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Arrhenius Equation Demystified

History, Background, and Common Usage in the Accelerated Aging of Packaging for Medical Devices

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Agenda

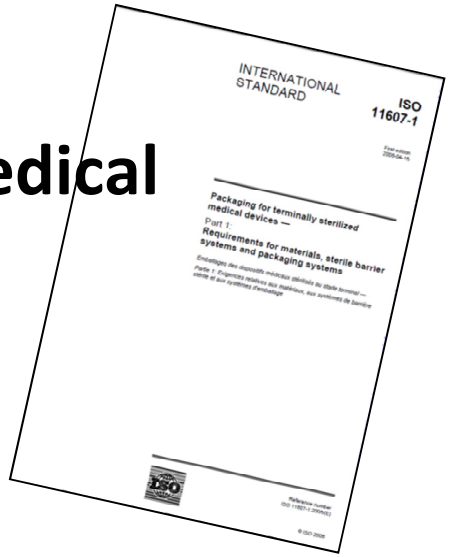
- ISO 11607 & the Requirement for Accelerated Aging
- Shelf Life Validation
- Meet Svante August Arrhenius
- The Arrhenius Equation
- The Arrhenius Equation Modified
- The Arrhenius Equation As Used in Medical Device Accelerated Aging
- How About Humidity and Other Interesting Topics?

ISO 11607

ISO 11607-1

2006-04-15

Packaging for Terminally Sterilized Medical Devices



Part 1

REQUIREMENTS FOR MATERIALS, STERILE BARRIER SYSTEMS AND PACKAGING SYSTEMS

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ISO 11607

Introduction

"The goal of a terminally sterilized medical device packaging system is to:

A) allow sterilization
B) provide physical protection
C) maintain sterility up to the point of use
D) allow aseptic presentation

The specific nature of the medical device, the intended sterilization methods(s), the intended use, **expiry date**, transport and storage all influence the packaging system design and choice of materials."

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3.5 **expiry date**

"…indication of the date, by which the product should be used, expressed at least as the year and month…"

3.28 **validation**

"….⟨general⟩ confirmation by examination and provision of objective evidence that the particular requirement for a specific intended use can be consistently fulfilled…."

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6 Design and Development Requirements for Packaging Systems

6.1.4 The sterile barrier system shall maintain sterility until the point of use or until the **expiry date**.

6.2.3 The design and development of a package system shall consider many factors that include, but are not limited to:

i) **expiry date** limitations of the product

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6.4 Stability testing

6.4.1 Stability testing shall demonstrate that the sterile barrier system **maintains integrity over time.**

6.4.2 Stability testing shall be performed using **real-time aging**.

6.4.3 Stability testing, using accelerated aging protocols, shall be regarded as sufficient evidence for **claimed expiry dates** until data from real-time aging studies are available.

6.4.4 Real-time and accelerated aging tests should begin simultaneously.

NOTE **Stability testing and performance testing are separate entities**. Performance testing evaluates the interaction between the packaging system and the products in response to the stresses imposed by the manufacturing and sterilization processes and the handling, storage and shipping environment.

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6.4.5 When expiry dates are based upon product performance, stability testing for expiry dating should be conducted along with package stability testing.

6.4.6 If accelerated aging tests are performed, a documented rationale for the accelerated aging conditions and test duration chosen shall be established.

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7. Information to be provided…

– the expiry date, if applicable;

– any specific storage conditions, if applicable;

B.2 Packaging materials and preformed sterile barrier systems

Accelerated aging

ASTM F1980:2002 Standard guide for accelerated aging of sterile medical device packages

EN 868-8:1999 Packaging materials and systems for medical devices which are to be sterilized — Part 8:

SHELF LIFE VALIDATION

Most Acceptable Method

Accelerated aging validated with Real-Time aging. Complies with: ISO 11607

6.4.2 Stability testing shall be performed using real-time aging.

6.4.3 Stability testing, using accelerated aging protocols, shall be regarded as sufficient evidence for claimed expiry dates until data from real-time aging studies are available.

