf life of the product [32]. Downstream processing and manufacturing of the final product (dietary supplement) needs to happen under strict temperature- and humidity-controlled conditions. Establishing a low-water-activity product starts with sourcing dry carriers, excipients, and other active ingredients that will be blended with the probiotic. Small amounts of high-water-activity ingredients can be added as long as the **total water activity remains below 0.2 or, ideally for long shelf lives, below 0.15**. The relative humidity of the processing facility must also be kept low so that the probiotic dietary supplement does not absorb moisture from the environment during production

Once the low-water-activity probiotic format has been produced, those conditions can be maintained by choosing packaging with adequate moisture vapor transmission rates (MVTR) (Table 5). The lower the MVTR, the slower the moisture ingress. Preventing moisture ingress helps to maintain a viable probiotic cell count over the shelf life of the product.

Not all plastic bottles are equal in terms of sustaining probiotic viability. Polyethylene terephthalate (PET) bottles should never be used, as their structure allows migration of too much moisture compared with high-density polyethylene (HDPE). While glass bottles have the best MVTR, a bottle seal that adheres well to glass must be chosen to prevent moisture ingress from the bottle opening. The addition of desiccant packs into the bottles aids in maintaining the low water activity of the probiotic contents. **CSP® brand vials with a desiccant in the bottle wall have proven to be highly effective at maintaining the low water activity of the probiotic contents throughout shelf life, even at high-humidity storage conditions, as recommended by the International Conference on Harmonization (ICH)**.

When considering other active ingredients to be mixed with probiotics, there are generally two stages that should be evaluated. In the dietary supplement format, it will typically be the water activity of the other active ingredient(s) that can be detrimental to probiotic survival if they increase water activity. The second consideration is the impact of the active ingredient(s) on the freeze-dried probiotics upon rehydration, which occurs after ingestion in the stomach or when a buffer solution is added before enumeration of the product in the laboratory [16].

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Short communication

Water activity in dry foods containing live probiotic bacteria should be carefully considered: A case study with *Lactobacillus rhamnosus* GG in flaxseed

Satu Vesterlund *, Kari Salminen, Seppo Salminen

Functional Foods Forum, University of Turku, 20014 Turku, Finland

This study evaluated the effect of water activity on the long-term storage stability of the probiotic Lactobacillus rhamnosus GG (LGG) in a dry food matrix. Viability of LGG was further studied in a crushed flaxseed matrix – anew possible product matrix to deliver probiotics – as well as in reference matrices as maltodextrin. Three different water activities (aw = 0.11, 0.22 and 0.43) were used, and preparations were stored at room temperature for up to 14 months. The viability of LGG was less dependent on the matrix used, but strongly dependent on the water activity. Viability in flaxseed was lost rapidly with aw 0.43: with aw 0.22 the reduction was 2.4log10 units and with aw 0.11 the reduction of viability was only 0.29 log10 units during the entire storage time. Taken together, regulating water activity to a low value may offer possibilities for extending the shelf life of dry probiotic products

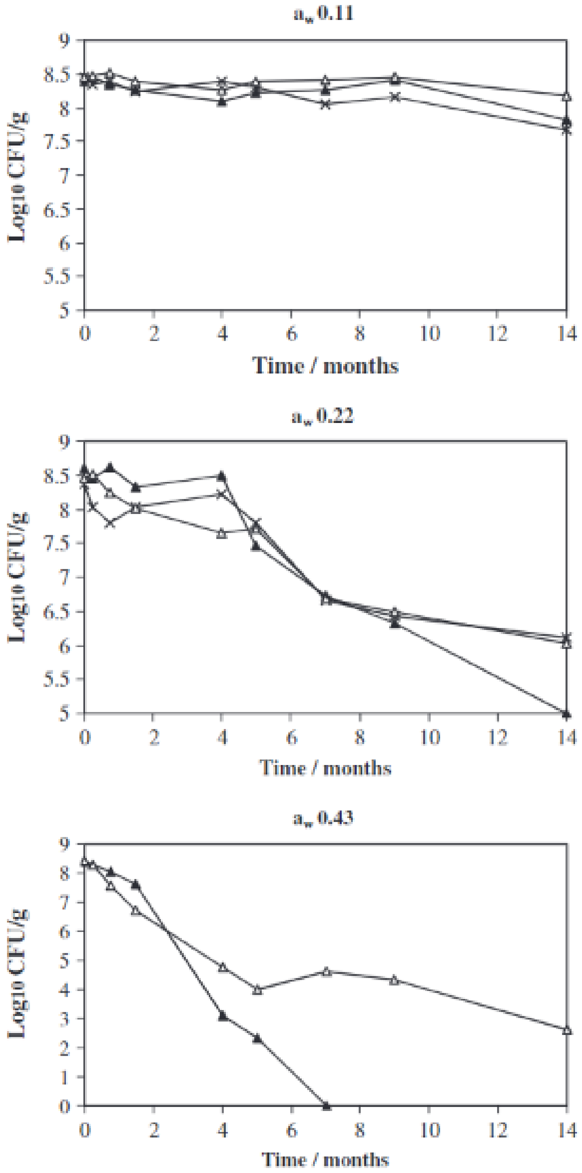
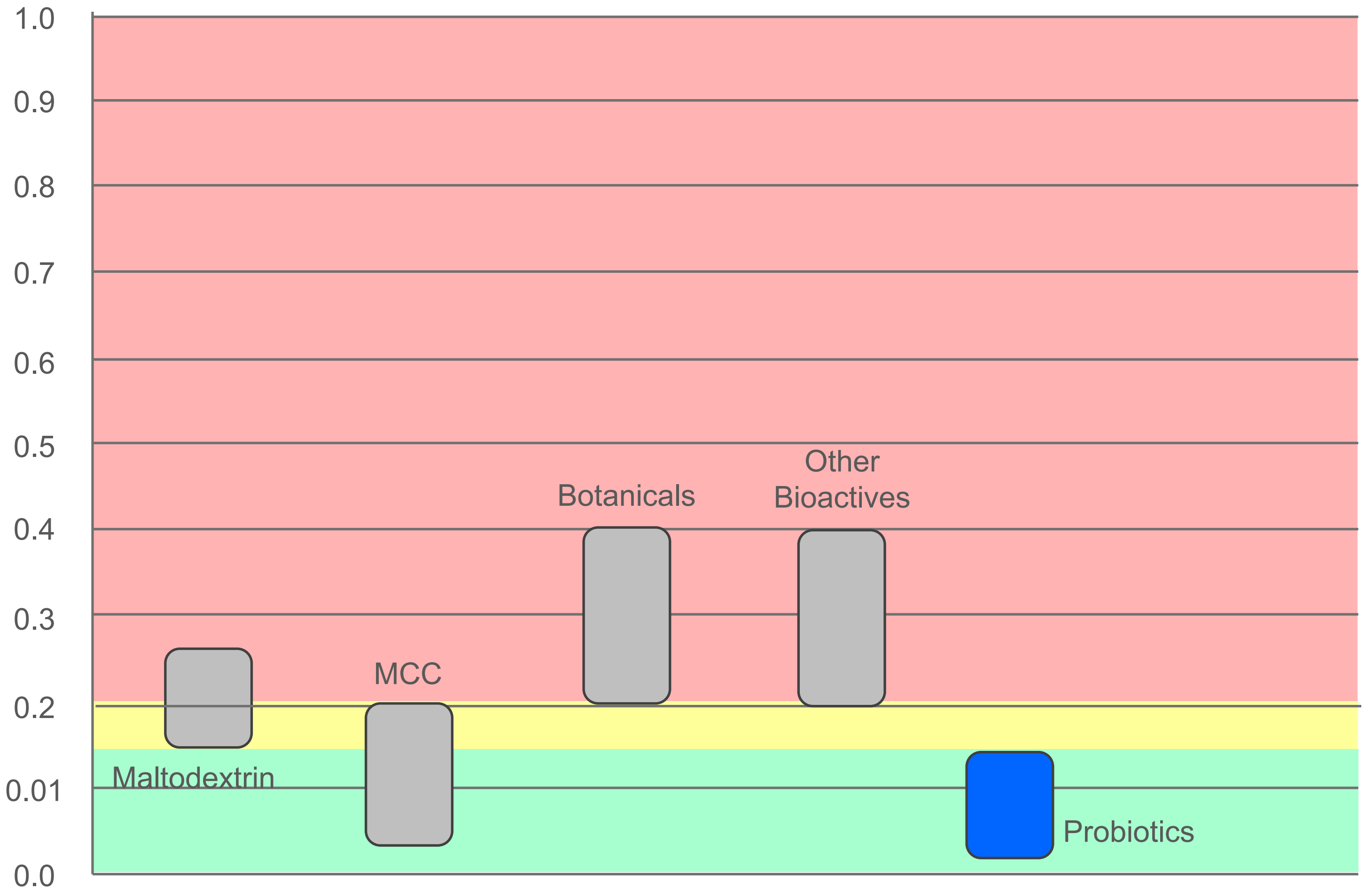


