# Formulating two classes of power priors to leverage historical accelerated stability data


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Manufacturing and Applied Statistics (MAS)



Janssen PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Stability studies

Kinetics of degradation

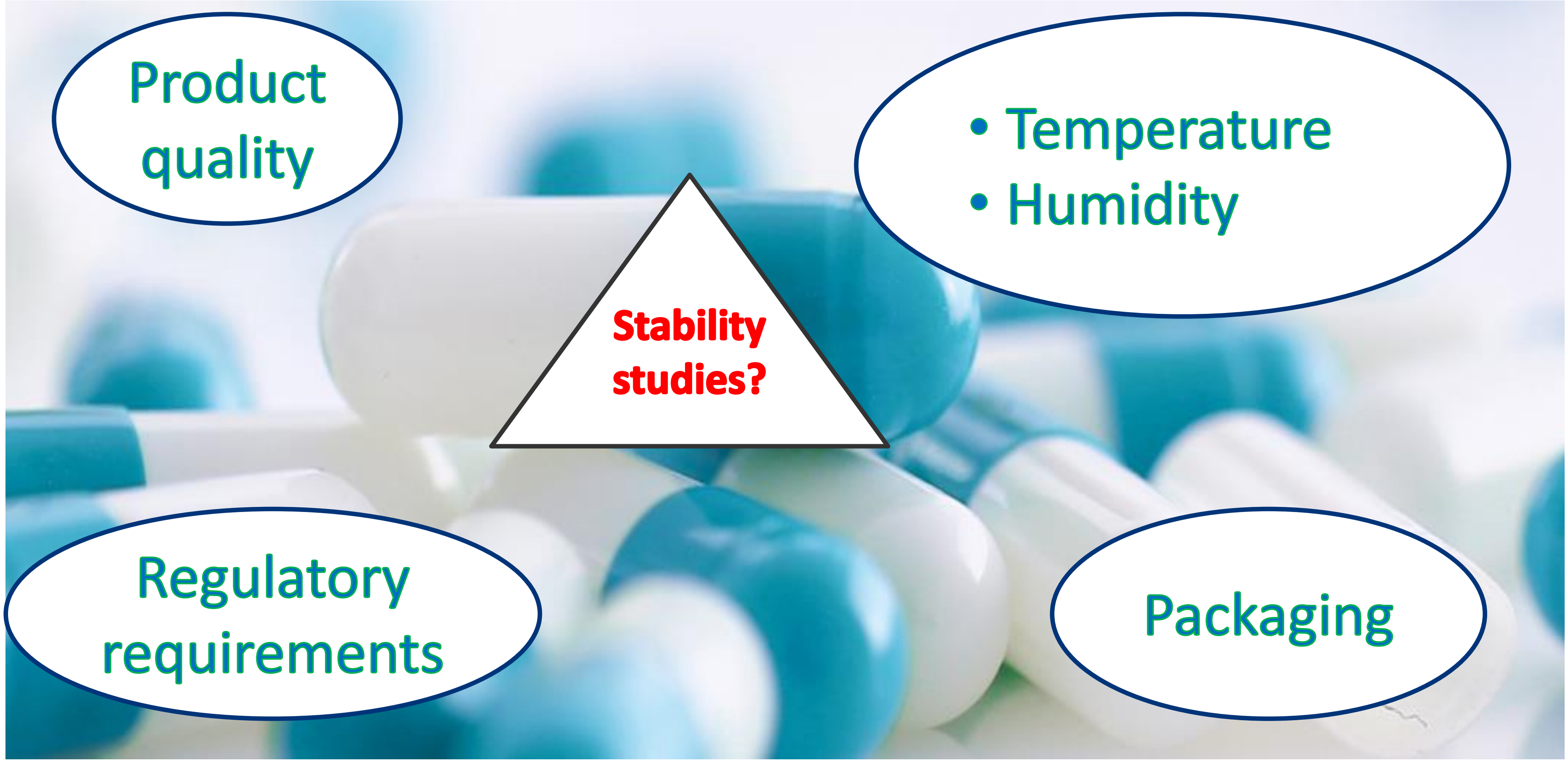
Model selection results

Formulating power priors and applications

Summary

# STABILITY STUDIES

## ACCELERATED STABILITY STUDIES


Product quality
• Temperature
• Humidity
Stability studies?
Regulatory requirements
Packaging

# Types of stability studies

- Prediction
- Shelf-life

## Real-time stability studies

- A product is stored at recommended storage conditions
- Longer storage time (in months/years)

## Accelerated stability studies

- A product is stored at elevated stress conditions
- Shorter storage time (in days/weeks)

# Advantages of accelerated stability studies

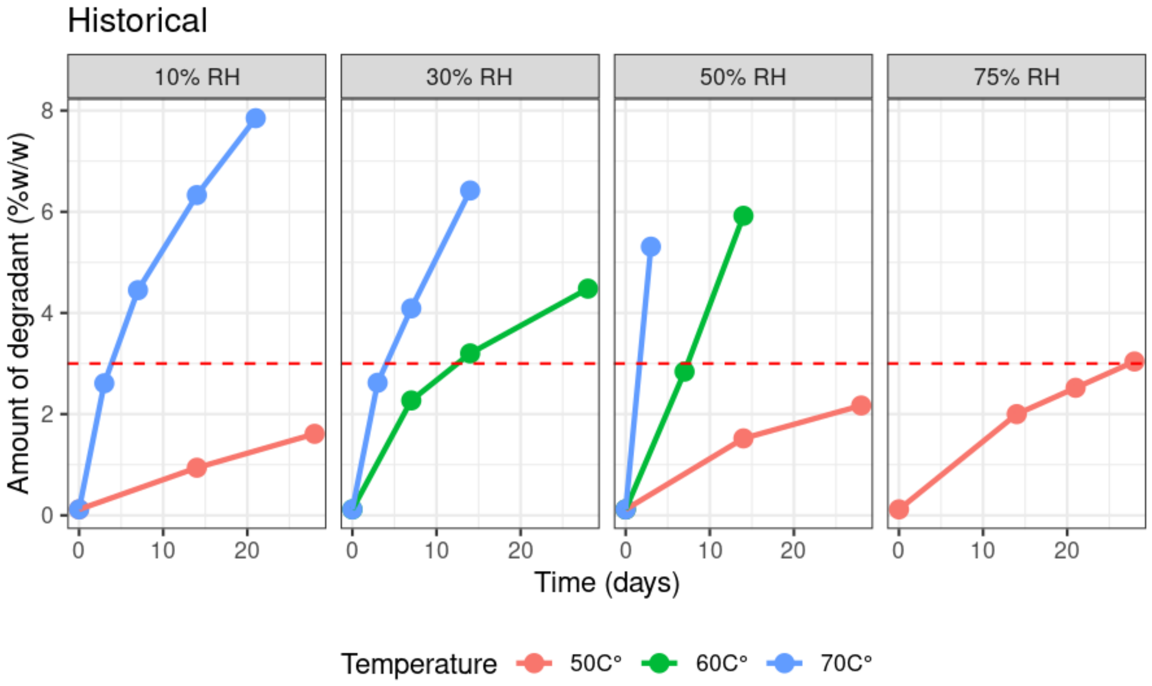
**Time & Cost Efficiency**: Accelerated studies save time and resources.

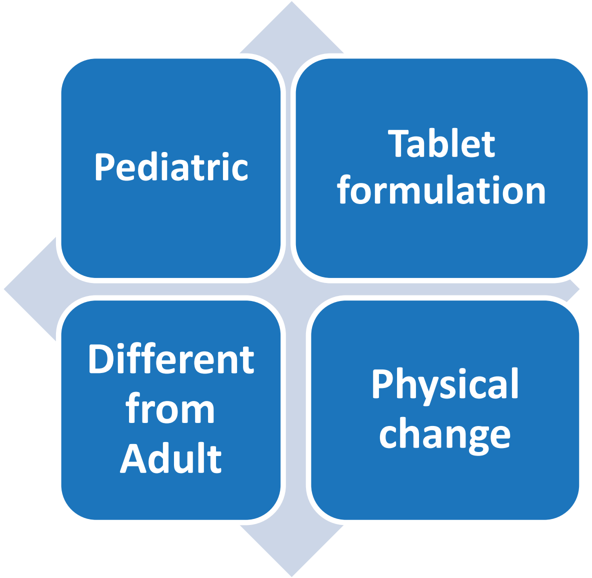
**Early Issue Detection**: Identify stability problems early.