SHELF LIFE VALIDATION

ASTM F1980 agrees:

- 1.4 Real-time aging protocols are not addressed in this guide; however, **it is essential that real-time aging studies be performed to confirm the accelerated aging test results** using the same methods of evaluation.

- 7.2.3.3 When elevated temperature aging is not feasible due to material characteristics, then real-time aging is the only option.

Examples of Accelerated Aging at Various Temperatures and Equivalent Real Time Aging

Accelerated Aging (55°C) Days	Accelerated Aging (50°C) Days	Accelerated Aging (60°C) Days	Real-Time Aging (23°C)
3.3	4.7	2.3	30 days
6.6	9.4	4.6	60 days
9.9	14	7	90 days
19.9	28.1	14	6 months
39.7	56.2	28.1	1 year
59.6	84.3	42.1	1.5 years
79.4	112.3	56.2	2 years
119.2	168.5	84.3	3 years
158.9	224.7	112.3	4 years
198.6	280.9	140.4	5 years

Who Was This "ARRHENIUS" Dude?

- **Svante August Arrhenius**
- **Born:** 19 February 1859, Vik, Sweden
- **Died:** 2 October 1927, Stockholm, Sweden
- **Affiliation at the time of the award:**
  Stockholm University, Stockholm, Sweden
- **Field:** chemical kinetics, physical chemistry

- **Nobel Prize, Chemistry:** "in recognition of the extraordinary services he has rendered to the advancement of chemistry by his electrolytic theory of dissociation"

Svante Arrhenius – Interesting Facts

- He considered radiation pressure as accounting for comets, the solar corona, the aurora borealis, and zodiacal light.
- He thought of the idea of a universal language, proposing a modification of the English language.
- Developed a theory to explain the ice ages, was the first scientist to attempt to calculate how changes in the levels of carbon dioxide in the atmosphere could alter the surface temperature through the greenhouse effect.
- First person to predict that emissions of carbon dioxide from the burning of fossil fuels were large enough to cause global warming.

The Arrhenius Equation

- The **Arrhenius equation** is a simple but remarkably accurate formula for the temperature dependence of **reaction rates.**
- Arrhenius' equation gives the dependence of the rate constant ***k*** of a chemical reaction on the absolute temperature T (in kelvin), where A is the pre-exponential factor (or simply the prefactor), Ea is the activation energy, and R is the universal gas constant:

$$k = Ae^{-E_a/RT}$$

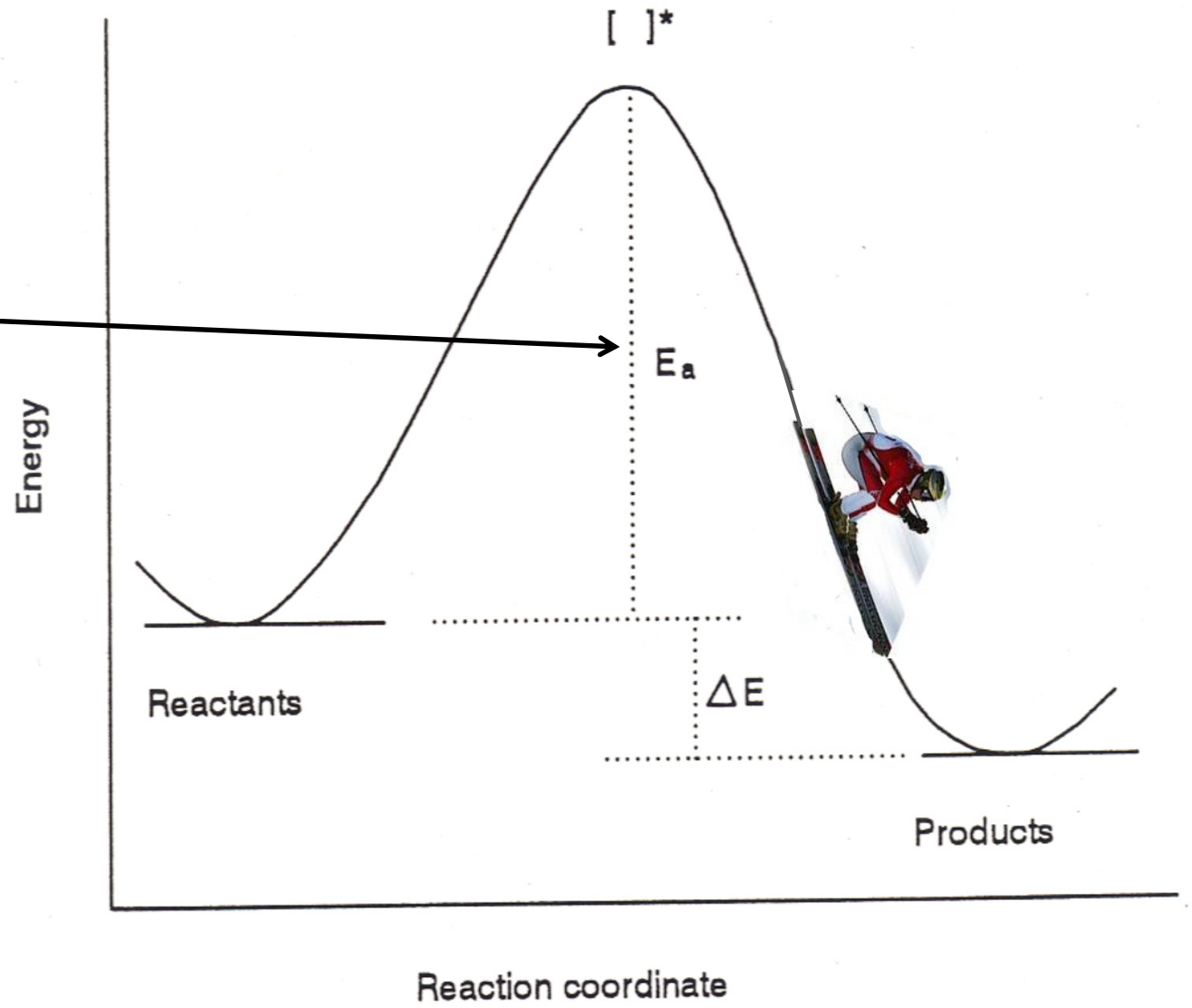
The Arrhenius Equation (con't)

- Most simply, k is the number of collisions that result in a reaction per second, A is the total number of collisions (leading to a reaction or not) per second and $e^{-E_a/RT}$ is the probability that any given collision will result in a reaction.
- It can be seen that either increasing the temperature or decreasing the activation energy (for example through the use of catalysts) will result in an increase in rate of reaction.

$$k = Ae^{-E_a/RT}$$

The Arrhenius Equation (con't)

E_a = Activation energy



Relation between Arrhenius and Aging

How do we go from:

$$k = Ae^{-Ea/RT}$$

To:

$$AFF = Q_{10}^{(T_{AA}-T_{RT})/10}$$

?

Combining Two Arrhenius Equations

- Let's start by combining two first order Arrhenius equations to understand the relationship between the reaction rate and temperature

$$k = Ae^{-E_a/RT}$$

$$k_1 = Ae^{-E_a/RT_1} \qquad k_2 = Ae^{-E_a/RT_2}$$

Combining Two Arrhenius Equations Con't

- Next, let's take the natural log of each side of the equation

$$ln(k_1) = ln(Ae^{\frac{-E_a}{RT_1}}) \qquad ln(k_2) = ln(Ae^{\frac{-E_a}{RT_2}})$$

- Next, let's use the natural log product rule

$$ln(k_1) = ln(A) + ln(e^{\frac{-E_a}{RT_1}}) \quad ln(k_2) = ln(A) + ln(e^{\frac{-E_a}{RT_2}})$$

