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Stabilization of Live Attenuated Virus Vaccines

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Outline

- Model System
- Stabilization Strategy
- Processing Options
- Results
- Conclusions

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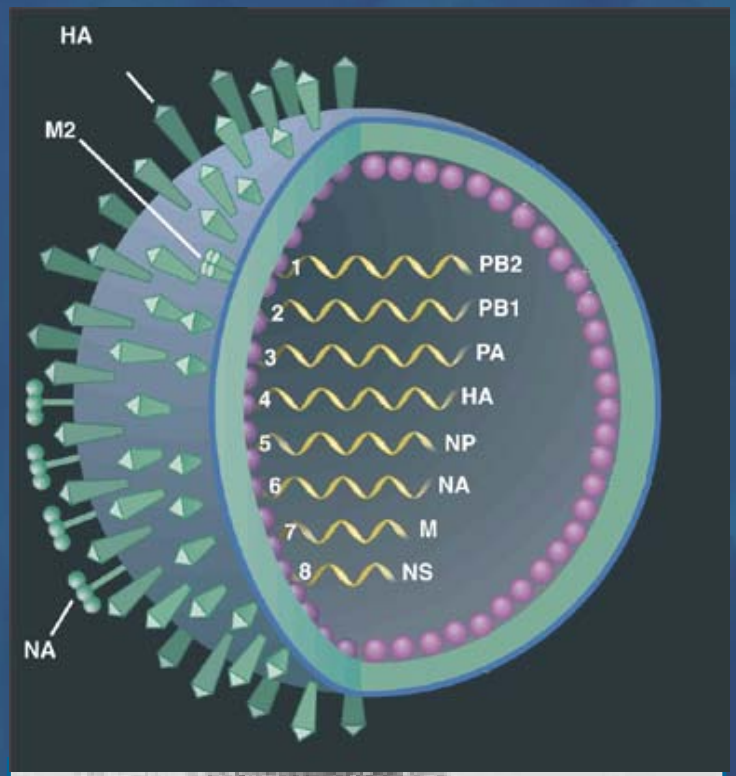
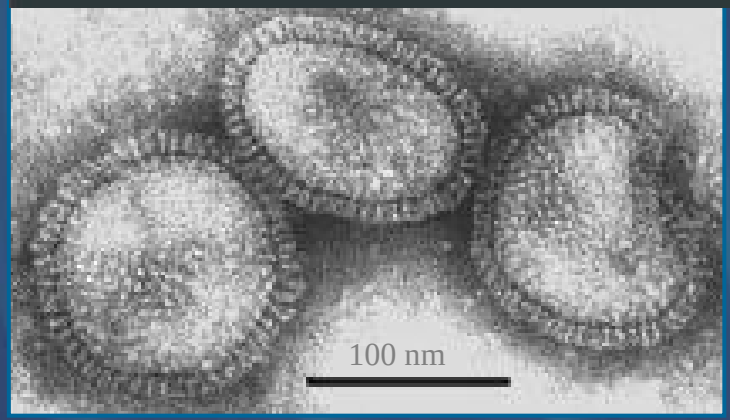
Live, Attenuated Influenza Virus Vaccine





- **Enveloped RNA virus**
  - Live, cold adapted, attenuated
  - Temperature sensitive
- **< 0.1% w/w of total protein is virus**
  - Mainly egg derived proteins & metabolites
  - Only 1 - 10 % of virus is infectious
- **Relatively poorly characterized**
  - Limited molecular analytical assays
  - Limited spatially resolved assays
  - Primary formulation tool is potency assay
- **Physically unstable**