**Regulatory Compliance**: Expedite approvals.

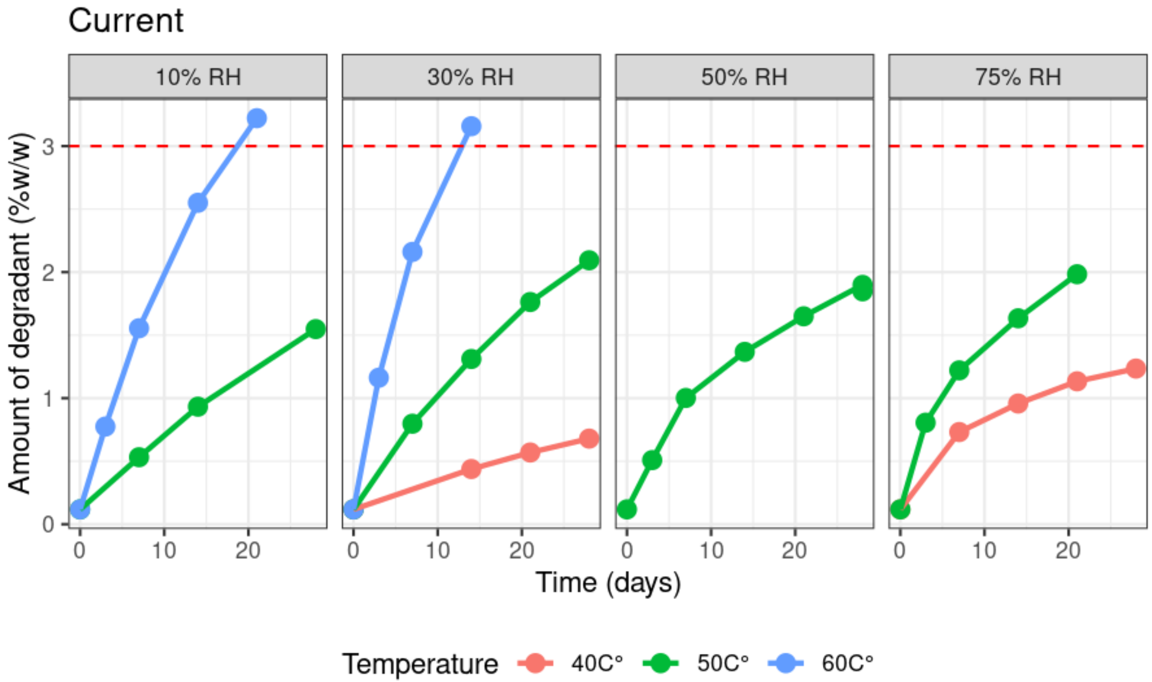
**Formulation Optimization**: Improve product quality.

# Initial accelerated stability data



# Follow-up accelerated stability data




**Revised experimental design**

# KINETICS OF DEGRADATION

## BAYESIAN KINETIC MODEL FORMULATION

# Kinetics of degradation

- Chemical degradation of a degradant $C(t)$ mechanism can be defined as:

$$\frac{dC(t)}{dt} = k * f(C(t))$$

- **Arrhenius equation**

$$k_i = A * \exp\left(\frac{-E_a}{R * T_i}\right)$$

- $k_i$ = the rate of degradation depending on the $i^{th}$ temperature $T_i$
- $A$ = the pre-exponential factor
- $E_a$ = the activation energy
- $R = 0.0083144$ , the gas constant

# Two humidity extended Arrhenius equations

- **GK (Genton and Kesselring formulation)**

$$k_{ij} = \exp\left(\ln(A) - \frac{E_a}{R * T_i} + B * RH_j\right)$$

- **$B$=Sensitivity parameter on the actual scale of the $j^{th}$ relative humidity ($RH_j$ in %)**

- **CL (Clancy et al. formulation)**

$$k_{ij} = \exp\left(\ln(A) - \frac{E_a}{R * T_i} + B * \ln(RH_j)\right)$$

- **$B$= Sensitivity parameter on the logarithmic scale of the $j^{th}$ relative humidity ($RH_j$ in %)**

# Common kinetic models

- First order
- Power law
- Second order
- Third order

# Bayesian kinetic model (BKM): First-order kinetics with GK formulation

$$
\begin{cases}
Y_{ijl} & = & C_0 + (C_1 - C_0) * \left(1 - exp\left(-k_{ij} * t_\ell\right)\right) + \epsilon_{ij\ell} \\
k_{ij} & = & exp\left( ln(A) - \frac{E_a}{R * \mathrm{T}_i} + B * \mathrm{RH}_j \right) \\
\epsilon_{ij\ell} & \sim & N(0, \sigma^2)
\end{cases}
$$

- $Y_{ijl}$ = the observed degradation at the $l^{th}$ timepoint $t_l$, the $i^{th}$temperature $\mathrm{T}_i$ and the $j^{th}$relative humidity $\mathrm{RH}_j$
- $C_0$ = Amount of degradation as time tends to zero➔**Fixed**
- $C_1$= Amount of degradation as time tends to +∞➔**Fixed**
- $\sigma^2$ = The variance of error $\epsilon_{ij\ell}$

# Bayesian kinetic model (BKM): Power-law kinetics with GK formulation

$$\begin{cases} Y_{ijl} & = & C_0 + (C_1 - C_0) * \left(\left(k_{ij} * t_l\right)^m\right) + \epsilon_{ij\ell} \\ k_{ij} & = & exp\left(ln(A) - \dfrac{E_a}{R * \mathrm{T}_i} + B * \mathrm{RH}_j\right) \\ \epsilon_{ij\ell} & \sim & N(0, \sigma^2) \end{cases}$$

- m=0.5, 1, 2, 3, 4

# Weakly informative prior distributions

- $E_a \sim N(120, 25.5)$
- $ln(A) \sim N(35, 15)$
- $B \sim N(0.04, 0.025)$ for GK formulation
- $B \sim N(1, 0.375)$ for CL formulation
- $\sigma \sim Half - Student - t(3, 0, 2.5)$

**Regularization**

**Improved Convergence**

**Robustness**

# MODEL SELECTION FOR INITIAL STUDY

SELECTED MODEL RESULTS

# Posterior summary of parameters

| Model | Parameter | Estimate | SD | Lower | Upper |
|---|---|---|---|---|---|
| Power law GK m=0.5 | lnA | 51.03 | 4.54 | 41.90 | 59.81 |
| Power law GK m=0.5 | Ea | 143.66 | 13.06 | 117.46 | 168.94 |
| Power law GK m=0.5 | B | 0.02 | 0.01 | 0.01 | 0.03 |
| **Power law GK m=0.5** | $\sigma$ | **0.74** | **0.14** | **0.54** | **1.10** |

**Selected model based on LOOIC and WAIC**

# MODEL SELECTION FOR FOLLOW-UP STUDY

SELECTED MODEL RESULTS

# Posterior summary of parameters

| Model | Parameter | Estimate | SD | Lower | Upper |
|---|---|---|---|---|---|
| Power law GK m=0.5 | lnA | 52.93 | 3.45 | 46.00 | 59.58 |
| Power law GK m=0.5 | Ea | 149.58 | 9.55 | 130.41 | 168.00 |
| Power law GK m=0.5 | B | 0.01 | 0.00 | 0.01 | 0.02 |
| **Power law GK m=0.5** | **$\sigma$** | **0.21** | **0.03** | **0.16** | **0.28** |

Selected model based on LOOIC and WAIC

# FORMULATING POWER PRIORS

LEVERAGING HISTORICAL ACCELERATED STABILITY DATA

# Two classes of power priors

Power prior with **fixed** discounting parameter

Power prior with **random** discounting parameter (Normalized power prior )