Fig. 1. The viable counts of L. rhamnosus GG in crushed flaxseed preparation (open triangle) and in the two reference matrices, maltodextrin (filled triangle) and in laboratory sand (cross). Three different water activities and matrices were tested, and preparations were stored at room temperature. Each point is a mean for three determinations. Coefficient of variation (CV%) for crushed flaxseed and maltodextrin was b 25%,and for laboratory sand b 19%, in all tested water activity values and time-points.320 S. Vesterlund et al. / International Journal of Food Microbiology 157 (2012) 319–321

Most excipients and bioactives that mixed with probiotics have higher water activity than the probiotic itself. This will accelerate probiotic degradation. The use of packaging that reduces water activity prevents such accelerated degradation.



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Consequences for failing to achieve end-of-shelf-life label claims

- Business loss
- Ineffective product
- Negative reviews
- Regulatory action
- Consumer watchdog outing
- Class action lawsuit
- Damaged reputation

To reduce their risk profile, CMOs and Brands can…

Control processing conditions, temper before opening, use proper overages, select higher stability strains

Employ cold chain through shipping, storage, distribution, retail sale

Utilize protective packaging that withstands real-world challenges of elevated moisture and temperature

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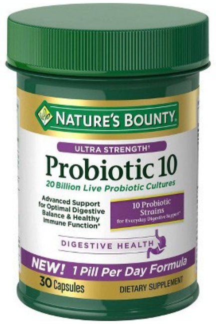
Let's look at real-world scenarios of the impact of packaging selection on Water Activity control, retention of Probiotic Stability over shelf life, and potential product cost savings.

Packaging Selection Options

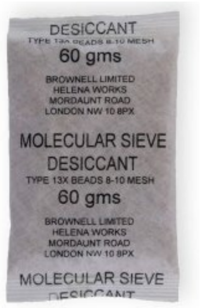
Amber Glass Bottle

HDPE Bottle

Activ-Vial™ Portfolio



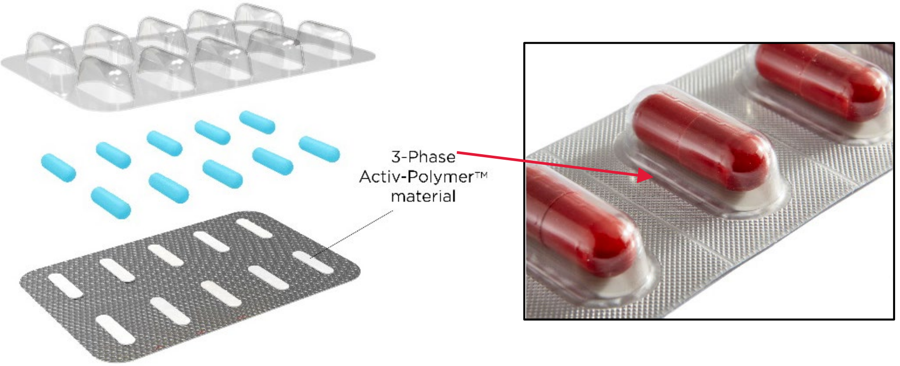
Loose Desiccant Sachet



Thermoformed (PVC.PVdC) Blister

ALU/ALU Blister

Activ-Blister™ Solutions



Stick Pack

(with or without Activ-Film™ material)

