

**Root Cause Analysis  
of the Worldwide  
*Fusarium* Keratitis  
Epidemic of 2004-2006  
and Prescriptions for  
Preventing Future  
Epidemics**



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**[No Financial Disclosures in the past year/ No Off-Label Use Discussed]**

# ReNuML Timeline

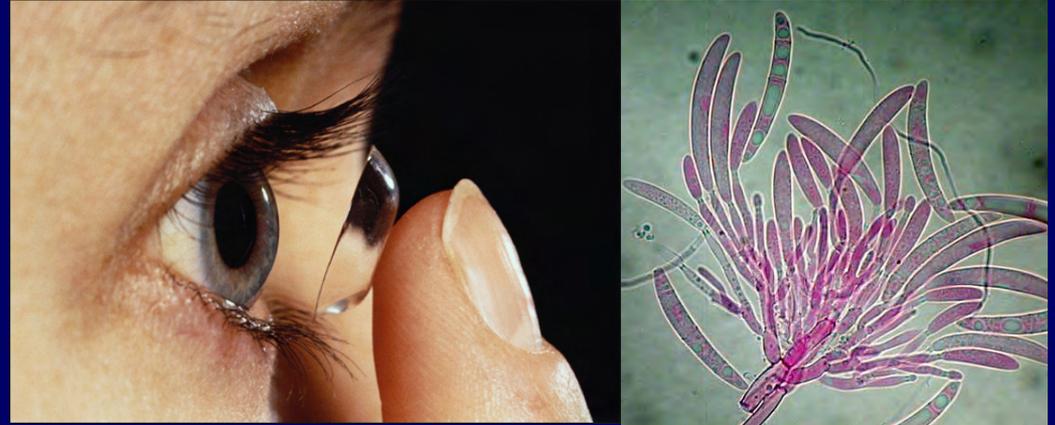
DATE	EVENT
Aug. 2004	Bausch & Lomb introduced ReNuML contact lens solution
May 2006	ReNuML withdrawn from world market due to <i>Fusarium</i> keratitis
May 2008	Bullock et al reported temperature instability of ReNuML to the AOS

# QUESTIONS

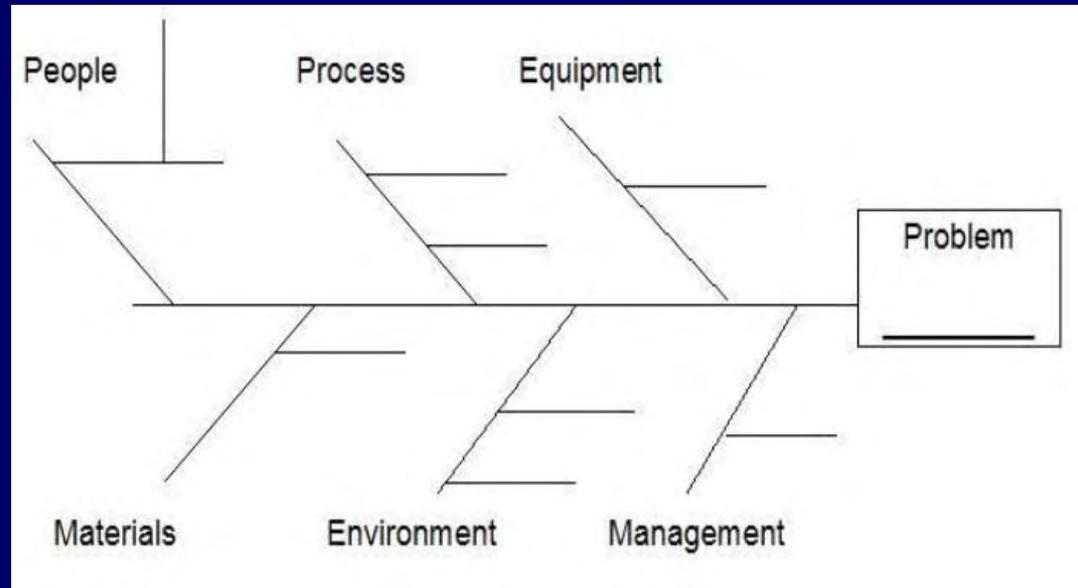
- Could the *Fusarium* keratitis epidemic have been prevented ?
- Could the *Fusarium* keratitis epidemic, and its cause, have been recognized earlier ?