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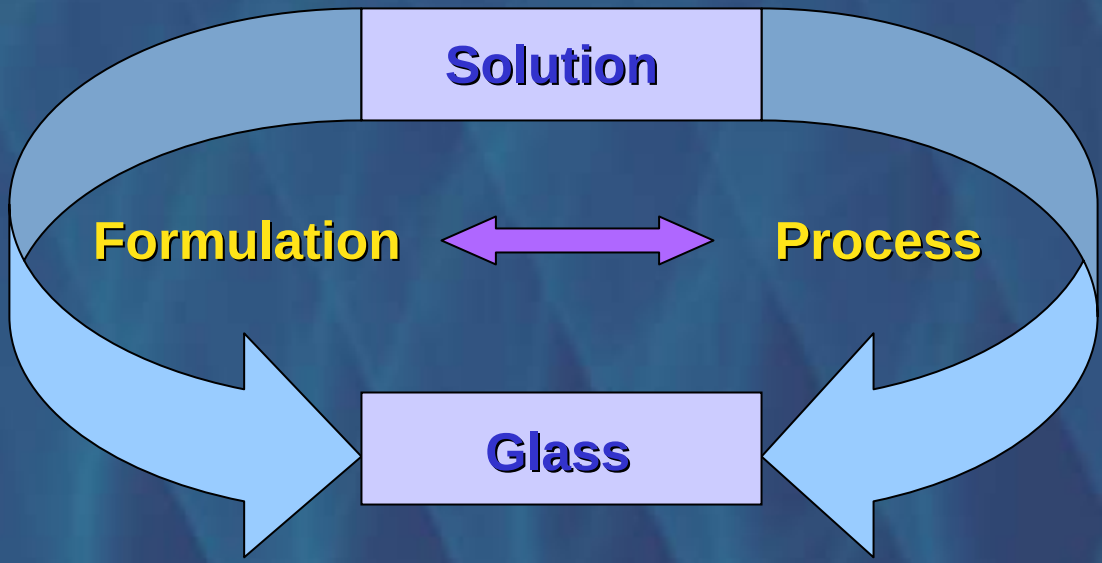
Stabilization Strategy

Water provides mobility, facilitates degradation



- Cryo- Desiccoprotectants
- H-bond donors
- Surfactants
- Glass former
- Antioxidants

- Remove water
- Create morphology
- Determine solid state
  - Mixing
  - Residual water content
  - Glass properties

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Processing Options: Spray Drying

Benchtop Scale

Büchi 191

Intermediate Scale

Niro Mobile Minor

Advantages:

- Highly scalable
- Short manufacturing time
- Versatile solid dosage form
- Enables broad delivery options
  - Different delivery routes
  - Different delivery devices

Challenges:

- Shear and thermal stress

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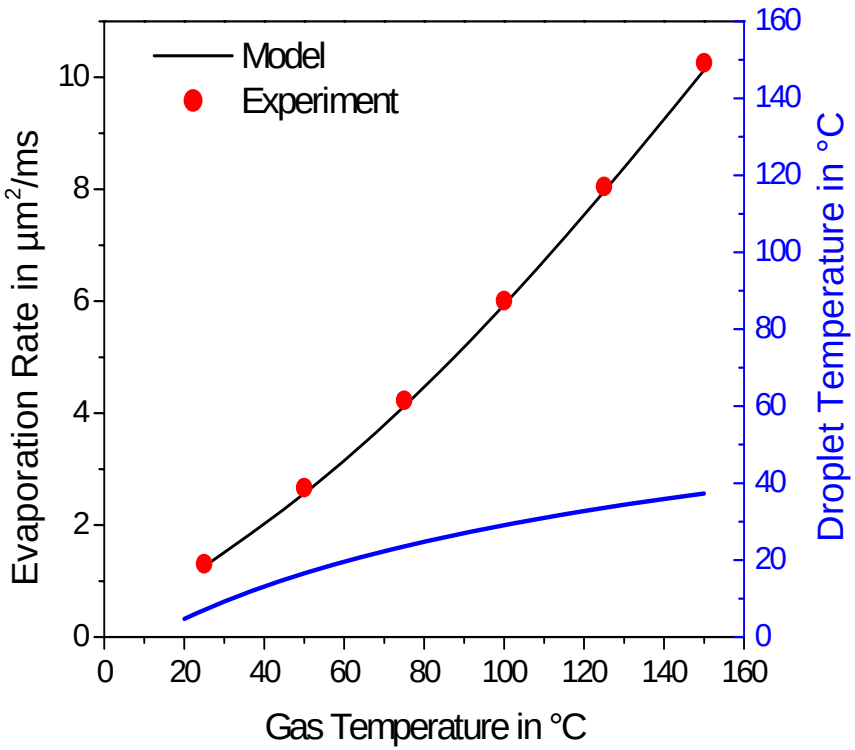
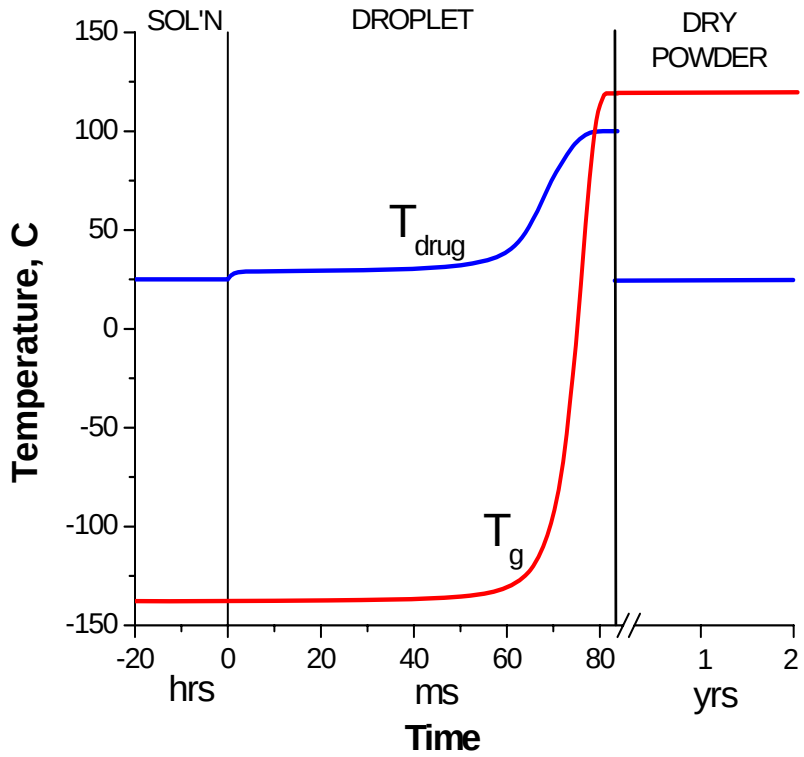
Spray Drying: Thermal Stress and Stabilization