Activ-Film™ material inside

CSP™ Flip-Top Activ-Vial™ vs. HDPE Bottle + Desiccant

Investigator:	Leading US-based CMO
Formulation:	12-strain Lactobacillus and Bifidobacterium blend
Storage Conditions:	22ºC / 40% RH
Shelf life:	18 months
Format:	Size 1 HPMC capsule
Packaging:	CSP™ Flip-Top Activ-Vial™ vs. HDPE bottle + 2 gm silica pillow pack

CSP™ Flip-top Activ-Vial™ technology drives down water activity over shelf life…

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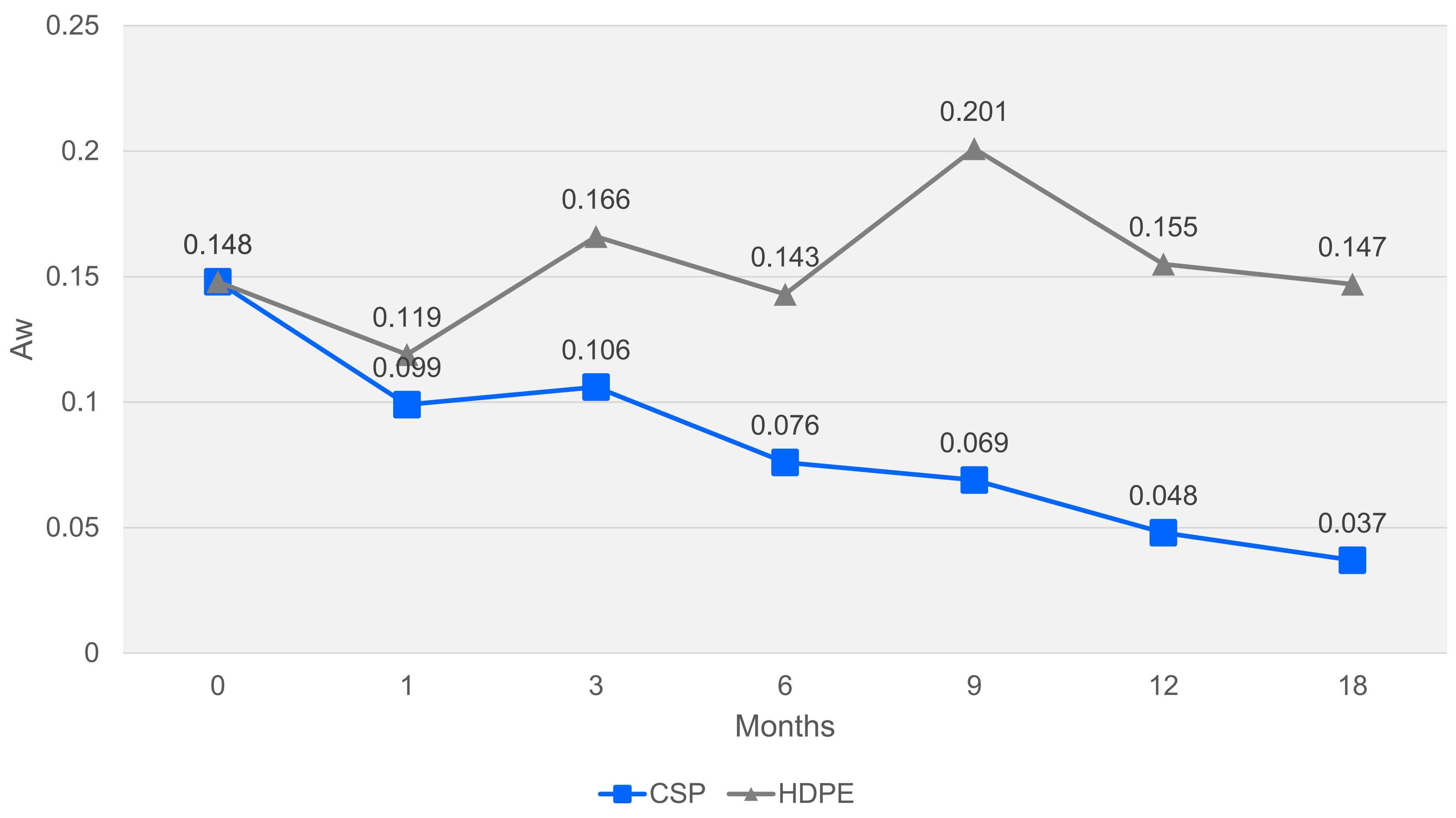
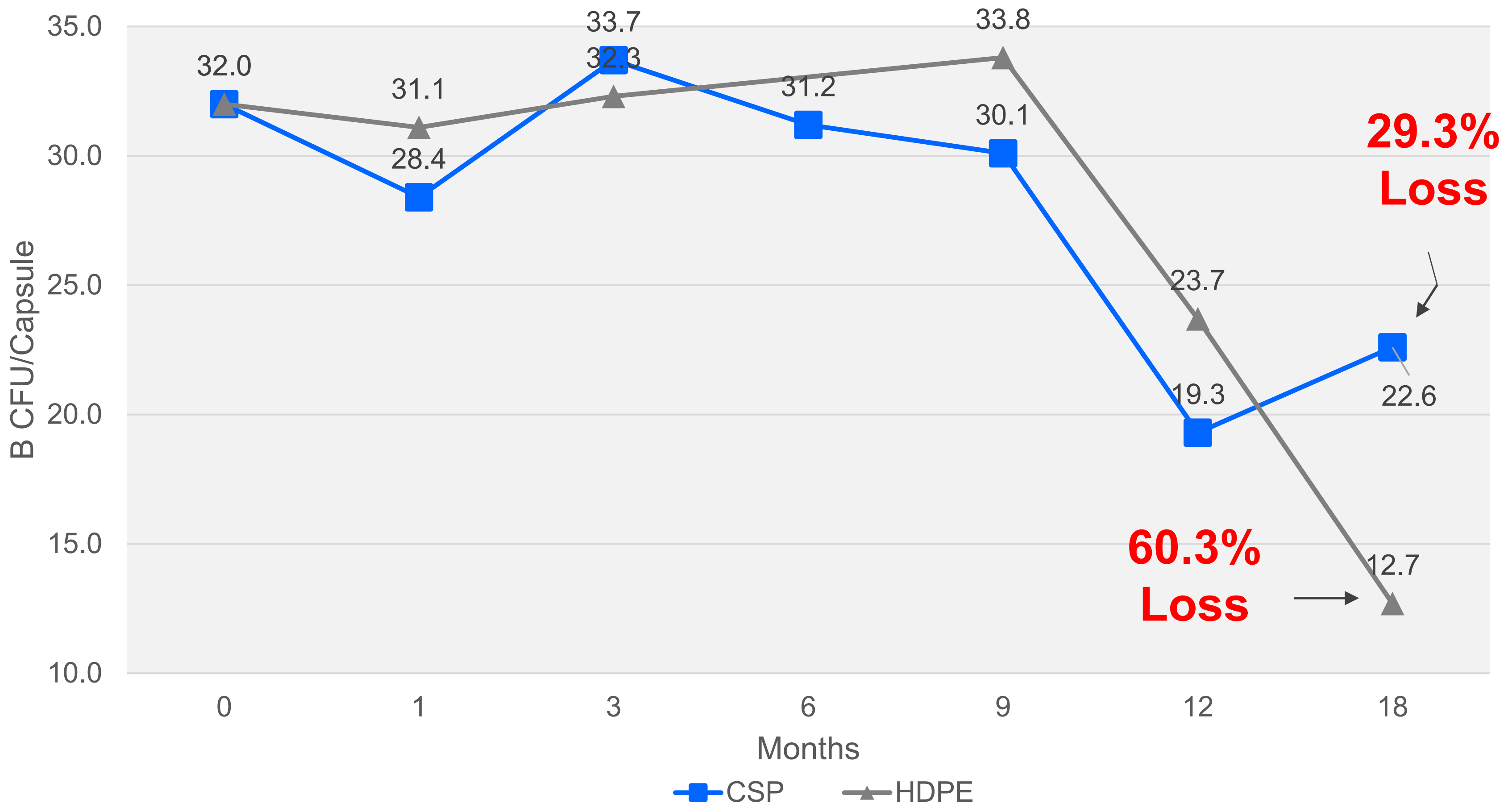