# BASIC TENETS OF PUBLIC HEALTH

- To **prevent** the occurrence of disease
- To **control** the spread of disease within the initial population at risk
- To **prevent** its spread to additional populations



# Root Cause Analysis



“Fishbone” Diagram

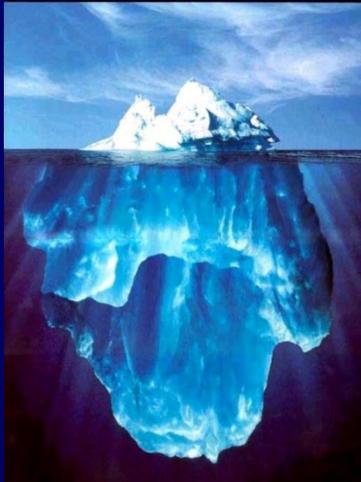
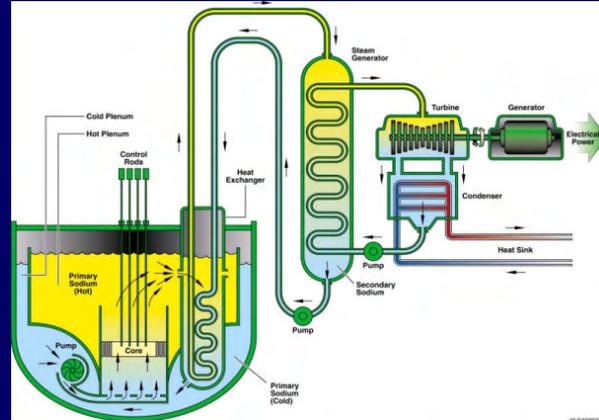
# Titanic



# Challenger



# Chernobyl



# ROOT CAUSE ANALYSIS

- **Physical** Failures
- **Human** Failures
- **Organizational** Failures

# Limited Tripartite Root Cause Analysis

1. Review of **FDA documents**
2. Theoretical retrospective **statistical analysis** of the Singapore outbreak
3. Investigation of a **new prevention strategy**

**FDA**

**DOCUMENTS**

# 1997 FDA Guidelines

**WARNED ABOUT  
TEMPERATURE-  
RELATED  
SOLUTION  
INSTABILITY**



## Guidance for Industry

### PREMARKET NOTIFICATION (510(k)) GUIDANCE DOCUMENT FOR CONTACT LENS CARE PRODUCTS

This document represents the agency's current thinking on the preparation of a 510(k) for contact lens care products. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. The guidance is available on the Worldwide web on CDRH's home page at "<http://www.fda.gov/cdrh>."

While this guidance document represents a final document, comments and suggestions may be submitted at any time for agency consideration to Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., Rm. 1-23, Rockville, MD 20857 or by writing to James F. Saviola, O.D., Chief, Vitreoretinal and Extraocular Devices Branch (HFZ-460), Division of Ophthalmic Devices, Office of Device Evaluation, Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, MD 20850. This guidance document replaces the draft PREMARKET NOTIFICATION (510(k)) GUIDANCE DOCUMENT FOR CONTACT LENS CARE PRODUCTS, which issued on April 1, 1996.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Food and Drug Administration  
Center for Devices and Radiological Health  
May 1, 1997

# “Store at room temperature.”

Bausch & Lomb  
**ReNu**®

with  
**MoistureLoc™**  
Multi-Purpose Solution

**NEW!**

*Provides  
Sustained Comfort*

**No Rub**

Cleans, Disinfects, Rinses,  
Stores, Removes Protein Daily  
For Soft Contact Lenses



each lens surface and rubbing  
You may store your lenses up  
the unopened lens case.  
Store at room temperature.  
Use before expiration date per  
Toll Free Product Information



# “Substantial Equivalence”

FDA Document  
# K033854 (5/19/04)

## Substantial Equivalence

Bausch & Lomb Multi-Purpose Solution NRC07 is substantially equivalent to Bausch & Lomb Multi-Purpose Solution NRC03, Bausch & Lomb ReNu MultiPlus Multi-Purpose Solution, Opti-Free Express Multi-Purpose Disinfecting Solution and Complete MoisturePLUS Multi-Purpose Solution.