Foss, W. R., Vehring, R. AAAR Annual Conference, 2004, Atlanta, GA

- During drying, the active is protected from high temperature by evaporative cooling.
- When almost dry, the particle temperature will reach the drying gas temperature but the active is by then immobilized and protected in an amorphous phase.

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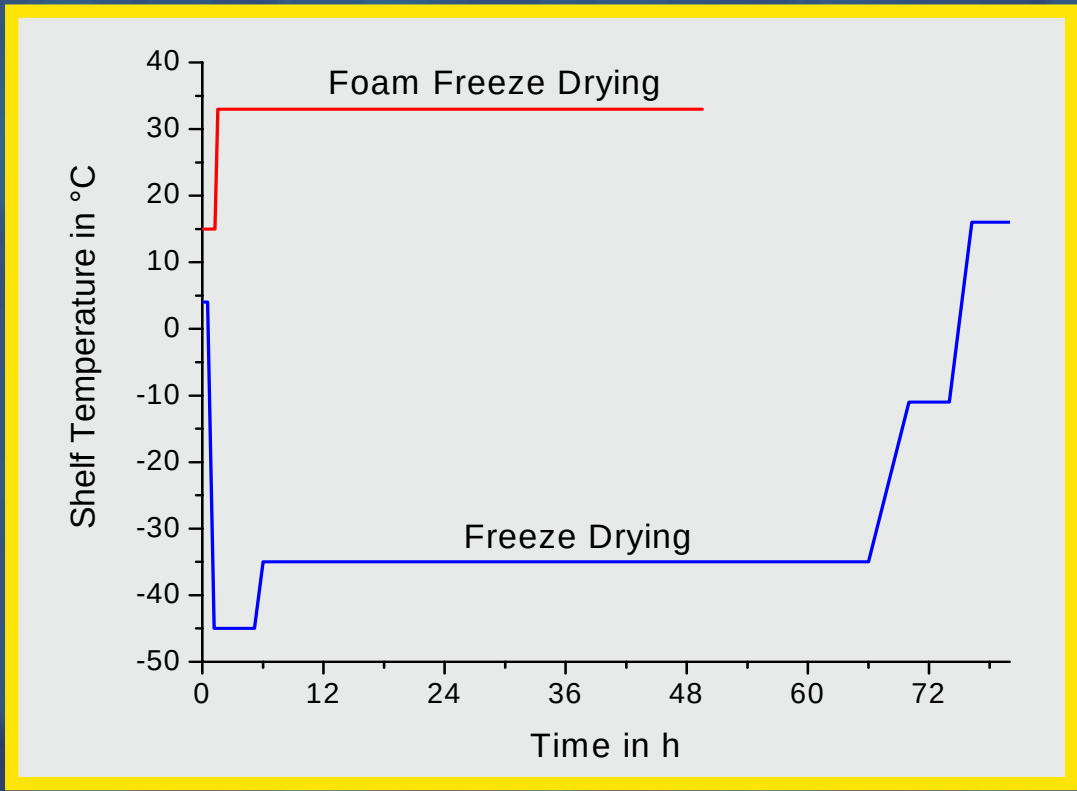
Processing Options:
Foam Freeze Drying and Freeze Drying