…resulting in greater retention of probiotic potency.



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Now let's **calculate the initial potency required to achieve 10B at end-of-shelf-life** with CSP™ and HDPE *and* quantitate the benefit

Initial potency calculation for CSP

Initial potency = EOSL potency target ÷ (1 - % loss over 18 mos.)

Initial potency = 10B ÷ (1 – 29.3% loss)

Initial potency = 14.1B

Initial potency calculation for HDPE

Initial potency = EOSL potency target ÷ (1 - % loss over 18 mos.)

Initial potency = 10B ÷ (1 – 60.3% loss)

Initial potency = 25.2B

Now let's calculate the initial potency required to achieve 10B at end-of-shelf-life with CSP™ and HDPE and **quantitate the benefit – step 1**

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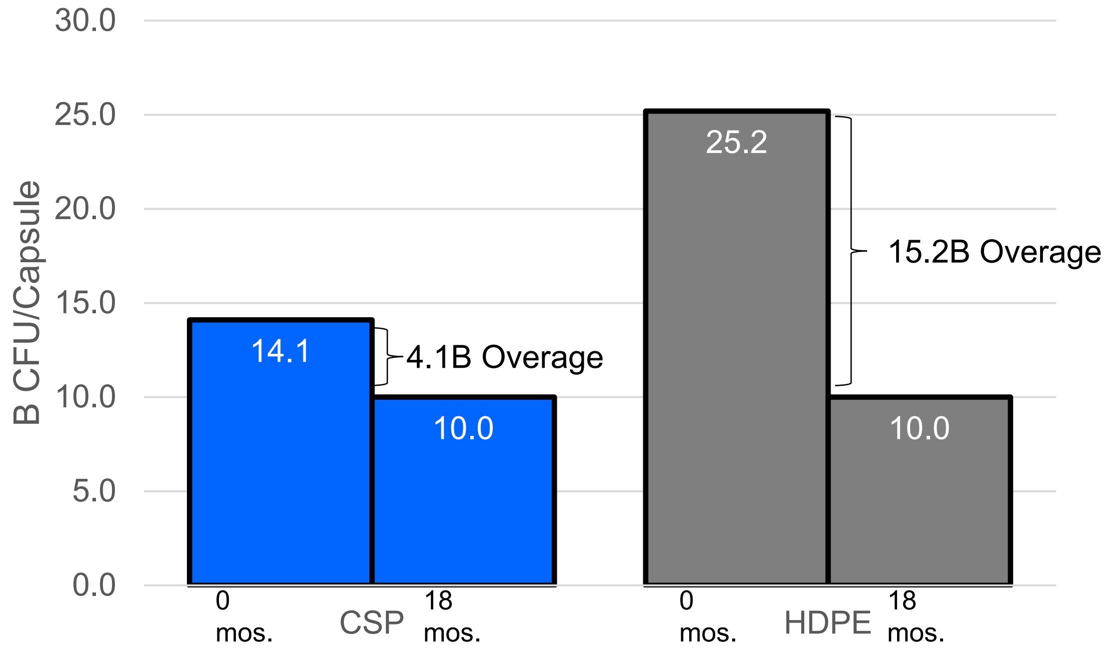
Strain		Strain 1	Strain 2	Strain 3	Strain 4	Strain 5	Strain 6	Strain 7	Strain 8	Strain 9	Strain 10	Strain 11	Strain 12		
Concentrate Potency (CFU/gm)		1.40E+11	4.20E+11	4.20E+11	1.40E+11	7.00E+10	2.80E+11	4.20E+11	5.60E+11	5.60E+11	1.40E+11	4.90E+11	4.20E+11	3.62E+11	Weighted Avg Potency
Gms/Kg	1000														
Mgs/Gm	1000														
Conc Price $/kg		$247.00	$859.00	$850.00	$229.00	$234.00	$310.00	$300.00	$516.00	$487.00	$300.00	$650.00	$490.00	$397.67	Weighted Avg Price
Mgs/Cap		1.000	0.167	1.999	1.000	1.150	57.521	0.992	20.063	0.981	1.000	7.143	1.100	93.116	Total Mgs/Cap
CFUs/cap		1.40E+08	7.01E+07	8.40E+08	1.40E+08	8.05E+07	**1.61E+10**	4.17E+08	**1.12E+10**	5.49E+08	1.40E+08	3.50E+09	4.62E+08	3.35E+10	Total CFUs/Cap
Cost/Cap		$0.0002	$0.0001	$0.0017	$0.0002	$0.0003	$0.0178	$0.0003	$0.0104	$0.0005	$0.0003	$0.0046	$0.0005	$0.0368	Total $ Culture/Cap
# Caps/Bottle	30													$1.10	Total $ Culture/30 Cap Bottle
	60													$2.21	Total $ Culture/60 Cap Bottle