## Description of the Device

Bausch & Lomb Multi-Purpose Solution NRC07 is a sterile isotonic solution containing boric acid, sodium chloride, sodium phosphate, Hydranate® (hydroxyalkylphosphonate), poloxamer 407, polyquaternium-10, poloxamine 1107, purified water and preserved with Alexidine dihydrochloride (0.00045%). The product is indicated for use in the daily cleaning, removing protein deposits, rinsing, chemical (not heat) disinfection and storage of soft (hydrophilic) contact lenses as recommended by your eye care practitioner.

Chang et al. *JAMA*.  
2006;296:953-963

“The MoistureLoc formula contains 2 ingredients not found in other soft contact lens solutions currently on the market: **alexidine** (a disinfectant) and **polyquaterium-10** (a moisture-retaining polysaccharide that holds water close to the contact lens surface).”

# 2006 FDA Form 483 Cited B&L for Regulatory Deviations

Bausch & Lomb was cited for inadequacies in temperature control in the production, storage, and transport of their products.

{Observations 8,12a/b,1}



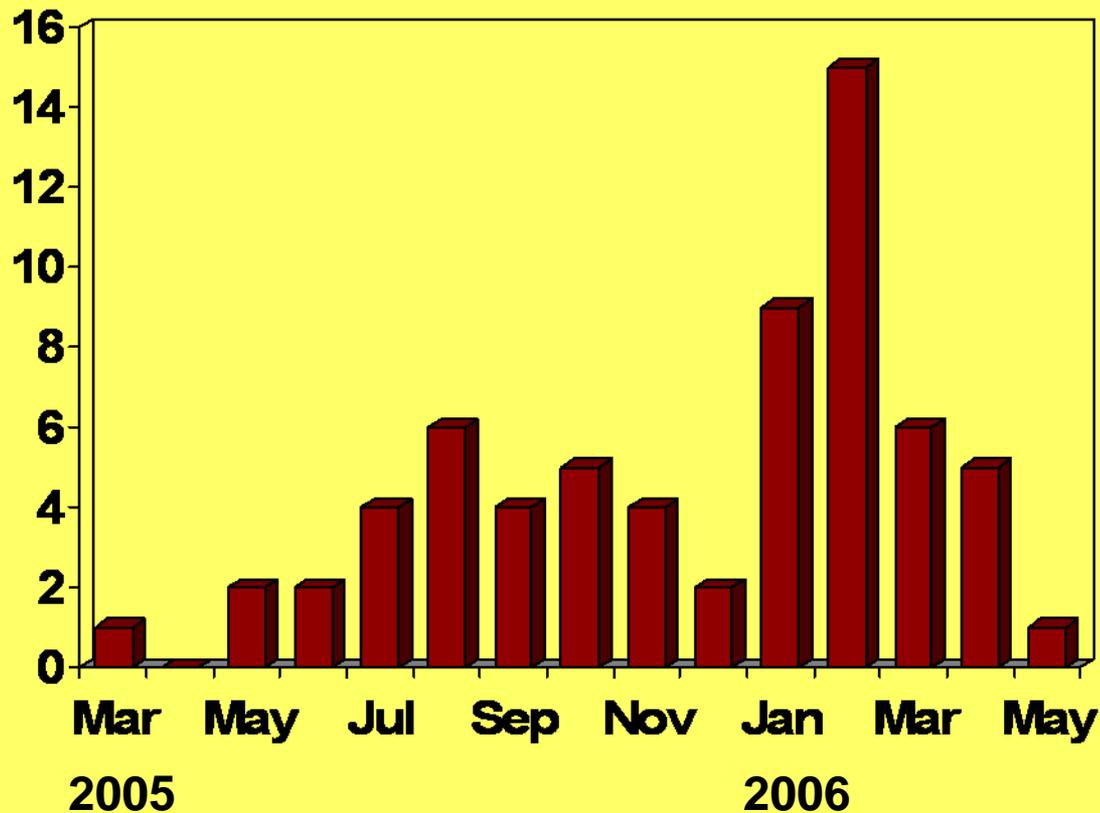
# 2006 FDA Form 483

## Cited Bausch & Lomb:

1. “...failed to notify the Agency of 35 serious injury reports of Fusarium Keratitis from Singapore's Minister of Health in February 2006 relating to ReNu MoistureLoc...” {Observation 4a}
2. “...failed to report the removal of ReNu MoistureLoc Multi-Purpose Solution from the market in Singapore and Hong Kong in February 2006.” {Observation 5}
3. “...investigation did not include ...biocidal testing for ReNu w/ MoistureLoc Multi-Purpose Solution product lots implicated in complaints received from Hong Kong.” {Observation 9a}