# Power prior with fixed discounting parameter

$$\pi(\boldsymbol{\theta} \mid D_0, a_0) \propto \frac{L(\boldsymbol{\theta} \mid D_0)^{a_0}\pi(\boldsymbol{\theta})}{\int \{L(\boldsymbol{\theta} \mid D_0)^{a_0}\pi(\boldsymbol{\theta})\}\, d\boldsymbol{\theta}}$$

$$\propto L(\boldsymbol{\theta} \mid D_0)^{a_0}\pi(\boldsymbol{\theta})$$

- $\boldsymbol{\theta} = (\ln(\mathrm{A}), E_a, B, \sigma)$ is the set of model parameters
- $L(\boldsymbol{\theta} \mid D_0)$= is the likelihood from the historical data $D_0$
- $\pi(\boldsymbol{\theta}) =$is the initial prior for $\boldsymbol{\theta}$ before the historical data $D_0$ are observed and
- $a_0$ is a discounting parameter ranging between 0 and 1
- $a_0$=0, 0.25, 0.5, 0.75, and 1

Details→Ibrahim and Chen (2000)

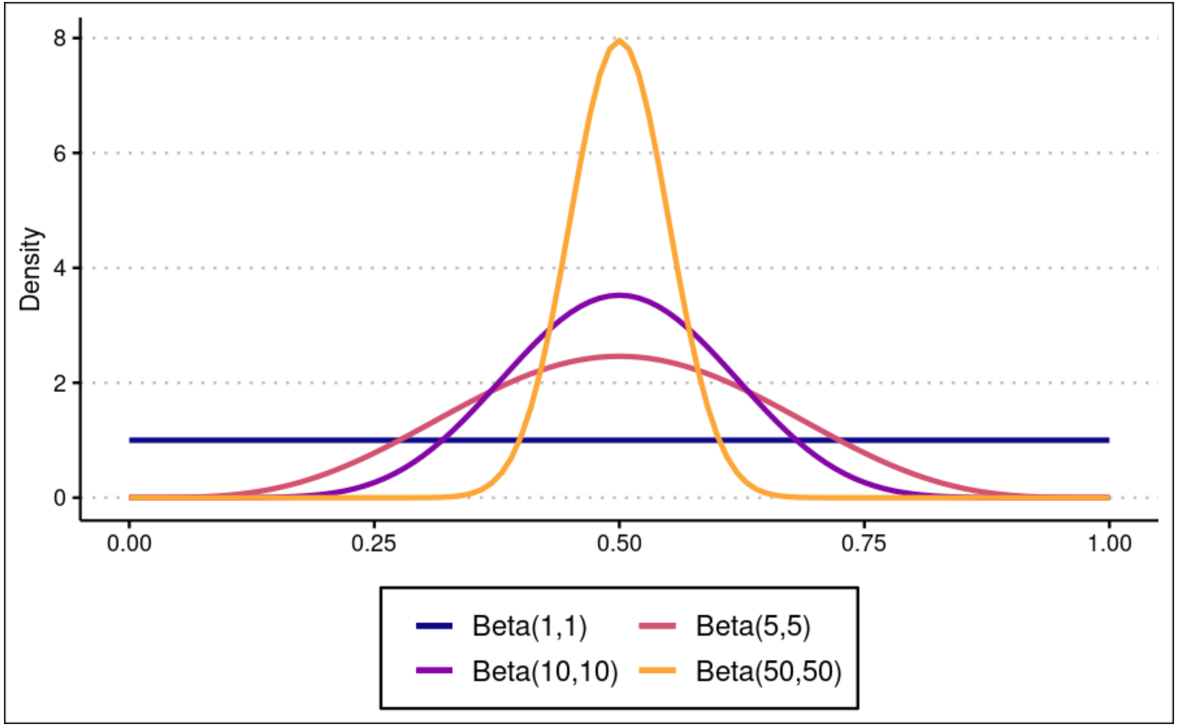
# Normalized power prior

$$\pi(\boldsymbol{\theta}, a_0 \mid D_0) \propto \frac{L(\theta \mid D_0)^{a_0} \pi(\theta) \pi(a_0)}{c(a_0)}$$

$$c(a_0) = \int L(\theta \mid D_0)^{a_0} \pi(\theta)\, d\theta$$

- $\boldsymbol{\theta} = (\ln(\mathrm{A}), E_a, B, \sigma)$ is the set of model parameters
- $c(a_0)$ = is the normalsing constant
- $\pi(a_0)$ = the initial prior for $a_0$

# Initial priors for $a_0$



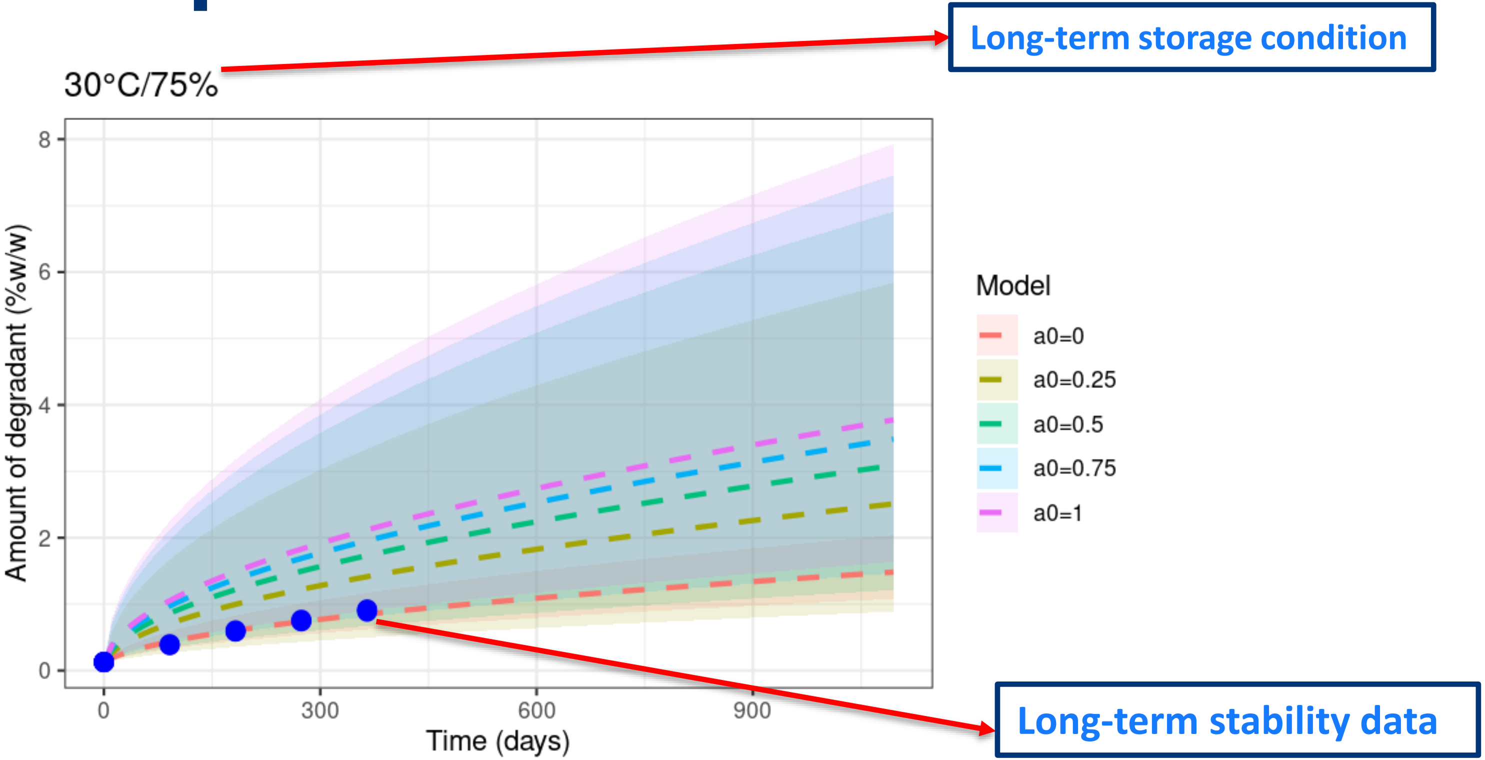
# POWER PRIOR WITH FIXED DISCOUNTING PARAMETER