Now let's calculate the initial potency required to achieve 10B at end-of-shelf-life with CSP™ and HDPE *and* **quantitate the benefit – step 2**

Target potency CFU/cap	10.0E+9
T0 potency CFU/cap to achieve 10B at T18 - CSP	14.2E+9
T0 potency CFU/cap to achieve 10B at T18 - HDPE	25.2E+9
Cost of probiotic per 30 caps - CSP	$0.467
Cost of probiotic per 30 caps - HDPE	$0.831
CSP cost savings for 30 cap bottle	**$0.364**
Cost of probiotic per 60 caps - CSP	$0.934
Cost of probiotic per 60 caps - HDPE	$1.662
CSP savings for 60 count bottle	**$0.728**

TAKEAWAY

CSP™ Activ-Vial™ technology requires less overage than HDPE to achieve 10B label claim, resulting in cost savings



Note that this study is 22C/40% RH…not even ICH Zone II.

CSP™ savings for 30 cap bottle = $0.364

CSP™ savings for 60 cap bottle = $0.728

STUDY 3

CSP™ Flip-Top Activ-Vial™ vs. ALU/ALU Blister

Investigator:	Leading CMO
Formulation:	L. acidophilus and B. lactis blend
Storage Conditions:	25ºC / 60% RH (ICH Zone II) 30ºC / 65% RH (ICH Zone IV)
Shelf life:	24 months
Format:	Size 1 HPMC capsule
Packaging:	CSP™ Flip-Top Activ-Vial™ vs. ALU/ALU Blister

CSP™ Flip-Top Activ-Vial™ shows Aw decline and maintains higher potency vs. ALU/ALU Blister under ICH Zone II conditions…

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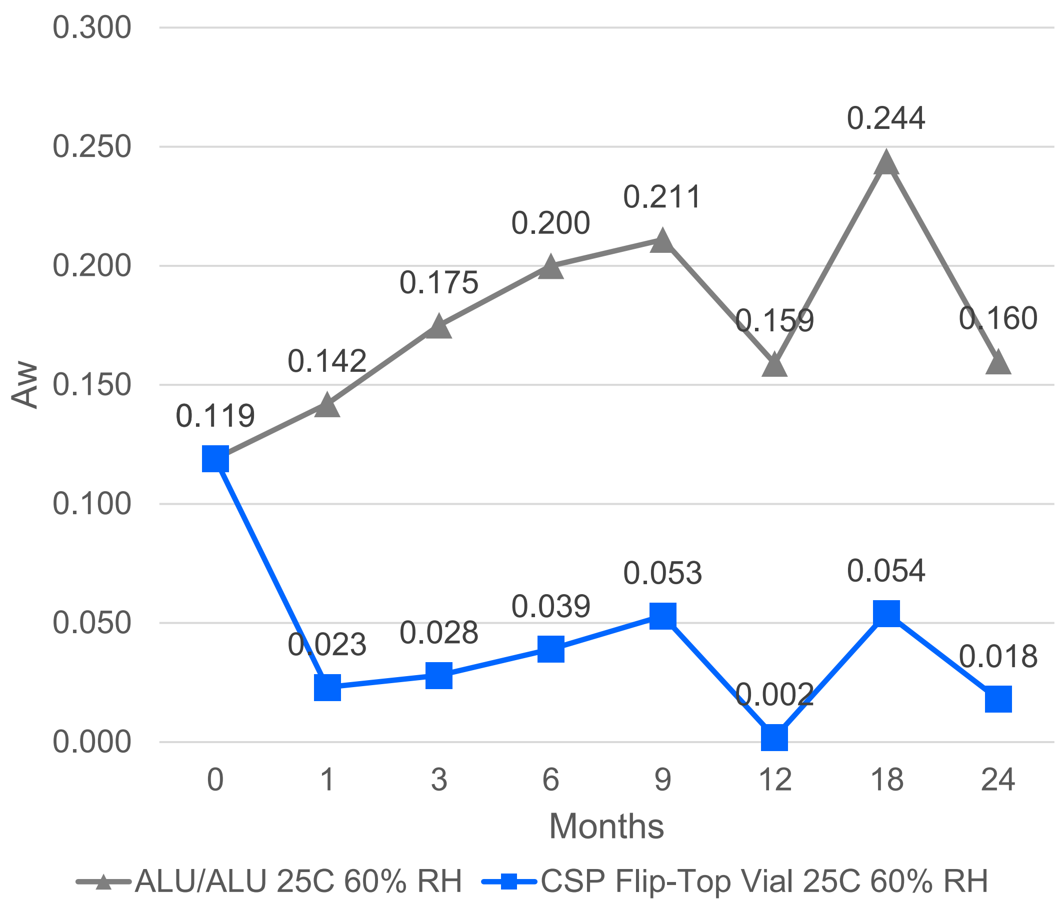