Foam Freeze Drying:

- **Higher shelf temperatures**
- **Shorter cycle time**

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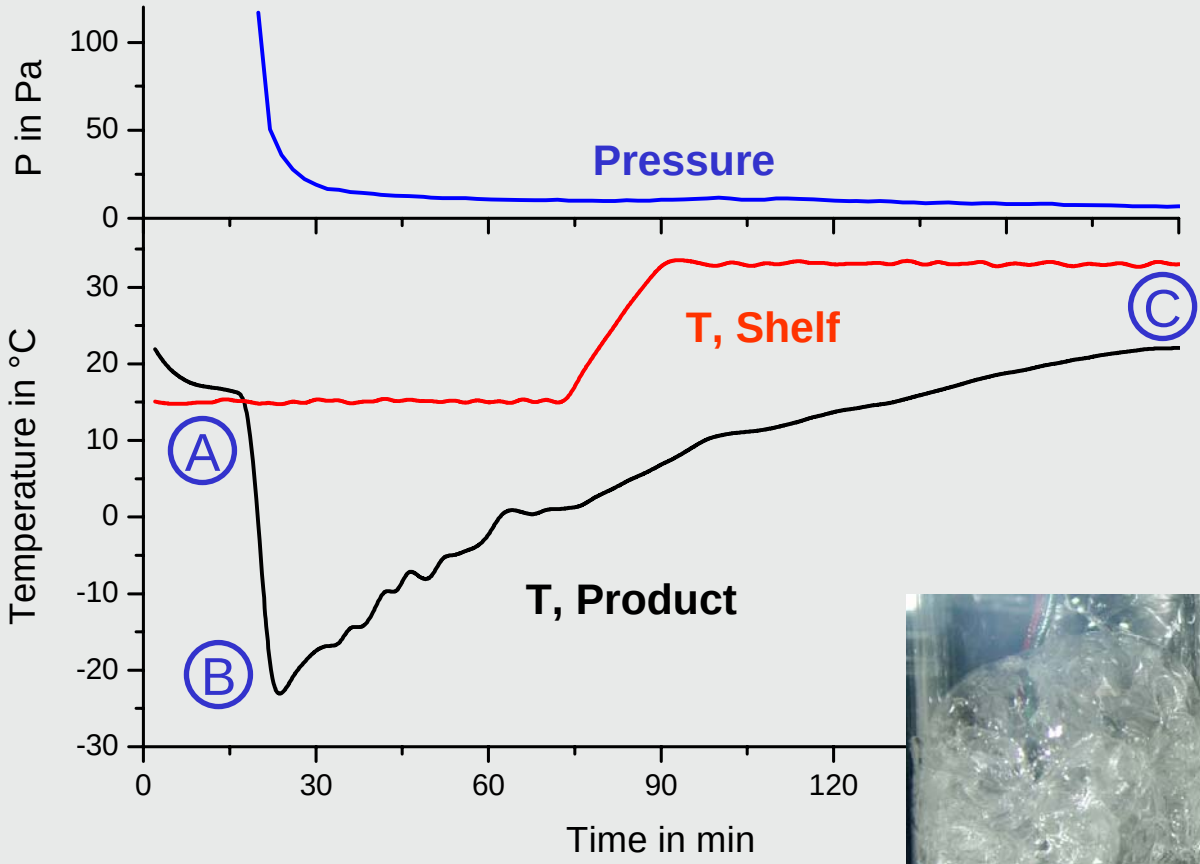
Characteristics of Foam Freeze Drying