RESULTS

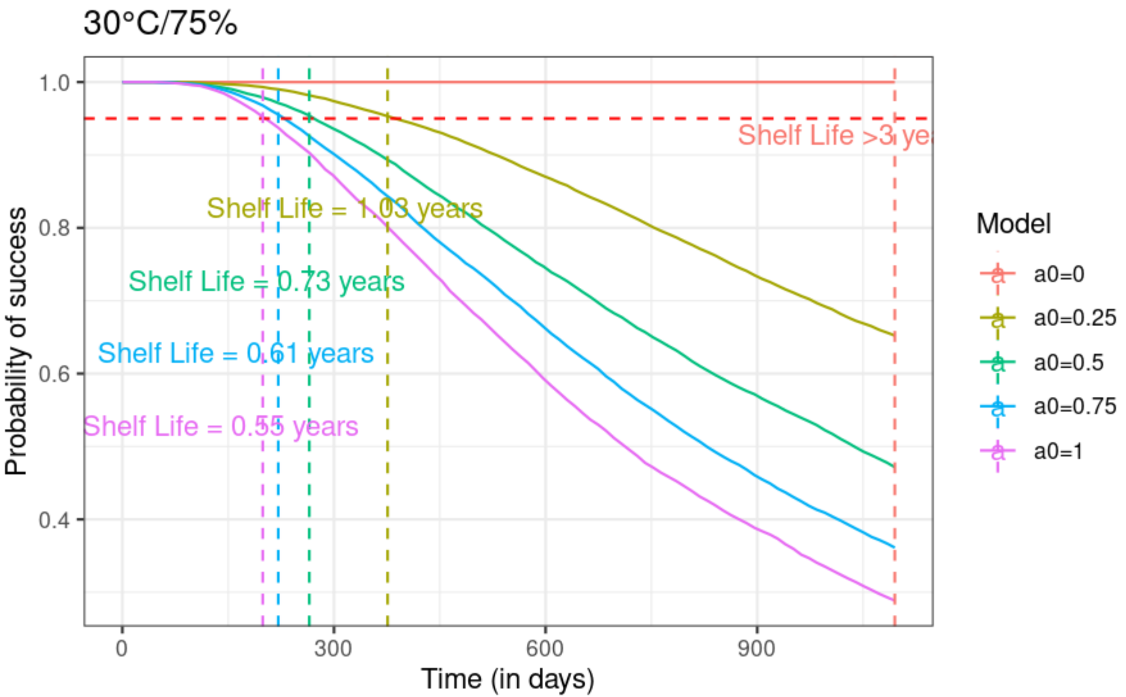
# Posterior summary of parameters

| Model | Parameter | Estimate | SD | Lower | Upper |
|---|---|---|---|---|---|
| a0=0 | lnA | 52.89 | 3.45 | 45.90 | 59.63 |
| | Ea | 149.45 | 9.56 | 130.15 | 168.20 |
| | B | 0.01 | 0.00 | 0.01 | 0.02 |
| | $\sigma$ | **0.21** | **0.03** | **0.16** | **0.28** |
| a0=0.25 | lnA | 42.64 | 7.61 | 27.58 | 57.45 |
| | Ea | 121.60 | 20.64 | 80.72 | 161.80 |
| | B | 0.03 | 0.02 | 0.00 | 0.06 |
| | $\sigma$ | **2.58** | **0.32** | **2.08** | **3.33** |
| a0=0.5 | lnA | 43.47 | 7.62 | 28.45 | 58.26 |
| | Ea | 122.59 | 20.77 | 81.96 | 163.57 |
| | B | 0.03 | 0.01 | 0.00 | 0.06 |
| | $\sigma$ | **3.22** | **0.37** | **2.63** | **4.06** |
| a0=0.75 | lnA | 44.66 | 7.55 | 30.06 | 59.49 |
| | Ea | 125.01 | 20.57 | 85.23 | 165.72 |
| | B | 0.03 | 0.01 | 0.00 | 0.05 |
| | $\sigma$ | **3.58** | **0.38** | **2.96** | **4.46** |
| a0=1 | lnA | 45.93 | 7.41 | 31.75 | 60.53 |
| | Ea | 127.82 | 20.32 | 88.94 | 167.68 |
| | B | 0.03 | 0.01 | 0.01 | 0.05 |
| | $\sigma$ | **3.79** | **0.38** | **3.15** | **4.65** |

# Long-term predictions



# Estimating shelf-life



# NORMALIZED POWER PRIOR

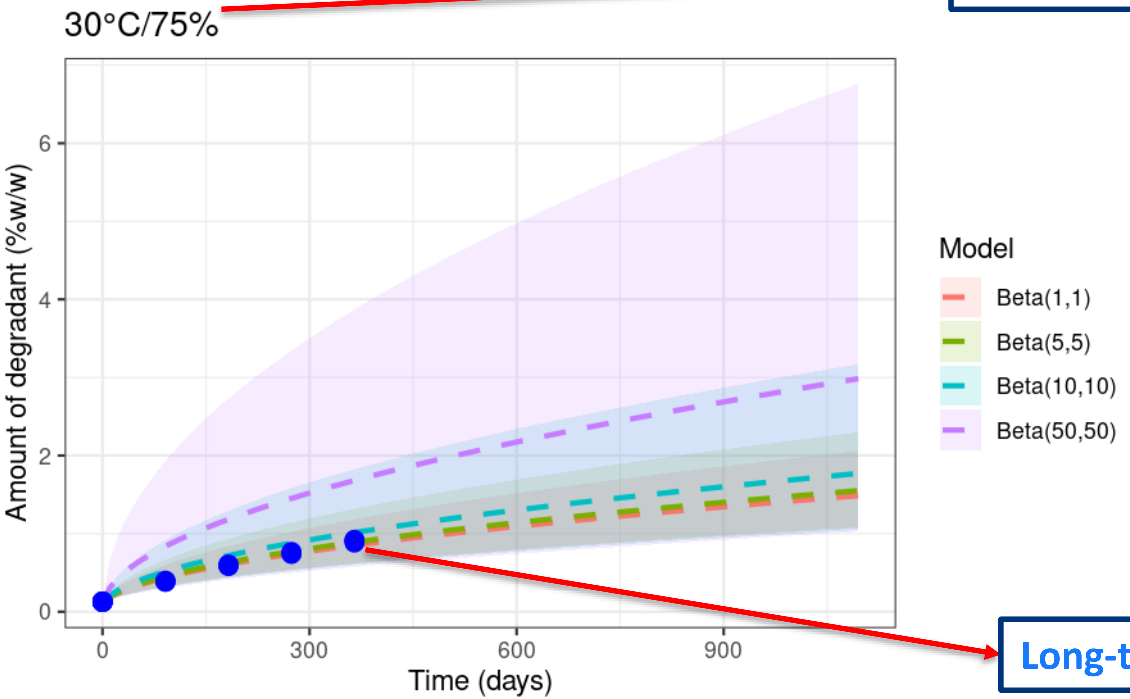
RESULTS

# Posterior summary of parameters

| Model | Parameter | Estimate | SD | Lower | Upper |
|---|---|---|---|---|---|
| a0~Beta(1, 1) | lnA | 52.82 | 3.49 | 45.78 | 59.62 |
| | Ea | 149.28 | 9.66 | 129.79 | 168.07 |
| | B | 0.01 | 0.00 | 0.01 | 0.02 |
| | $\sigma$ | 0.21 | 0.03 | 0.16 | 0.29 |
| | a0 | 0.0001 | 0.0001 | 0.0000 | 0.0004 |
| a0~Beta(5, 5) | lnA | 51.77 | 4.25 | 43.21 | 59.94 |
| | Ea | 146.40 | 11.73 | 122.82 | 168.99 |
| | B | 0.01 | 0.00 | 0.01 | 0.02 |
| | $\sigma$ | 0.26 | 0.05 | 0.19 | 0.39 |
| | a0 | 0.0008 | 0.0005 | 0.0002 | 0.0020 |
| a0~Beta(10, 10) | lnA | 48.41 | 6.01 | 35.82 | 59.70 |
| | Ea | 137.21 | 16.54 | 102.70 | 168.36 |
| | B | 0.01 | 0.01 | 0.00 | 0.03 |
| | $\sigma$ | 0.46 | 0.25 | 0.27 | 1.16 |
| | a0 | 0.0077 | 0.0165 | 0.0012 | 0.0348 |
| a0~Beta(50, 50) | lnA | 43.15 | 7.75 | 27.80 | 58.34 |
| | Ea | 122.18 | 20.87 | 81.11 | 163.78 |
| | B | 0.03 | 0.01 | 0.00 | 0.06 |
| | $\sigma$ | 3.13 | 0.38 | 2.51 | 4.01 |
| | a0 | 0.4502 | 0.0532 | 0.3482 | 0.5556 |