# STATISTICAL ANALYSIS

# Epidemic Curve of Contact Lens-Related *Fusarium* Keratitis in Singapore



[redrawn from *JAMA*.2006;295(24):2867-73]

# Variables For Theoretical Retrospective Statistical Analysis of the Singapore Outbreak

- [1] Number of cases that had actually used a ReNu brand contact lens solution (at least **62/66**)
- [2] Number of contact lens wearers in Singapore (approximately **224,800**)
- [3] Percentage market share of the ReNu brand solutions in Singapore (between 30% - 40% = **35%**)
- [4] Baseline endemic rate of cases of contact lens-related *Fusarium* keratitis in Singapore ( $R_B =$  **1-2** cases per year or **0.125** cases per month)

# SEQUENTIAL UNMATCHED CASE-CONTROL STUDIES

	CASE	CONTROL	TOTAL
ReNu Use	$(62/66) \cdot \Sigma$	$78,680 - [(62/66) \cdot \Sigma]$	$35\% \cdot 224,800 = 78,680$
ReNu Non-Use	$(4/66) \cdot \Sigma$	$146,120 - [(4/66) \cdot \Sigma]$	$65\% \cdot 224,800 = 146,120$
TOTAL	$\Sigma$	$224,800 - \Sigma$	224,800

# Earliest Identification of the Outbreak in Singapore

[Poisson Distribution]

$$\text{Pr}(x) = [ e^{-\lambda} \cdot \lambda^x ] / x!$$

**x** = observed  
# of cases

**$\lambda$**  = expected  
# of cases



Simeon-Denis Poisson

# POISSON PROBABILITIES

Month Ending	Duration of Outbreak (D)	# New Cases in Current Month	Cum. # of Observed Cases ( $\Sigma$ )	Expected # of Cases ( $\lambda = 0.125 \cdot D$ )	Poisson Probability ( $\Pr[x \geq \Sigma]$ )
3/31/05	1	1	1	0.125	0.1175
4/30/05	2	0	1	0.250	0.2212
5/31/05	3	2	3	0.375	0.0067

# Earliest Identification of Cause of Outbreak in Singapore

Month Ending	# New Cases in Current Month	Cum. # of Observed Cases ( $\Sigma$ )	# That Used ReNu = $(62/66) \cdot \Sigma$	# That Did Not Use ReNu = $(4/66) \cdot \Sigma$	P-value (Fisher's Exact Test)
3/31/05	1	1	0.94	0.06	0.35
4/30/05	1	1	0.94	0.06	0.35
5/31/05	2	3	2.82	0.18	<b>0.0429</b>

# Earliest Identification of Cause of Outbreak in Singapore (O.R. / 95% C.I.)

Month Ending	# New Cases in Current Month	Cum. # of Observed Cases ( $\Sigma$ )	# That Used ReNu = $(62/66) \cdot \Sigma$	# That Did Not Use ReNu = $(4/66) \cdot \Sigma$	Odds Ratio	95% C.I.
3/31/05	1	1	0.94	0.06	4.77	0.22-104.3
4/30/05	0	1	0.94	0.06	4.77	0.22-104.6
5/31/05	2	3	2.82	0.18	9.04	0.67-122.4
6/30/05	2	5	4.70	0.30	12.0	<b>1.15</b> -126.0

# Earliest Identification of Cause of Outbreak in Singapore (O.R. / 95% C.I.)

["Biased": assumes that the first four cases **did not** use ReNu]