Combining Two Arrhenius Equations Con't

- Since $\ln(e^x) = x$

$$ln(k_1) = ln(A) - \frac{E_a}{RT_1} \qquad ln(k_2) = ln(A) - \frac{E_a}{RT_2}$$

- Next, let's make both equations equal to ***ln (A)***

$$ln(A) = ln(k_1) + \frac{E_a}{RT_1} \qquad ln(A) = ln(k_2) + \frac{E_a}{RT_2}$$

Combining Two Arrhenius Equations Con't

- Since both equations are equal to ln(A), then

$$\boldsymbol{ln(k_1) + \frac{E_a}{RT_1} = ln(k_2) + \frac{E_a}{RT_2}}$$

- Let's rearrange the equation in the following manner

$$\boldsymbol{ln(k_2) - ln(k_1) = \frac{E_a}{RT_1} - \frac{E_a}{RT_2}}$$

Combining Two Arrhenius Equations Con't

- Let's use the natural log quotient rule

$$ln(\frac{k_2}{k_1}) = \frac{E_a}{RT_1} - \frac{E_a}{RT_2}$$

- Now, let's separate the $\frac{E_a}{R}$ factor

$$ln(\frac{k_2}{k_1}) = \frac{E_a}{R}(\frac{1}{T_1} - \frac{1}{T_2})$$

Relationship between E_a and $\frac{k_2}{k_1}$

- If $k_2 = 2$
- $k_1 = 1$
- $\frac{k_2}{k_1} = 2$

- $T_1 = 295°K$
- $T_2 = 305°K$
- Then, $\Delta T = 10°K$ (or 10°C)
- $R = 8.314 \frac{J}{mol\ K}$

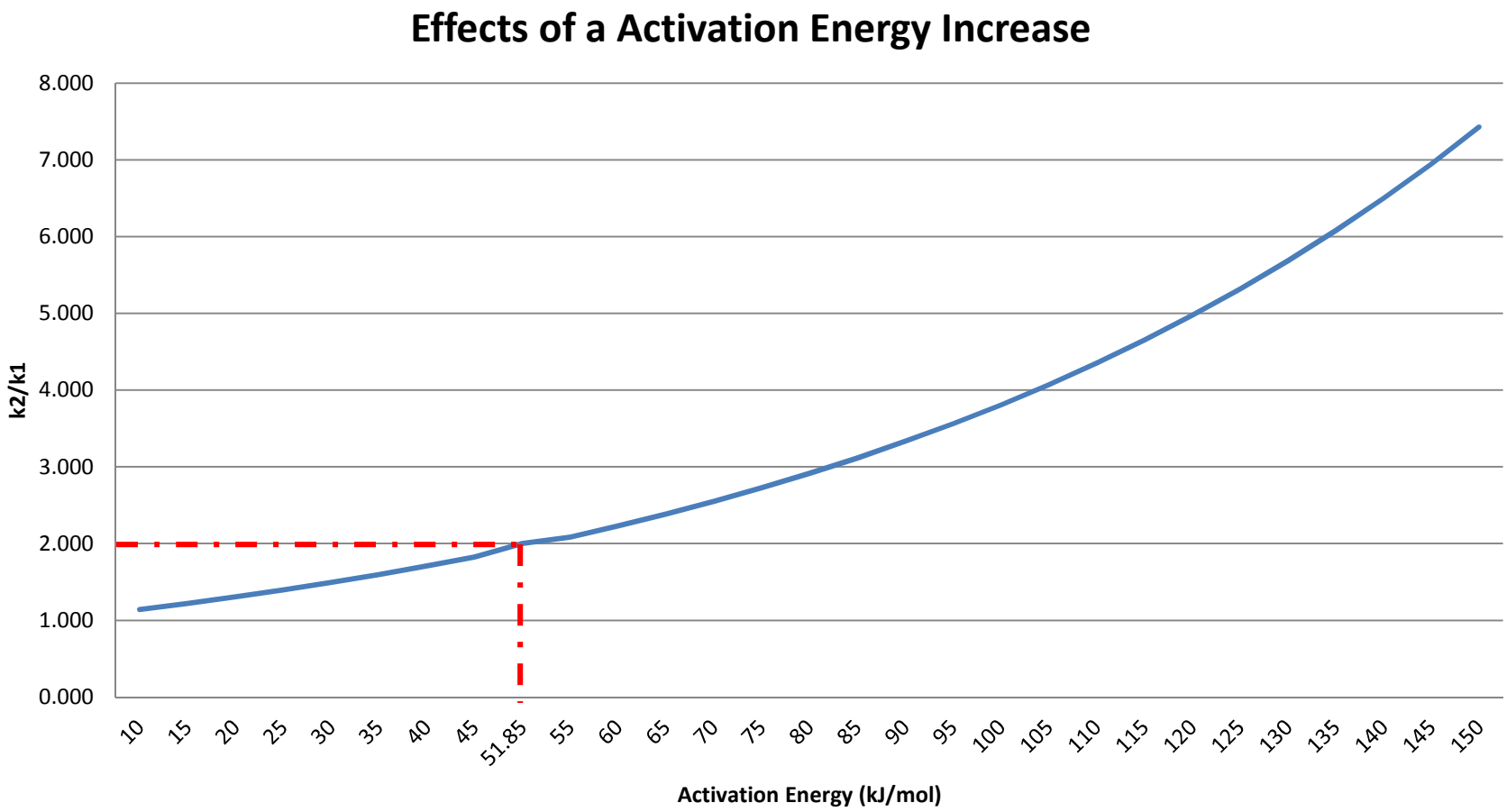
$$\ln(2) = \frac{E_a}{8.314}\left(\frac{1}{295} - \frac{1}{305}\right)$$