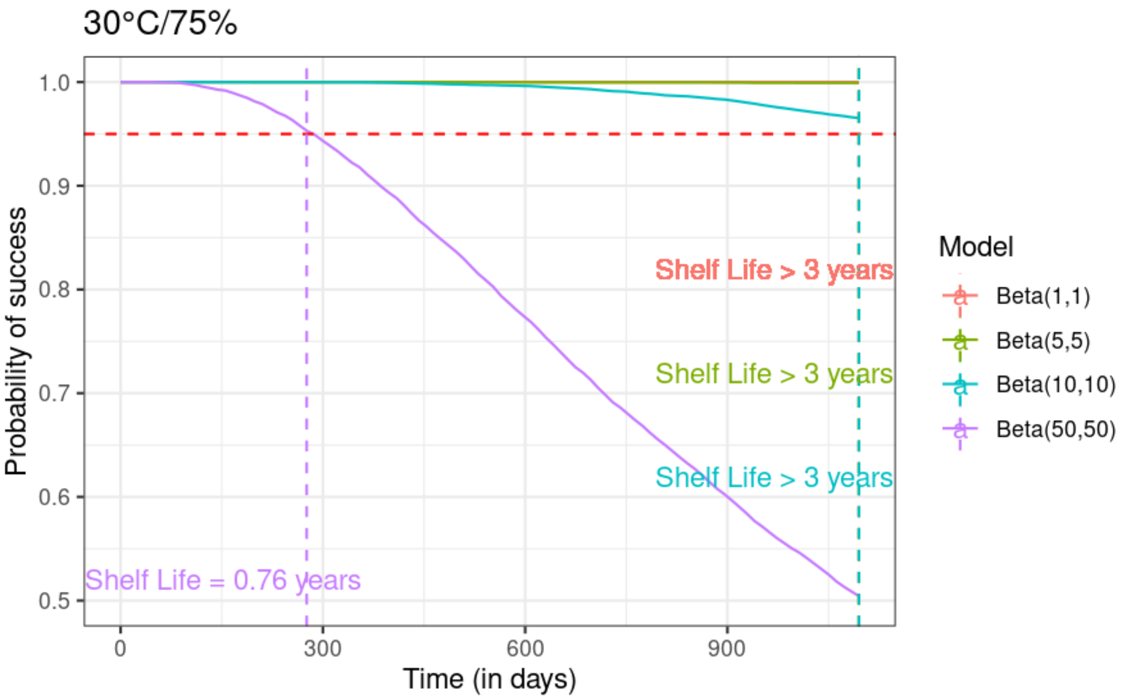
# Long-term predictions

Long-term storage condition




Long-term stability data

# Estimating shelf-life



# Summary

**The need to perform accelerated stability studies?**
- Save time and resources

**Exploring the different kinetic models?**
- Deserves careful treatment

**Informative priors to consider?**
- Power priors

**Power prior with fixed discounting parameter**
- When historical data is not compatible to the current data?

**Normalized power prior**
- Accounting for compatibility

# What is next?

Simulation study

→

Other informative priors

# References


- Ibrahim JG, Chen MH. Power prior distributions for regression models. Statistical Science. 2000 Feb 1:46-60.
- Ibrahim JG, Chen MH, Gwon Y, Chen F. The power prior: theory and applications. Statistics in medicine. 2015 Dec 10;34(28):3724-49.
- Carvalho LM, Ibrahim JG. On the normalized power prior. Statistics in Medicine. 2021 Oct 30;40(24):5251-75.
- Genton, D., and U. W. Kesselring. "Effect of temperature and relative humidity on nitrazepam stability in solid state." *Journal of Pharmaceutical Sciences* 66, no. 5 (1977): 676-680.
- Clancy, Don, Neil Hodnett, Rachel Orr, Martin Owen, and John Peterson. "Kinetic model development for accelerated stability studies." *AAPS PharmSciTech* 18, no. 4 (2017): 1158-1176.

# Thank You!

janssen

PHARMACEUTICAL COMPANIES OF

Johnson & Johnson

# Extra slides

# Bayesian kinetic model (BKM): Second-order kinetics with GK formulation

$$
\begin{cases}
Y_{ijl} & = & C_0 + (C_1 - C_0) * \left(1 - \dfrac{1}{1 + k_{ij} * t_l}\right) + \epsilon_{ij\ell} \\
k_{ij} & = & exp\left(ln(A) - \dfrac{E_a}{R * \mathrm{T}_i} + B * \mathrm{RH}_j\right) \\
\epsilon_{ij\ell} & \sim & N(0, \sigma^2)
\end{cases}
$$

# Bayesian kinetic model (BKM): Third-order kinetics with GK formulation

$$\begin{cases} Y_{ijl} = C_0 + (C_1 - C_0) * \left(1 - \dfrac{1}{\sqrt{1 + 2 * k_{ij} * t_l}}\right) + \epsilon_{ij\ell} \\ k_{ij} = exp\left(ln(A) - \dfrac{E_a}{R * \mathrm{T}_i} + B * \mathrm{RH}_j\right) \\ \epsilon_{ij\ell} \sim N(0, \sigma^2) \end{cases}$$

# Methods of model comparison

| Leave-one-out cross-validation (LOO-CV) | Widely applicable or Watanabe-Akaike information criterion WAIC |
| --- | --- |
| • Expected Log Pointwise Predictive Density (elpd_loo)<br>• Effective Number of Parameters (p_loo)<br>• Leave-One-Out Information Criterion (looic) | • Expected Log Pointwise Predictive Density based on WAIC (elpd_waic)<br>• Effective Number of Parameters based on WAIC (p_waic)<br>• Watanabe-Akaike information criterion (waic) |