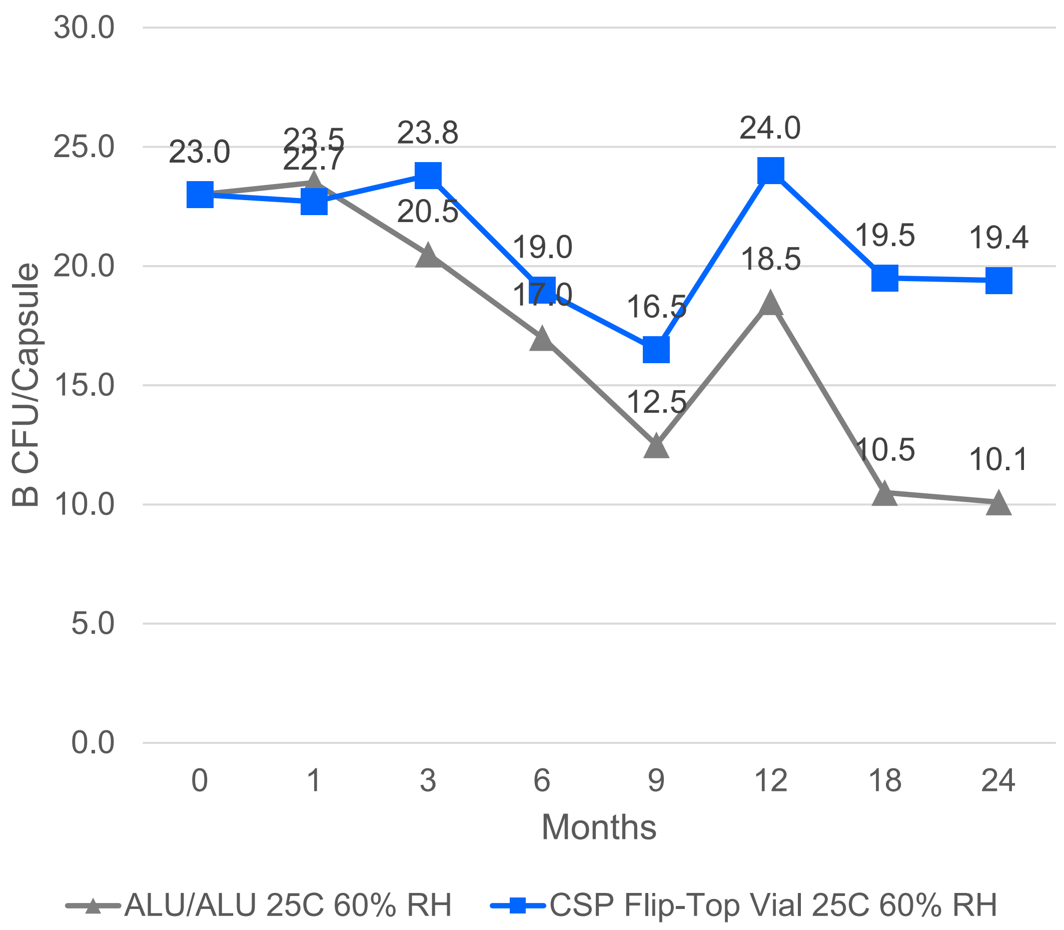

15.6% Loss

56.1% Loss

…and we see the same CSP Flip-Top Activ-Vial™ benefit under ICH Zone IV conditions

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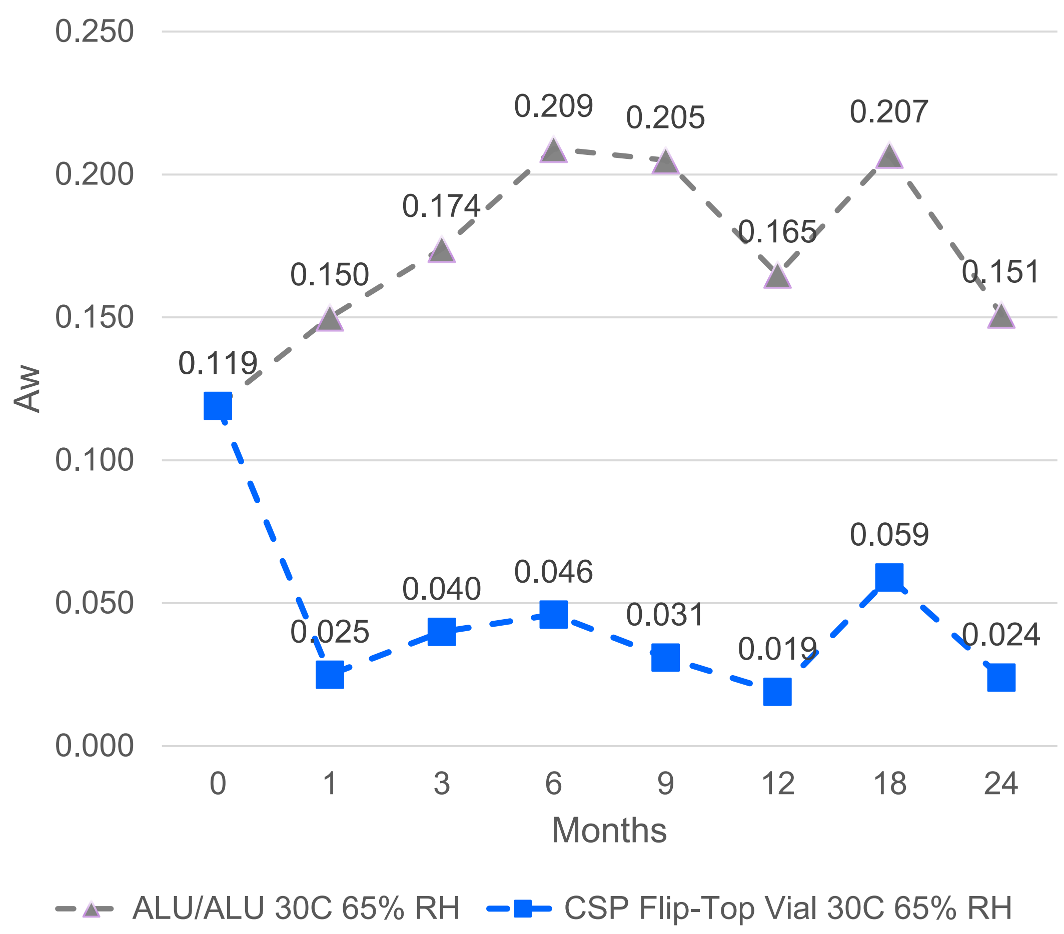