$$E_a = 51.85 \approx 50 \frac{kJ}{mol}$$

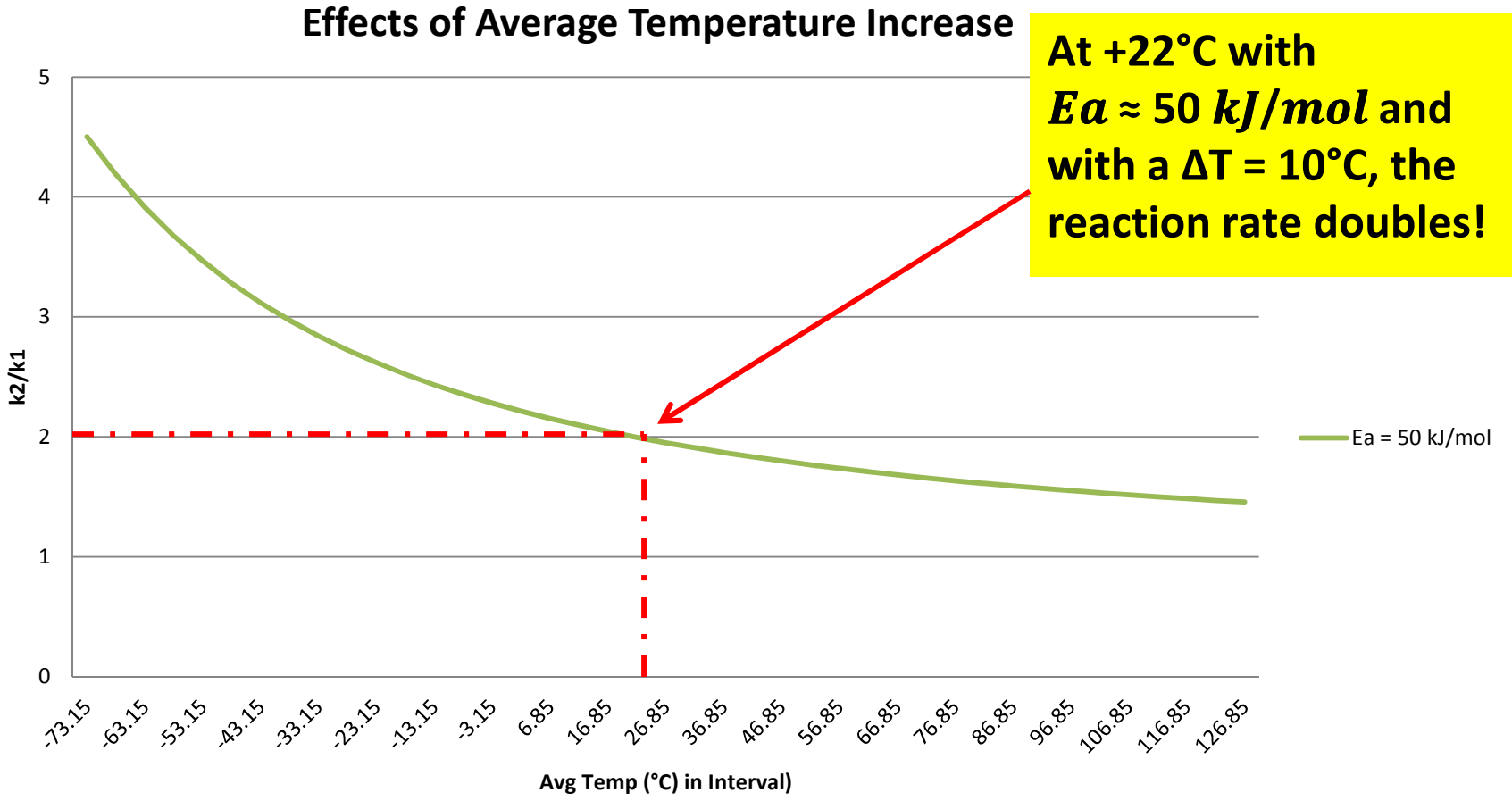
Relationship between E_a and $\frac{k_2}{k_1}$ con't