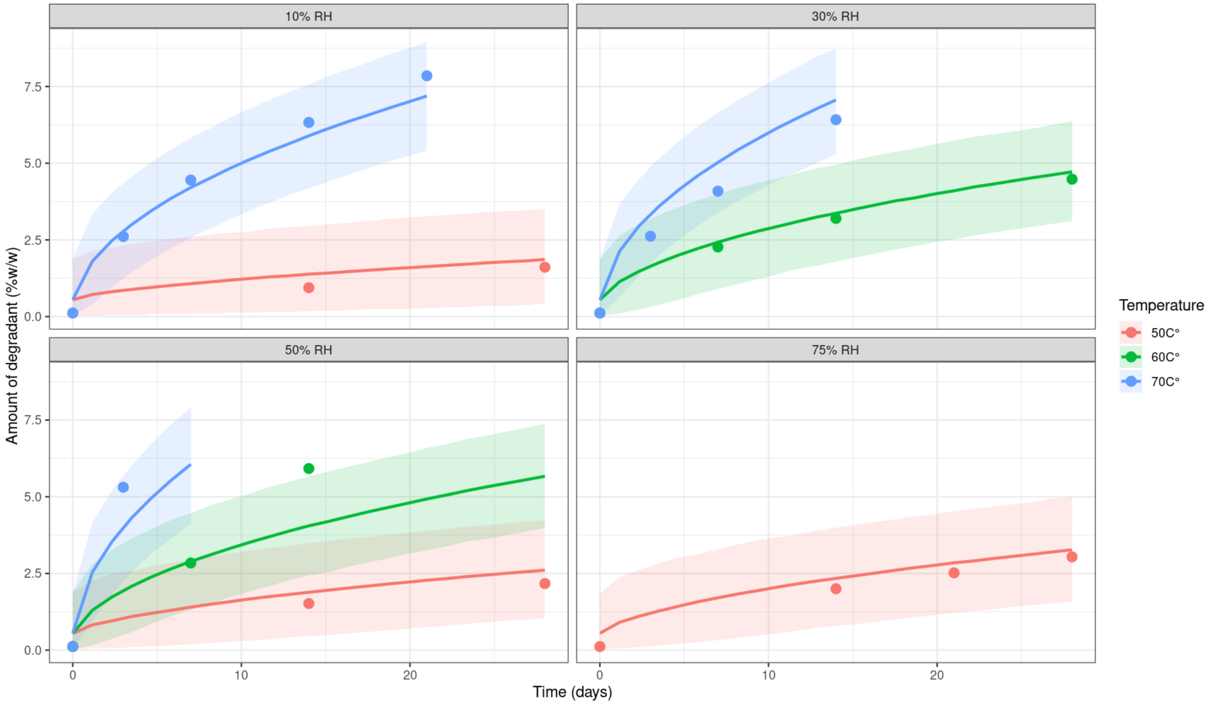
# Initial Study

# Model selection

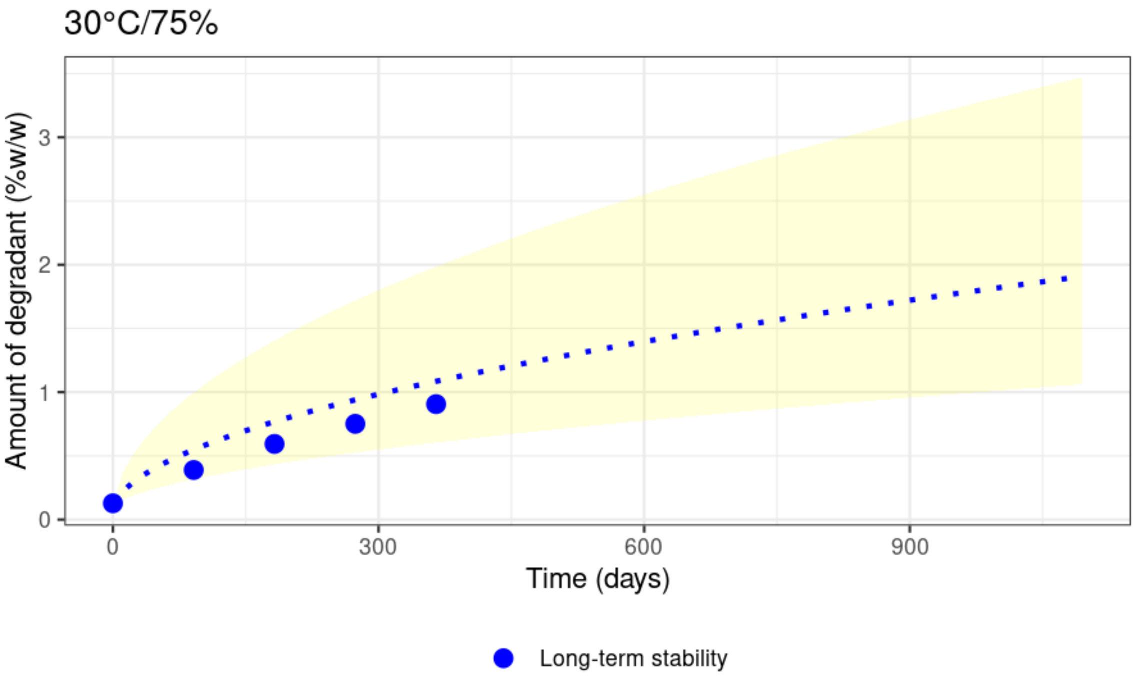
| Model | elpd_loo | p_loo | looic | elpd_waic | p_waic | waic |
|---|---|---|---|---|---|---|
| **Power law GK m=0.5** | **-25.19** | **4.76** | **50.38** | **-24.77** | **4.33** | **49.53** |
| Power law GK m=1 | -35.20 | 4.88 | 70.40 | -34.42 | 4.10 | 68.84 |
| Power law GK m=2 | -47.53 | 3.77 | 95.06 | -46.54 | 2.79 | 93.09 |
| Power law GK m=3 | -52.69 | 3.20 | 105.38 | -52.18 | 2.69 | 104.36 |
| Power law GK m=4 | -55.44 | 2.07 | 110.88 | -55.41 | 2.04 | 110.82 |
| **Power law CL m=0.5** | **-27.53** | **4.72** | **55.06** | **-27.05** | **4.23** | **54.09** |
| Power law CL m=1 | -38.13 | 5.59 | 76.26 | -37.05 | 4.51 | 74.11 |
| Power law CL m=2 | -50.10 | 4.62 | 100.20 | -48.93 | 3.46 | 97.86 |
| Power law CL m=3 | -54.62 | 3.17 | 109.24 | -54.19 | 2.74 | 108.38 |
| Power law CL m=4 | -56.19 | 1.53 | 112.38 | -56.02 | 1.36 | 112.04 |
| 1st Order GK | -34.68 | 4.93 | 69.36 | -33.93 | 4.18 | 67.86 |
| 1st Order CL | -37.43 | 5.34 | 74.86 | -36.64 | 4.55 | 73.27 |
| 2nd Order GK | -33.96 | 4.77 | 67.93 | -33.34 | 4.15 | 66.68 |
| 2nd Order CL | -36.93 | 5.37 | 73.86 | -36.09 | 4.53 | 72.18 |
| 3rd Order GK | -33.70 | 5.07 | 67.40 | -32.91 | 4.28 | 65.82 |
| 3rd Order CL | -36.41 | 5.38 | 72.82 | -35.61 | 4.59 | 71.23 |

- LOOIC and WAIC were used for model selection.
- Based on both criteria, **Power law GK m=0.5** is selected
- As expected, Power law CL m=0.5 is the second good model.