Month Ending	# New Cases in Current Month	Cum. # of Observed Cases ( $\Sigma$ )	# That Used ReNu	# That Did Not Use ReNu	Odds Ratio*	95% C.I.*
3/31/05	1	1	0	1	0.00	-
4/30/05	0	1	0	1	0.00	-
5/31/05	2	3	0	3	0.00	-
6/30/05	2	5	1	4	0.62	0.10 - 3.93
7/31/05	4	9	5	4	2.27	0.65 - 7.89
8/31/05	6	15	11	4	4.75	<b>1.60</b> -14.12

# Summary of Theoretical Statistical Tests as of August 31, 2005

QUESTION	TEST	RESULT
Outbreak?	Poisson	Pr = $5.0 \times 10^{-15}$
ReNu?	Fisher's Exact Test	P = $4.18 \times 10^{-6}$
ReNu?	O.R. 95% C.I. [Theoretical]	19.2 $3.4$ -108.4
ReNu?	O.R. 95% C.I. ["Biased"]	4.75 $1.60$ -14.12

**ReNuML was not  
withdrawn from the  
world market until  
May 15, 2006,  
8½ months later.**

**NEW  
PREVENTION  
STRATEGY**

# 2008 AOS Meeting

**Secondary Discussion:** “Temperature Instability of ReNu with MoistureLoc: A New Theory to Explain the Worldwide *Fusarium* Keratitis Epidemic of 2004-2006,”  
by Bullock JD, Warwar RE, Elder BL, et al.

**Dr. Evelyn A. Paysse:**

“Are there any controls being implemented for thermal protection of these solutions?”



# THERMOCHROMISM

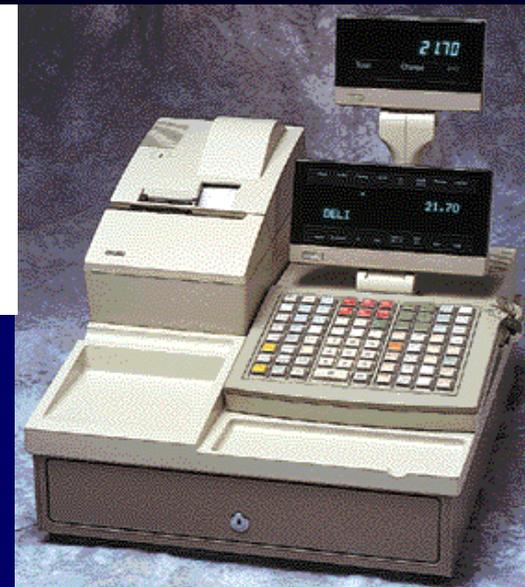
“...the ability of a substance to change color due to a change in temperature.”



“Mood Ring”

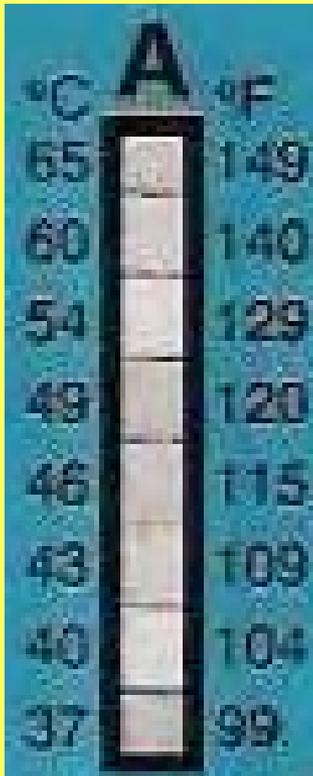
# THERMOCHROMIC PAPER

- Invented by the NCR Corporation of Dayton, Ohio for printing cash register receipts.
- When heated, a microencapsulated dye reacts with an acid and irreversibly shifts to a colored form, typically black.