A: Boiling



B: Frozen Foam

C: Dry Foam

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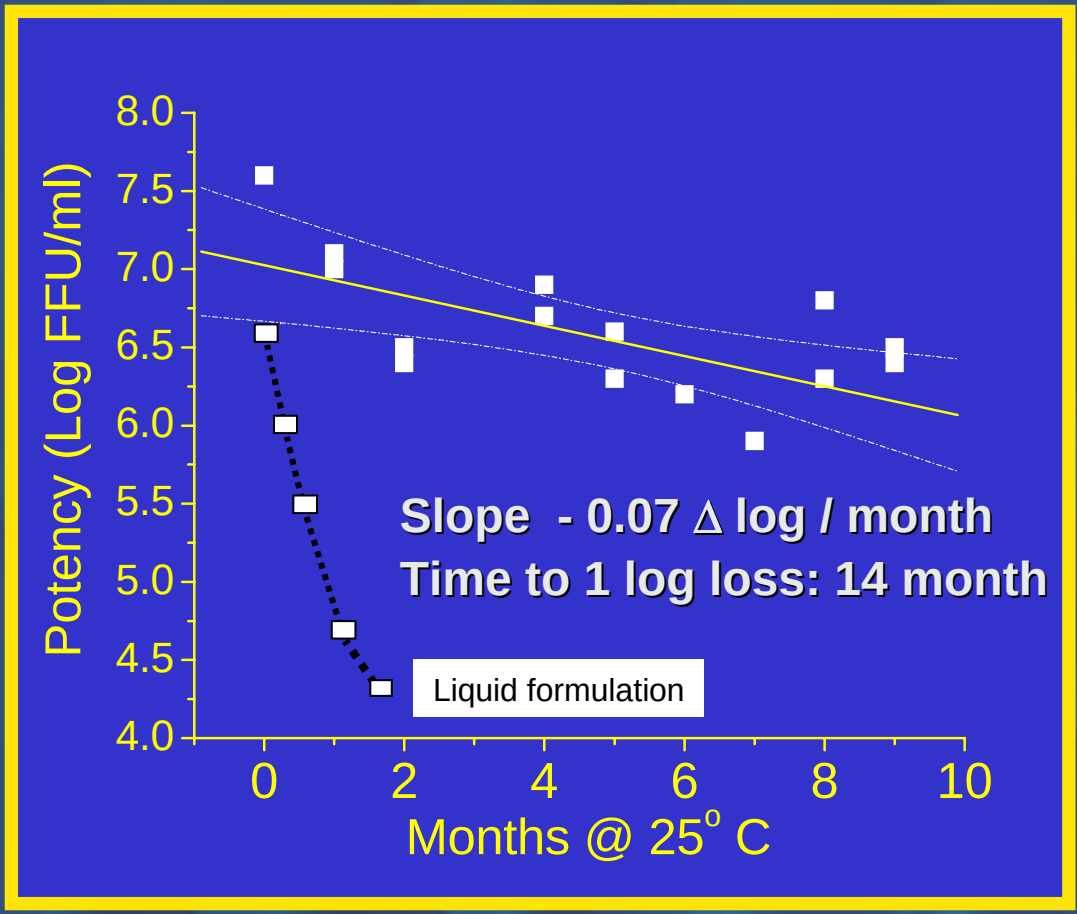
Spray Drying Stabilizes Live Virus Vaccine



- **Cold-adapted, attenuated influenza B/Harbin virus**
- **Spray drying conditions**
  - 55 - 65 °C drying gas temperature
  - 32 – 38 °C collector temperature
  - 1 – 15 µm particle diameter
- **Solid state properties**
  - Amorphous, sucrose based
  - 55 – 75 °C glass transition temperature
  - 1.5 – 4 % moisture content

Room temperature stability is feasible !