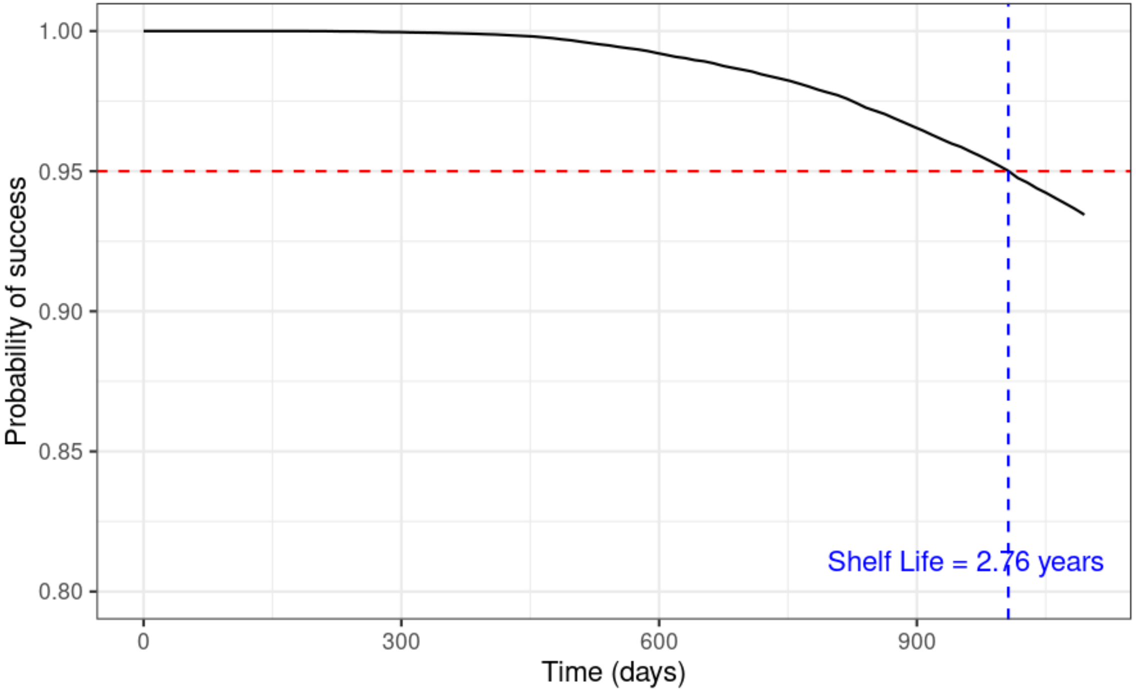
# Predicted Vs Observed



# Long-term predictions



# Estimating shelf-life



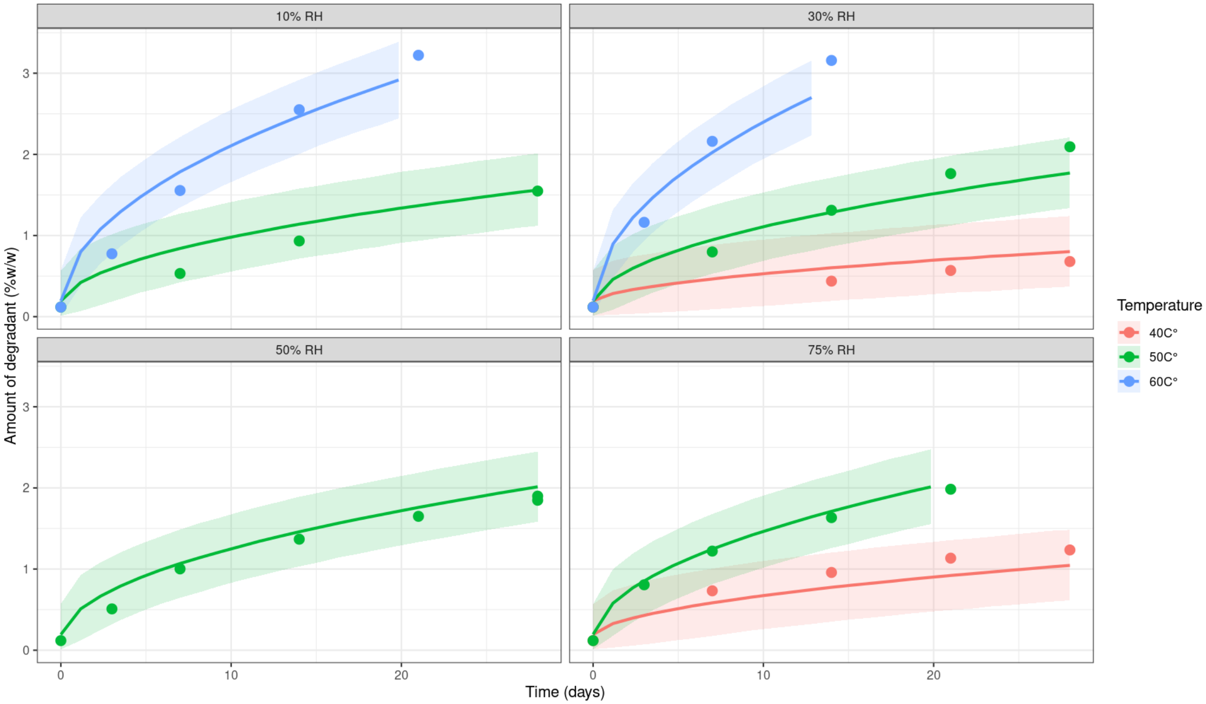
# Follow-up study

# Model selection

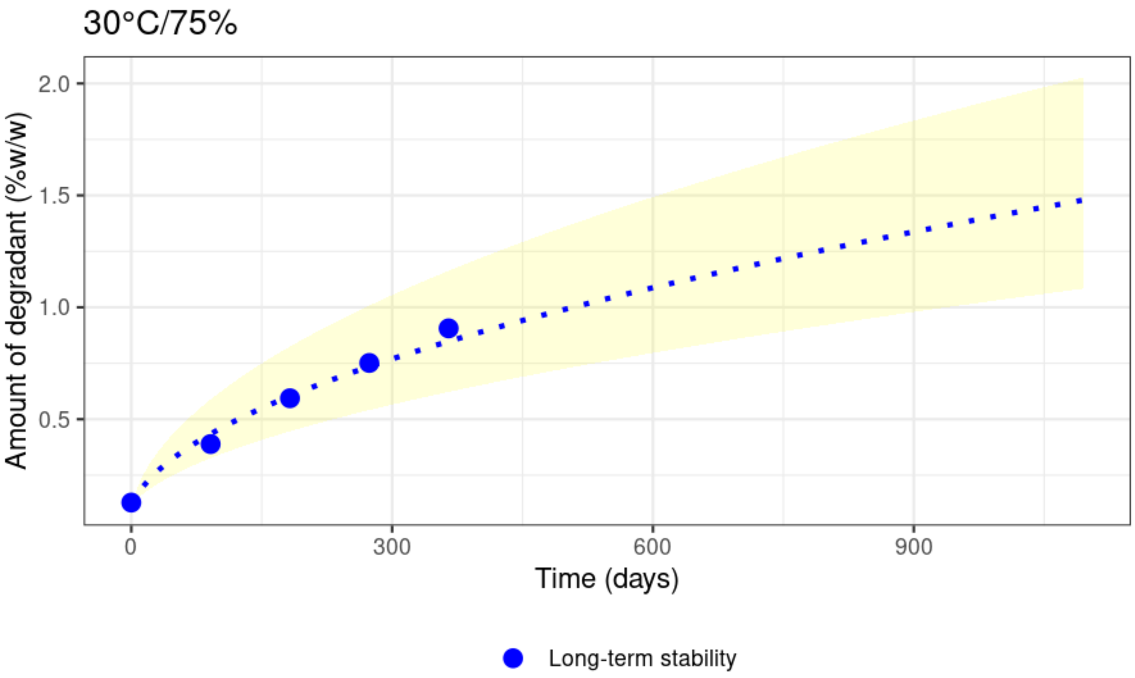
| Model | elpd_loo | p_loo | looic | elpd_waic | p_waic | waic |
|---|---|---|---|---|---|---|
| **Power law GK m=0.5** | **3.46** | **3.40** | **-6.92** | **3.58** | **3.28** | **-7.16** |
| Power law GK m=1 | -10.51 | 3.99 | 21.02 | -10.10 | 3.58 | 20.19 |
| Power law GK m=2 | -35.61 | 3.68 | 71.22 | -34.92 | 2.99 | 69.85 |
| Power law GK m=3 | -43.87 | 3.52 | 87.75 | -42.73 | 2.38 | 85.46 |
| Power law GK m=4 | -47.39 | 2.88 | 94.77 | -46.68 | 2.17 | 93.36 |
| **Power law Clancy m=0.5** | **3.07** | **3.54** | **-6.13** | **3.22** | **3.38** | **-6.45** |
| Power law Clancy m=1 | -9.93 | 3.34 | 19.87 | -9.72 | 3.13 | 19.44 |
| Power law Clancy m=2 | -35.15 | 3.17 | 70.30 | -34.56 | 2.59 | 69.13 |
| Power law Clancy m=3 | -43.11 | 2.85 | 86.21 | -42.51 | 2.25 | 85.02 |
| Power law Clancy m=4 | -47.72 | 3.07 | 95.43 | -47.40 | 2.75 | 94.80 |
| 1st Order GK | -10.05 | 3.88 | 20.10 | -9.66 | 3.49 | 19.32 |
| 1st Order Clancy | -9.72 | 3.45 | 19.43 | -9.46 | 3.19 | 18.92 |
| 2nd Order GK | -9.62 | 3.83 | 19.24 | -9.29 | 3.51 | 18.59 |
| 2nd Order Clancy | -9.23 | 3.32 | 18.46 | -9.04 | 3.14 | 18.09 |
| 3rd Order GK | -9.26 | 3.84 | 18.53 | -8.96 | 3.53 | 17.92 |
| 3rd Order Clancy | -8.89 | 3.35 | 17.77 | -8.68 | 3.14 | 17.36 |

- LOOIC and WAIC were used for model selection.
- Based on both criteria, **Power law GK m=0.5** is selected
- As expected, Power law CL m=0.5 is the second good model.