# THERMOCHROMIC STRIPS ( $\pm 2\%$ )

Room Temperature



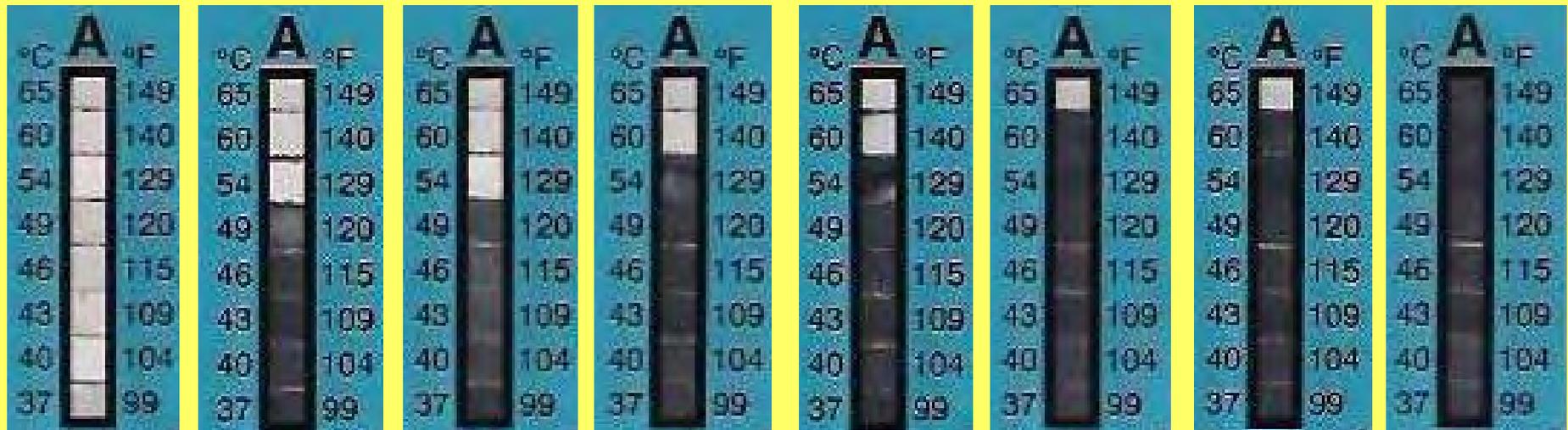
Exposed to 135°F



# EXPERIMENTAL STUDY

<b>72</b>	<b>120</b>	<b>125</b>	<b>130</b>	<b>135</b>	<b>140</b>	<b>145</b>	<b>150</b>
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(degrees Fahrenheit)



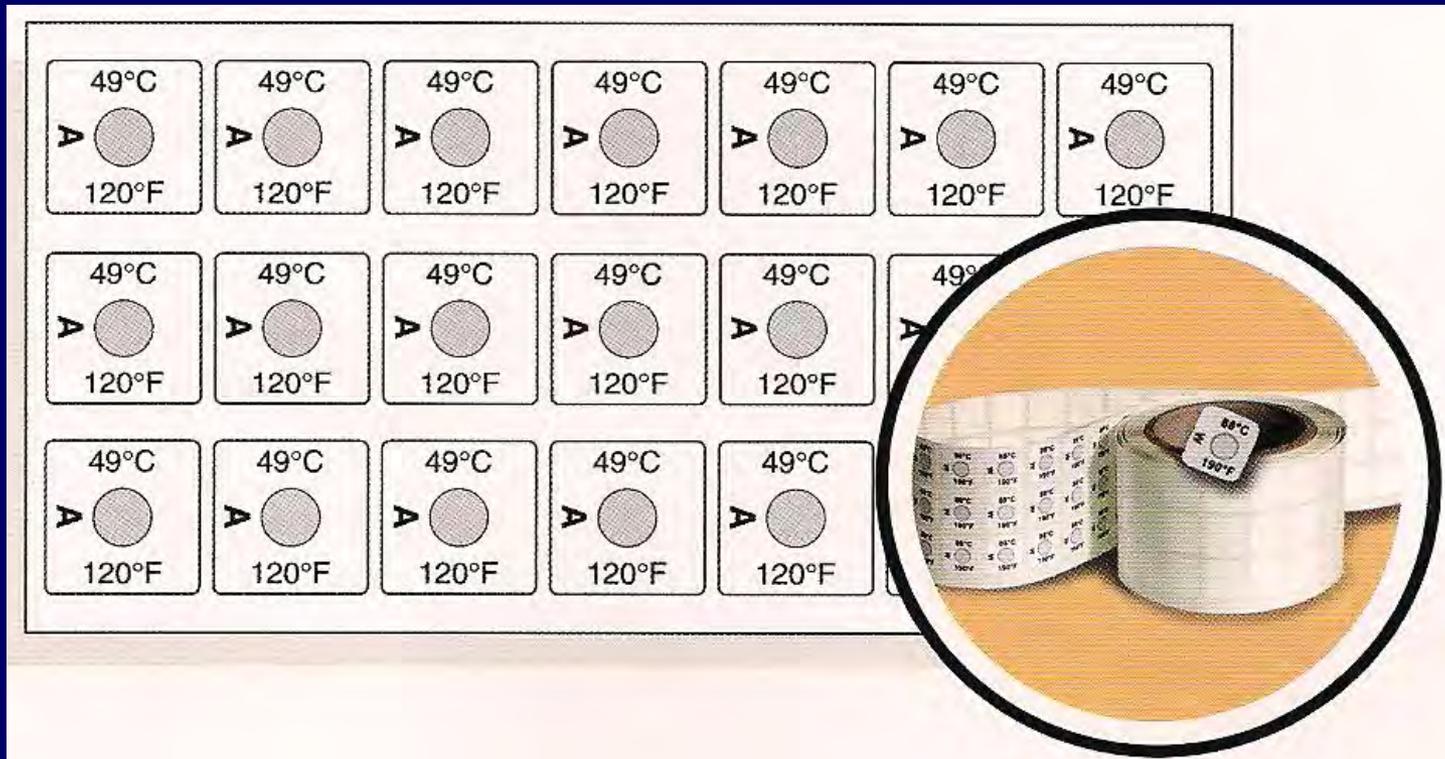
Oven Temperature (degrees F)	Strip Temperature (degrees F)
120	120
125	120
130	129
135	129
140	140
145	140
150	149