- $\frac{k_2}{k_1}$ rate doubles only if $E_a \approx 50 \frac{kJ}{mol}$
- If $T_1 = 295°K$ and $T_2 = 305°K$ remain constant
- $\frac{k_2}{k_1}$ increases as E_a increases

Relationship between E_a and $\frac{k_2}{k_1}$ con't



Temperature and $\frac{k_2}{k_1}$



The Arrhenius Equation Modified

- So, from all of this, how do we determine the AAF formula?
- From the Arrhenius equation, we now know that the rate of reaction $\frac{k_2}{k_1}$ doubles which, in our terms, represent Q_{10} = 2, when we have a ΔT = 10°C with an activation energy $\boldsymbol{E_a \approx 50\ \frac{kJ}{mol}}$

The Arrhenius Equation As Used in Medical Device Accelerated Aging – Summary (ASTM F1980)

6.3 … assumes that the chemical reactions involved in the deterioration of materials follow the Arrhenius reaction rate function. …. A 10°C increase in temperature of a homogeneous process results in, approximately, a two times change in the rate of a chemical reaction (Q_{10}).

6.4 Determining theQ_{10}involves testing materials at various temperatures and defining the differences in reaction rate for a 10°C change in temperature.

The Arrhenius Equation As Used in Medical Device Accelerated Aging – Summary (ASTM F1980)

[ASTM F1980] **...chemical reactions involved in the deterioration of materials follow the Arrhenius reaction rate function.**

[Observation] **"deterioration of materials" is never mentioned in the original Arrhenius Equation, only the rate of a chemical reaction.....**

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The Arrhenius Equation As Used in Medical Device Accelerated Aging – Summary (ASTM F1980)

[ASTM F1980] …. a 10°C increase in temperature of a homogeneous process results in, approximately, a two times change in the rate of a chemical reaction (Q_{10}).

[Observation] This comes from solving for ($^{k_2}/_{k_1}$) when ($T_{AA} - T_{RT}$) = 10°C for a slow rate (homogeneous) process.

SO, exactly what is a:

"slow rate (homogeneous) process"?