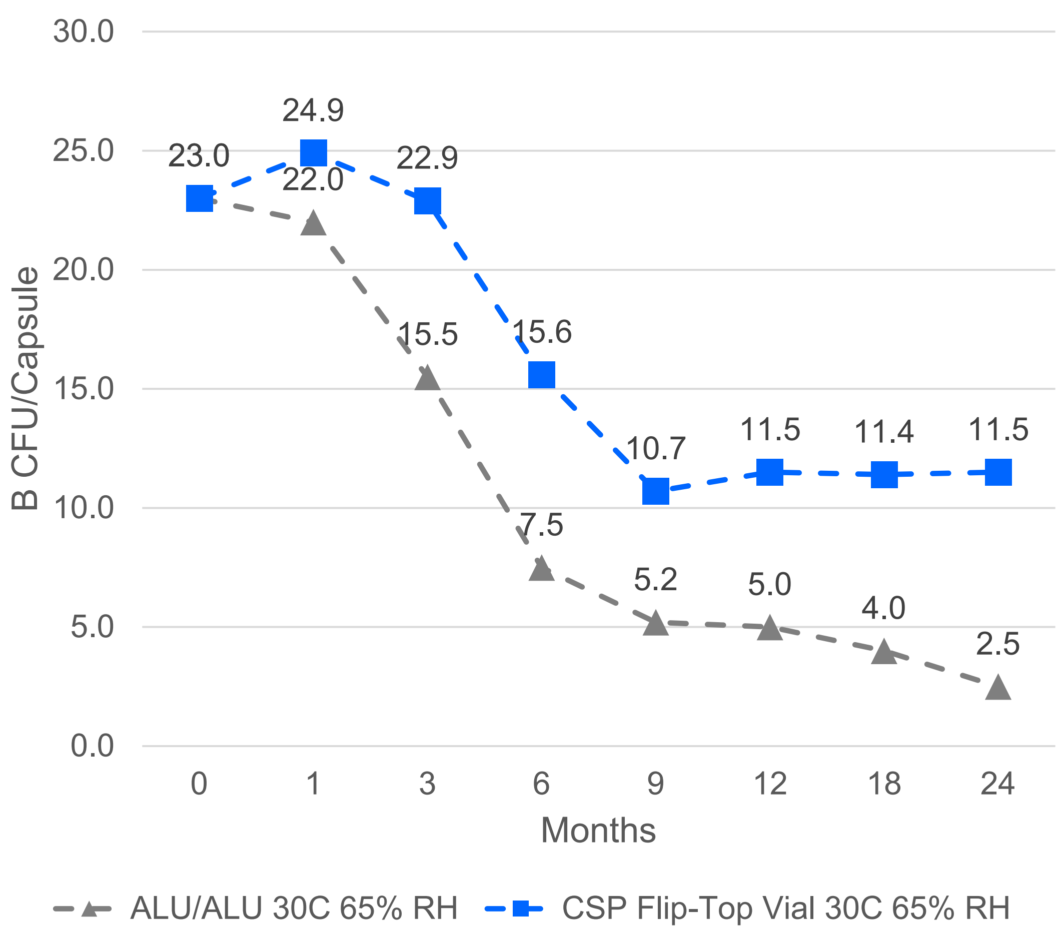

50.0% Loss

89.1% Loss

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Now let's **calculate the initial potency required to achieve 10B at end-of-shelf-life** for CSP™ Flip-Top Activ-Vial™ vs ALU/ALU blisters

Zone II

Initial potency calculation for CSP

Initial potency = EOSL potency target ÷ (1 - % loss over 24 mos.)

Initial potency = 10B ÷ (1 – 15.6% loss)

Initial potency = 11.9B

Initial potency calculation for ALU/ALU blisters

Initial potency = EOSL potency target ÷ (1 - % loss over 24 mos.)

Initial potency = 10B ÷ (1 – 56.1% loss)

Initial potency = 22.8B

Zone IV

Initial potency calculation for CSP

Initial potency = EOSL potency target ÷ (1 - % loss over 24 mos.)

Initial potency = 10B ÷ (1 – 50.0% loss)

Initial potency = 20.0B

Initial potency calculation for ALU/ALU blisters

Initial potency = EOSL potency target ÷ (1 - % loss over 24 mos.)

Initial potency = 10B ÷ (1 – 89.1% loss)

Initial potency = 91.7B

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Now let's calculate the initial potency required to achieve 10B at end-of-shelf-life with CSP's Activ-Vial™ and ALU/ALU blister *and* **quantitate the benefit – step 2**