**Pearson Correlation Coefficient**  
 **$r = 0.971, P = 0.0003$**

# COST ANALYSIS

{ [ \$217.30/1000 LABELS ] X [ 1 LABEL/CASE ] } /  
[ 12 BOTTLES/CASE ] = 1.8 CENTS / BOTTLE

Retail price [12 oz.] = \$8.93 [0.2% of Retail]



# Q. Could the *Fusarium* keratitis epidemic have been prevented?

Yes, by:

1. Much more rigorous oversight by the FDA's approval process
2. Strict adherence to package instructions and FDA guidelines by providing temperature controlled factories, storage areas, and cargo trucks and ships
3. Use of readily available, inexpensive, irreversible, accurate thermochromic labels.



Store at room temperature.



# Q. Could the epidemic, and its cause, have been recognized earlier?

Yes, by:

1. Strict adherence to the FDA's reporting regulations
2. Compiling all cases of *Fusarium* keratitis immediately upon diagnosis
3. Application of basic statistical methods



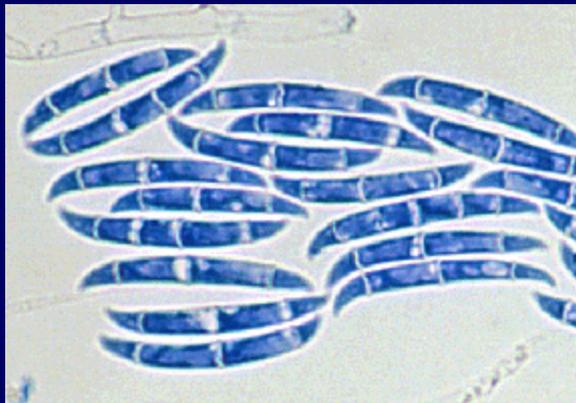
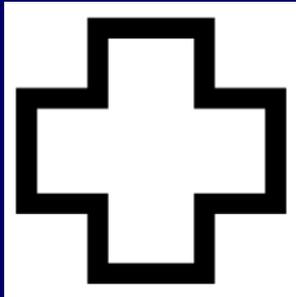
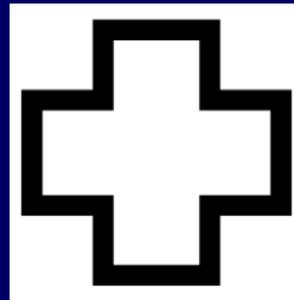
$$P(x) = [ e^{-\lambda} \cdot \lambda^x ] / x!$$

# Richard Feynman 1918-1988

“For a successful technology, reality must take precedence over public relations, for nature cannot be fooled.”



# Lessons Learned



# THANK YOU