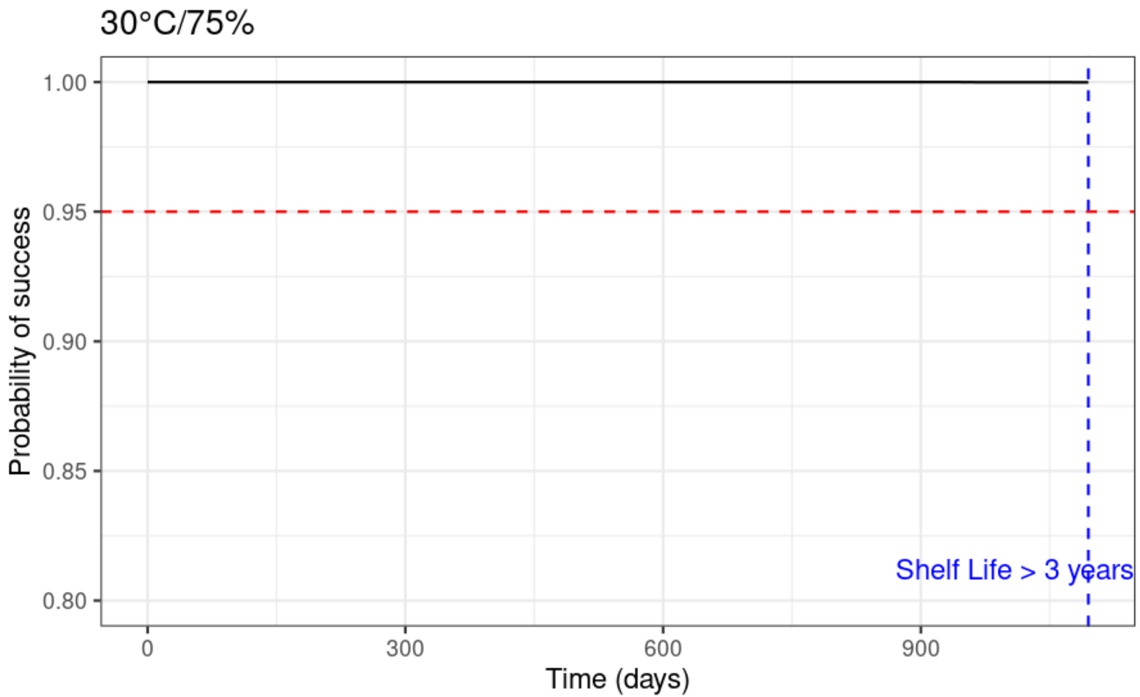
# Predicted Vs Observed



# Long-term predictions



# Estimating shelf-life

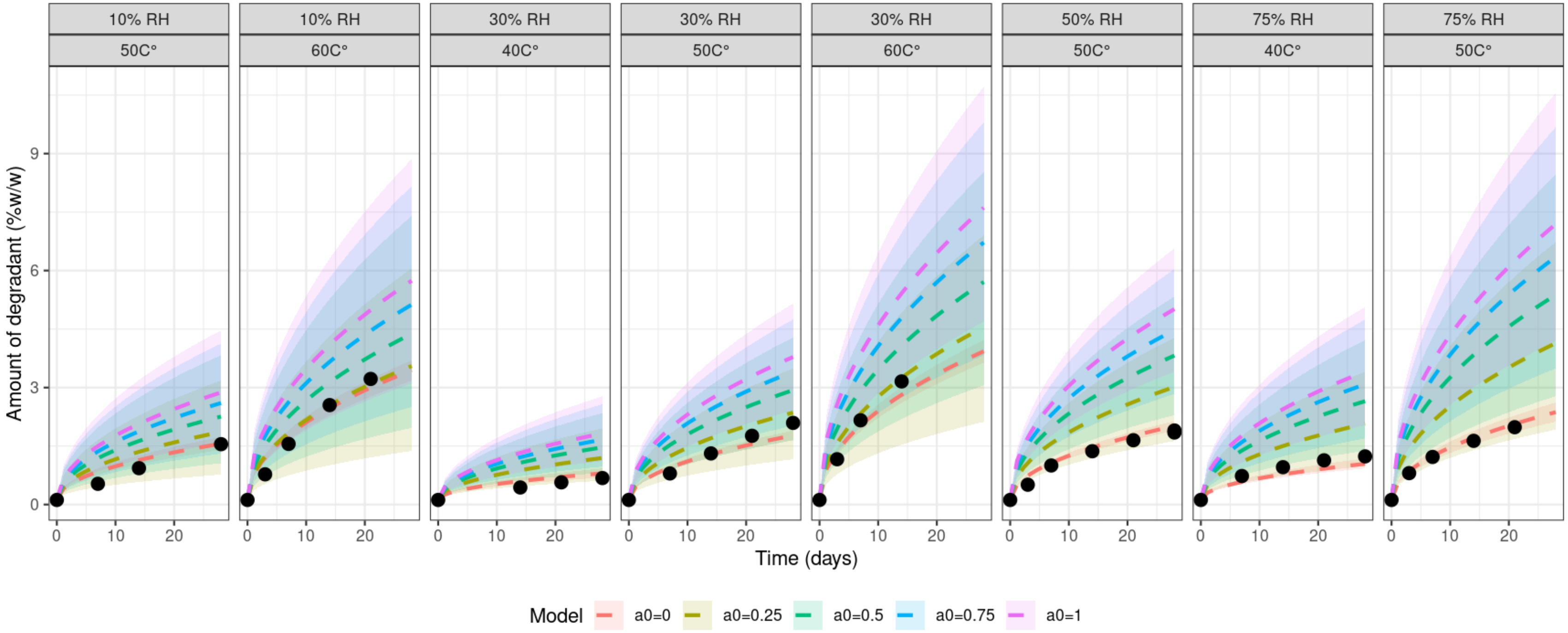


# Fixed a0

# Model comparison

| Model | elpd_loo | p_loo | looic | elpd_waic | p_waic | waic |
|---|---|---|---|---|---|---|
| PowerLaw_GK_a0=0 | 3.42 | 3.42 | -6.83 | 3.55 | 3.29 | -7.10 |
| PowerLaw_GK_a0=0.25 | -60.24 | 0.63 | 120.48 | -60.23 | 0.63 | 120.47 |
| PowerLaw_GK_a0=0.5 | -68.13 | 0.66 | 136.25 | -68.12 | 0.65 | 136.24 |
| PowerLaw_GK_a0=0.75 | -72.38 | 0.70 | 144.76 | -72.37 | 0.69 | 144.74 |
| PowerLaw_GK_a0=1 | -75.17 | 0.75 | 150.34 | -75.16 | 0.74 | 150.32 |

# Predicted Vs Observed



# Random a0

# Model comparison

| Model | elpd_loo | p_loo | looic | elpd_waic | p_waic | waic |
|---|---|---|---|---|---|---|
| PowerLaw_GK_a0~Beta(1, 1) | 3.35 | 3.18 | -6.69 | 3.47 | 3.06 | -6.94 |
| PowerLaw_GK_a0~Beta(5, 5) | 1.30 | 2.48 | -2.61 | 1.37 | 2.42 | -2.73 |
| PowerLaw_GK_a0~Beta(10, 10) | -12.41 | 3.99 | 24.82 | -12.31 | 3.89 | 24.62 |
| PowerLaw_GK_a0~Beta(50, 50) | -66.97 | 0.69 | 133.95 | -66.97 | 0.69 | 133.93 |

# Predicted Vs Observed