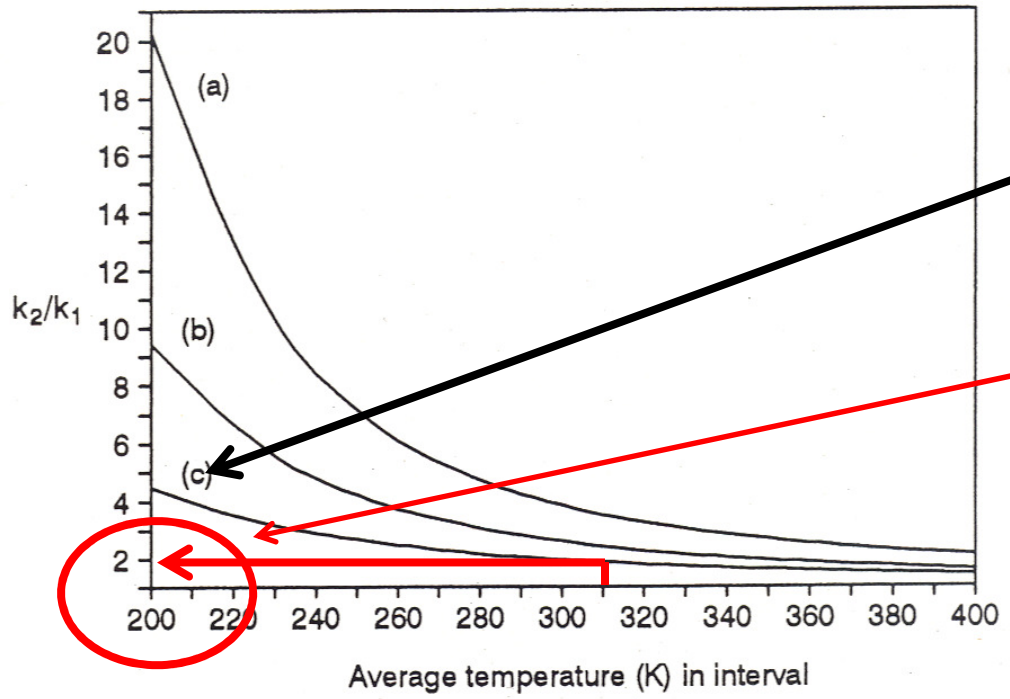


Figure 2.12 The effect of a 10 degree rise in temperature on k_2/k_1 for different activation energies. Curves (a), (b), and (c) correspond to activation energies of 100, 75, and 50 kJ/mol, respectively.

This is a "slow rate process" – about 50kJ/mol

Notice that the rate ($^{k_2}/_{k_1}$) has a value of 2 for temperatures at or near room temp [about 305°K]

Source: J.E. House; ***Principles of Chemical Kinetics,*** Dept. of Chem., Univ of Ill.

NOW we have the basis for Accelerated Aging based on the Arrhenius Equation

Ref: ASTM F1980

$$AAF = Q_{10}^{(T_{AA}-T_{RT})/10}$$

Where:

- Q_{10} = an aging factor for 10°C increase or decrease in temperature.
- T_{AA} = accelerated aging temperature (°C)
- T_{RT} = *ambient temperature (°C)*

The accelerated aging time (AAT) needed to establish equivalence to real time aging is determined by dividing the desired (or required) shelf life (RT) by the AAF.

Accelerated Aging Time (AAT) = Desired (RT)/AAF

Steps in using the Arrhenius Equation for Accelerated Aging

1. Select the Q_{10} value.
2. Define the desired shelf life of the sterile barrier system, such as, marketing needs, product needs, and so forth.
3. Define aging test time intervals, including time zero.
4. Define test conditions, room temperature (T_{RT}), and accelerated aging temperature (T_{AA}).
5. Decide if humidity conditions will be used in the aging study. If used, define the relative humidity (RH) conditions and allowable tolerances to be utilized around a targeted value. (More about humidity later…)

Steps in using the Arrhenius Equation for Accelerated Aging

6. Calculate the test duration using the Q_{10}, T_{RT}, and T_{AA}.
7. Define the sterile barrier system material properties, seal strength and integrity tests, sample sizes, and acceptance criteria.
8. Age samples at T_{AA}. In parallel, age samples at real-life aging conditions (T_{RT}).
9. Evaluate the sterile barrier system performance after accelerated aging relative to the initial sterile barrier system requirements, for example, package seal strength and package integrity.
10. Evaluate the sterile barrier system after real time aging relative to their initial design requirements.