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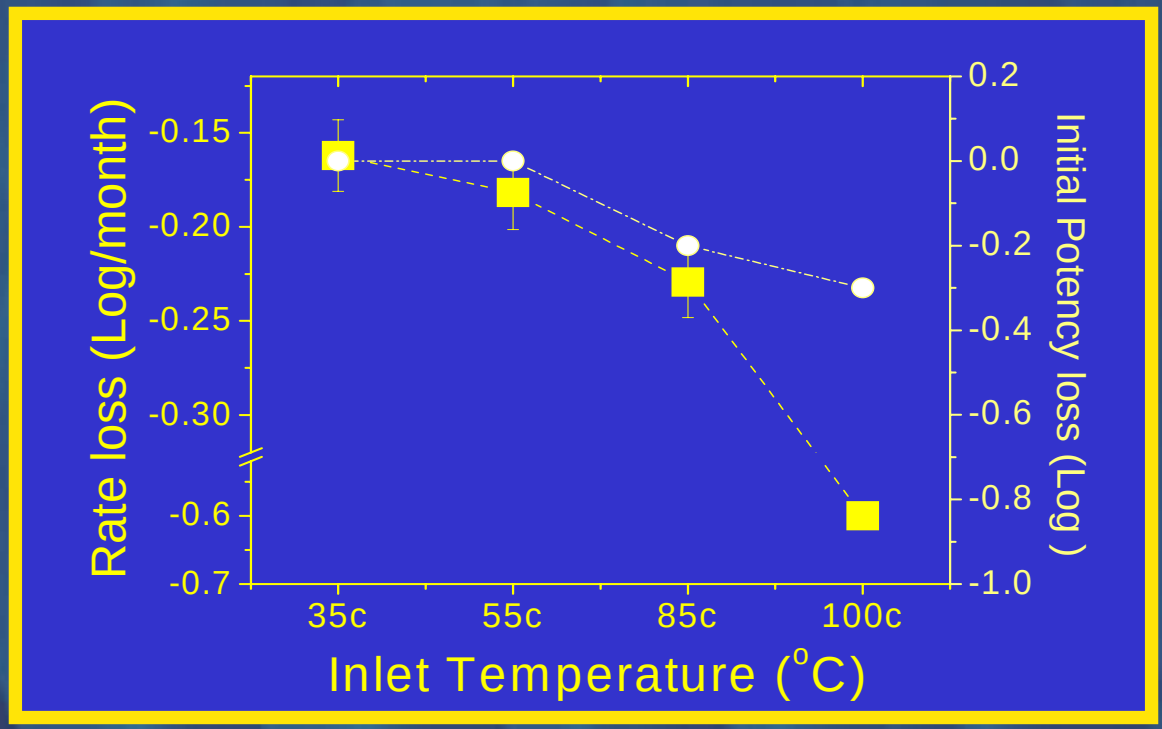
Process Conditions Affect Initial Loss and Stability



Truong-Le, V. Protein and Peptide Formulation Strategies, 2004, San Francisco, CA

T Gas	35 °C	55 °C	85 °C	100 °C
T Product	23 °C	33 °C	44 °C	53 °C
T_G	38 °C	41 °C	44 °C	47 °C
Moisture	2.0 %	1.6 %	1.2 %	1.0 %

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Same Formulation – Different Processes

Freeze Drying

Foam Freeze Drying

	Lyo	Foam	
T_G	53	46	°C
Specific Surface Area	0.9	0.06	m^2/g
Moisture Content	2.2	2.0	%
Process Loss	- 0.15	- 0.2	Δ log potency
Stability at 25 °C	- 0.6	- 0.04	Δ log / month

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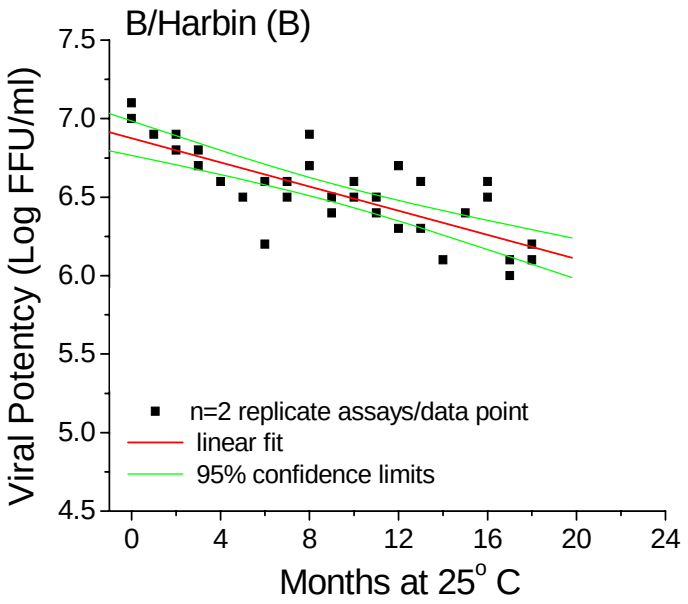
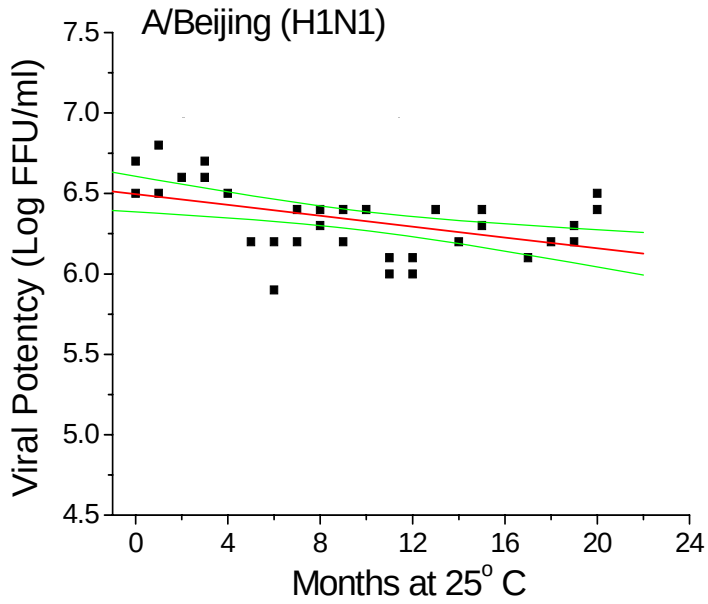
Foam Freeze Drying Stabilizes Live Virus Vaccine