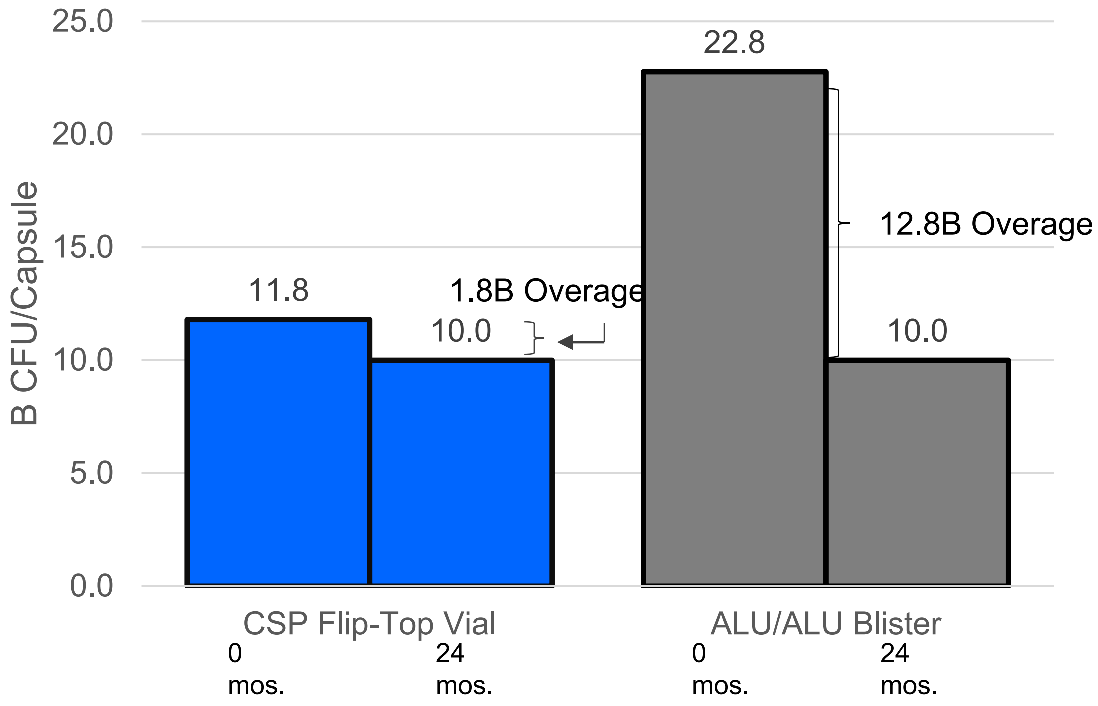
Zone II

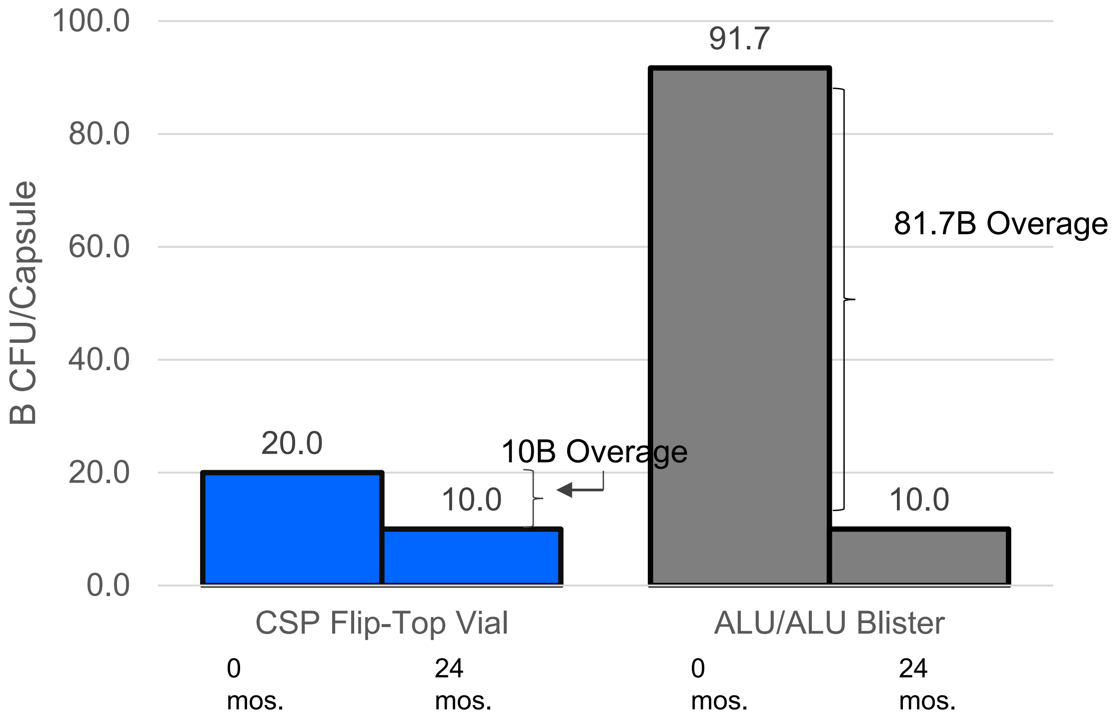
Target potency CFU/cap	10.0E+9
T0 potency CFU/cap to achieve 10B at T24 - CSP	11.9E+9
T0 potency CFU/cap to achieve 10B at T24 - ALU/ALU	22.8E+9
Cost per 30 caps - CSP	$0.391
Cost per 30 caps - ALU/ALU	$0.751
CSP cost savings for 30 cap bottle	**$0.360**

Zone IV

Target potency CFU/cap	10.0E+9
T0 potency CFU/cap to achieve 10B at T24 - CSP	20.0E+9
T0 potency CFU/cap to achieve 10B at T24 - ALU/ALU	92.0E+9
Cost per 30 caps - CSP	$0.660
Cost per 30 caps - ALU/ALU	$3.034
CSP cost savings for 30 cap bottle	**$2.375**

…resulting in significant savings





CSP's Activ-Vial™ savings per 30 capsules = $0.36 under ICH Zone II

CSP's Activ-Vial™ savings per 30 capsules = $2.33 under ICH Zone IV

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Concluding Comments

- Water Activity control is critical to maximizing probiotic shelf life while minimizing probiotic overages
- Choosing probiotic packaging with strong barrier and desiccation properties can maintain, and even reduce, Water Activity over shelf life.
- Reduced Water Activity translates directly to reduced overages and savings in product cost.
- **CSP’s Activ-Vial™ portfolio and Activ-Film™ material offer unique technology to effectively control and even reduce Water Activity over probiotic shelf life.**
- **This technology is available across formats — Bottles, Blisters, Sticks, Sachets and Oil Drops.**
- **Advantages to Activ-Vial™ and Activ-Film™ solutions are cost savings, risk mitigation, and peace of mind.**