Acceptance Criteria (ASTM F1980):

- Aging or stability testing and performance testing are **separate entities.**
- Acceptance criteria are established prior to any aging testing.
- Several different methods of evaluation may be used.
- One is to use the zero-time performance data as a comparison to final performance data at the end of the shelf life test;
- another is to trend the data over all periods of evaluation;
- use only the final period test results.

Priorities: Aging or Pkg Performance First?

On occasion, package performance testing may be performed on packaging systems ***after aging*** to evaluate the performance of the aged packaging system during simulated distribution, handling, and storage as well as to gather evidence of the device components aging characteristics. If this is an objective, all aging samples will include the devices, or simulated devices, and all the packaging materials that make up the packaging system.

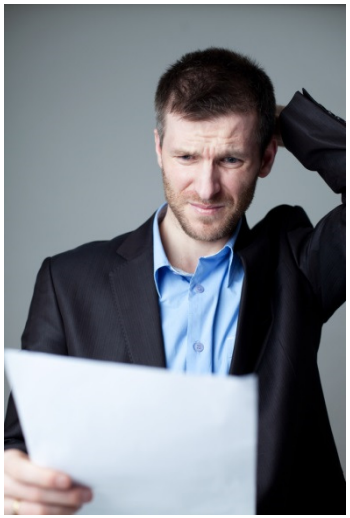
SO…. Either way works. Different acceptances may apply.

ISO 11607

- The guidance document for validating sterilized medical device packaging
- **Compliance shows that your packaging system allows sterilization, provides physical protection, and maintains sterility up to the point of use.**
- FDA Recognized Consensus Standard and required for European Regulation for a CE mark

CE

Possible Problems…..



- Time/temperature correlations may occur for some properties but not for others
- "Arrhenius extrapolations" may not be linear in the temperature range of interest.

Source:

An Ultrasensitive Technique For Testing The Arrhenius Extrapolation Assumption For Thermally Aged Elastomers

Authors: J. Wise, K.T. Gillen, R.L. Clough

How About Humidity?

Mentioned in ISO 11607:

5.0 Materials and preformed sterile barrier systems
5.1.4 As a minimum, the following shall be considered:

a) temperature range
b) pressure range
c) humidity range
d) maximum rate of change of the above, where necessary
e) exposure to sunlight or UV light
f) cleanliness
g) bio burden
h) electrostatic conductivity

OK; Now How About Humidity?

From ASTM F1980:

"A humidity factor to calculate the accelerated aging time (T_{AA}) **is not applicable for accelerated aging protocols**. Unrealistic or extreme temperature and humidity conditions may be of interest in overall sterile barrier system performance. However, this must be evaluated in a separate study and **is not related to aging of the materials**."

ALSO From ASTM F1980:

"Decide if humidity conditions will be used in the aging study. If used, define the relative humidity (RH) conditions and allowable tolerances to be utilized around a targeted value."

OK; Now How About Humidity?

OBSERVATIONS:

1. **Can I use humidity in AA tests? YES, but it just adds complexity without a clearly defined benefit.**
2. **ISO 11607 mentions humidity only in passing.**
3. **Arrhenius doesn't mention it; temperature only.**
4. **When is humidity important? Perhaps when dealing with hydroscopic materials (absorb water). This should be evaluated on a case-by-case basis, not applied universally without careful examination.**
5. **The Psychometric Chart clearly tells us that the activation energy of moist air is greater than dry air.**

Conclusions

1) Accelerating aging of medical device packaging does in fact have a basis in the Arrhenius reaction rate equation.
2) Significant questions still remain about the applicability of the Arrhenius rate equation as modified to derive an accelerated aging factor (AAF) and extrapolated to the temperature ranges of interest for medical device package testing.
3) Accelerated aging validated with real-time aging seems the best approach for complying with ISO 11607, section 6.4.1 “Stability testing shall demonstrate that the sterile barrier system **maintains integrity over time.”**

De END

QUESTIONS??

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THANK YOU !

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