	Process loss	Potency loss rate	Time to 1 log loss
	Log FFU/ml	Log FFU/month	Years @ 25 °C
A/Beijing (H1N1)	-0.3	-0.017 ± 0.005	4.9 ± 1.4
A/Sydney (H3N2)	0	-0.021 ± 0.004	3.9 ± 0.8
B/Harbin (B)	0	-0.038 ± 0.005	2.2 ± 0.3

- **Room temperature stability is feasible**
- **Significant differences between virus species and strains**

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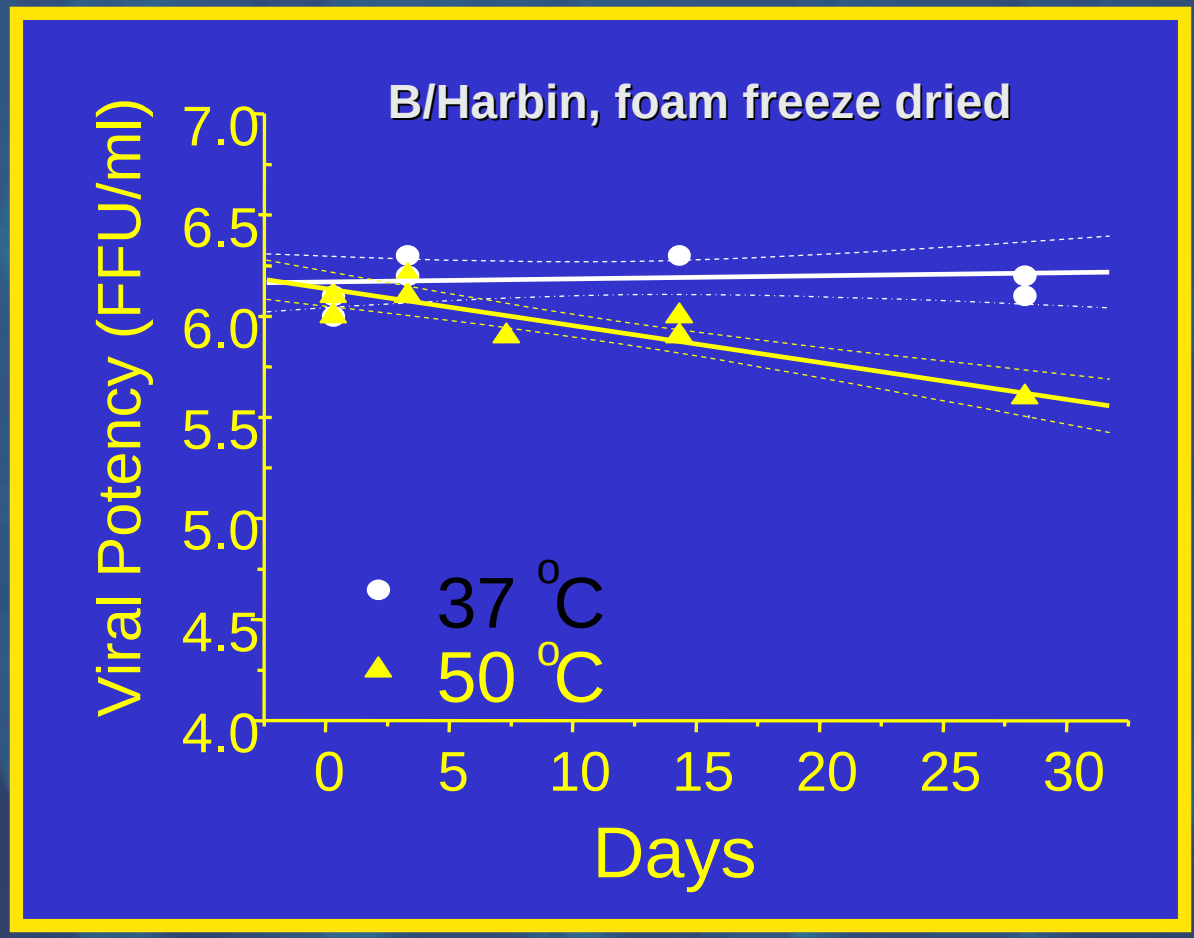
Stability at Elevated Temperatures



Dried virus vaccine tolerates excursions to higher temperatures for several days

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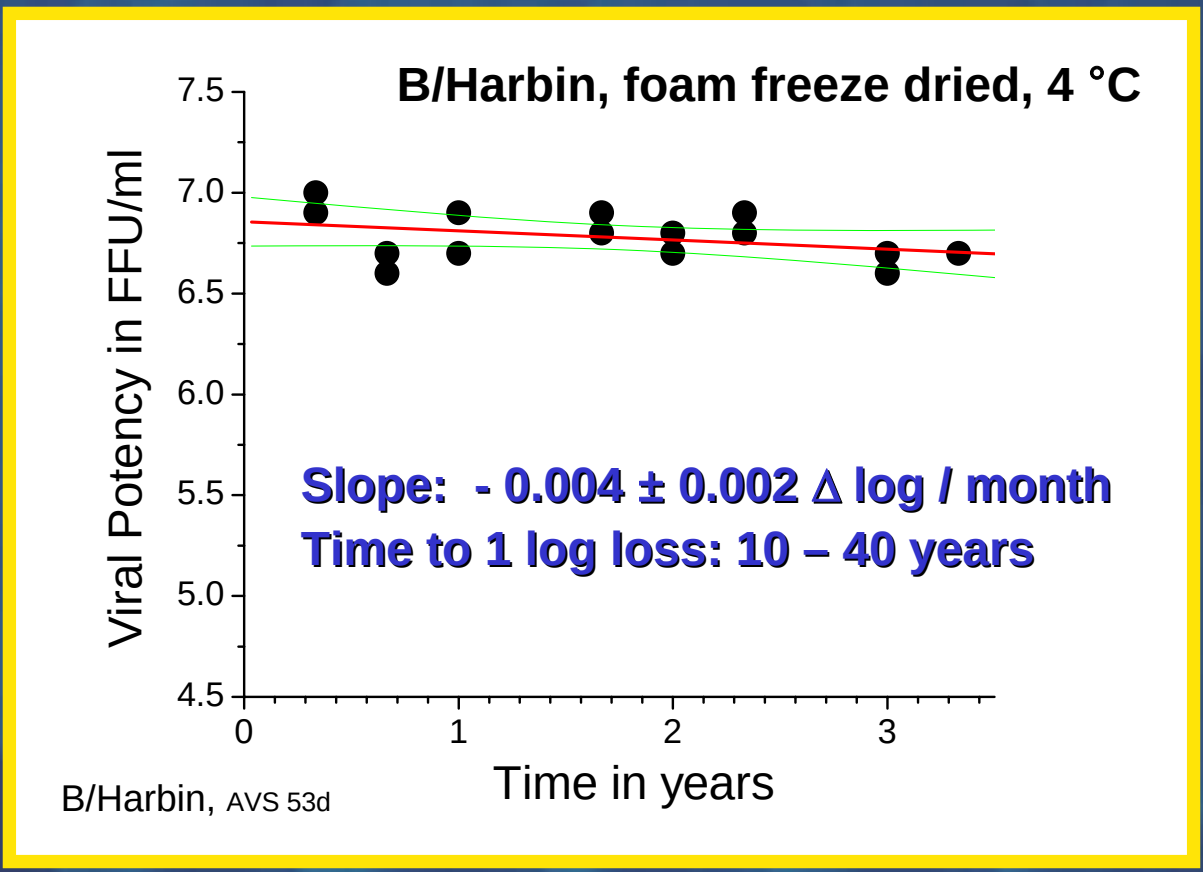
Shelf Life at Refrigerated Conditions



Long time storage is feasible.

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Conclusions

- Virus vaccines can be stabilized in dry form
  - Room temperature stability for years is achievable
  - Excursions to higher temperatures can be tolerated for weeks
  - Refrigerated storage opens option of stockpiling vaccines for decades
- Different processing options exist
  - Spray Drying using mild process conditions
  - Freeze Drying or Foam Freeze Drying
- Stabilization depends on processing conditions
- Unite Formulation and Process Development
- Study mechanisms of stabilization and damage

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