ROOT CAUSE ANALYSIS OF THE *FUSARIUM* KERATITIS EPIDEMIC OF 2004-2006 AND PRESCRIPTIONS FOR PREVENTING FUTURE EPIDEMICS

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ABSTRACT

Purpose: A root cause analysis of the *Fusarium* keratitis epidemic of 2004-2006 was performed.

Methods: Three US Food and Drug Administration (FDA) documents were analyzed. Poisson and case-control studies were performed on outbreak data from Singapore. Irreversible thermochromic labels were applied to cartons of contact lens solution bottles, which were then subjected to elevated temperatures.

Results: The 1997 FDA guidance document concerning storage temperatures of contact lens care products predicted temperature-related solution instability. Bausch & Lomb (B&L) requested FDA approval for ReNu with MoistureLoc, claiming that it was substantially equivalent to other products. FDA Form 483 stated that cases of ReNu-related *Fusarium* keratitis from Asia had not been reported, the removal of the product from the Asian markets was unreported, and B&L had not performed biocidal testing on samples associated with Asian cases. The outbreak in Singapore could have been recognized after only 3 cases ($Pr = .0067$). The cause of the Singapore outbreak could have been determined after the recognition of only 3 ($P = .0429$), 5 (95% confidence interval [CI], 1.15-126.0), or 15 cases (95% CI, 1.60-14.1). Thermochromic labels can irreversibly change color when exposed to elevated temperatures, thus warning of potential antimicrobial failure.

Conclusions: The worldwide *Fusarium* keratitis epidemic of 2004-2006 could, theoretically, have been prevented entirely, recognized much earlier, or mitigated by much more rigorous oversight by the FDA, by strict adherence by B&L to FDA guidelines and requirements, by the application of basic statistical methods, and/or by the use of temperature indication technology. The lessons learned from a root cause analysis of this pharmacologic catastrophy may help avert or mitigate future epidemics.

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

Richard P. Feynman
US physicist, 1918-1988; 1965 Nobel Laureate in Physics; member of the 1986 Rogers Commission (Presidential Commission on the Space Shuttle *Challenger* Accident)

INTRODUCTION

In May 1997, the US Food and Drug Administration (FDA) issued a new guidance document for contact lens care products,[1] and in May 2004, the FDA gave official clearance for Bausch & Lomb (B&L, Rochester, New York) to market its new product, ReNu with MoistureLoc multipurpose contact lens solution (RML), on the basis that it was substantially equivalent to, among others, B&L's current product, ReNu MultiPlus.[2] In August 2004, B&L introduced RML to the market,[3] and in July 2005, an increased incidence of *Fusarium* keratitis was noted in Hong Kong.[4] In February 2006, the first 35 of 62 cases of ReNu-related *Fusarium* keratitis were reported from the Republic of Singapore,[5] and RML was then withdrawn from the Asian market. Several weeks later, the first 5 US cases of ReNu-related *Fusarium* keratitis were reported from Newark, New Jersey (3 cases) and Dayton, Ohio (2 cases).[6,7] Between March 22 and May 15, 2006, the FDA inspected B&L's Greenville, South Carolina, plant, which had manufactured the suspected RML and then issued FDA Form 483.[8] B&L subsequently withdrew RML from the world market. At the termination of the epidemic, hundreds of cases of RML-related *Fusarium* keratitis had occurred worldwide, with many resulting in permanent blindness. In May 2008, Bullock and associates[9] reported experimental findings of temperature instability and antimicrobial failure of RML to the American Ophthalmological Society. The investigators found that the failure temperature was ≤60°C (140°F), when stored for 4 weeks.

Since the basic tenets of public health are to prevent the occurrence of disease, to control the spread of disease within the initial population, and to prevent its spread to additional populations, questions have arisen as to how this epidemic could have been recognized earlier or prevented altogether. To address these questions, a root cause analysis was performed. The limited tripartite root cause analysis included (1) a review of specific FDA documents pertaining to contact lens care products; (2) a theoretical retrospective statistical analysis of the outbreak in Singapore; and (3) the investigation of a new strategy to prevent the failure of potentially thermally labile pharmaceuticals.

METHODS

FDA DOCUMENTS

The following 3 documents were analyzed: the 1997 FDA Premarket Notification Guidance Document for Contact Lens Care Products[1]; the 510(k) document K033854 from the FDA[2]; and the 2006 FDA Form 483, Inspectional Observations from 3/22/2006-5/15/2006 of B&L's Greenville, South Carolina, manufacturing facility.[8]

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ANALYSIS OF THE SINGAPORE OUTBREAK

A theoretical retrospective statistical analysis was performed. The purpose of this analysis was to determine when the *Fusarium* keratitis outbreak in Singapore could have been identified and when the probable cause of the outbreak could have been determined. For the purposes of this study, it was assumed that all cases were immediately tabulated upon diagnosis.

Data Source

The earliest peer-reviewed published details concerning the Singapore outbreak were analyzed.[10] The data included the epidemic curve (Figure 1) and the following variables: (1) the number of cases of *Fusarium* keratitis that involved use of a ReNu brand contact lens solution (at least 62 of 66); (2) the number of (presumably, multipurpose solution utilizing) contact lens wearers in Singapore (approximately 224,800); (3) the percentage market share of the ReNu brand solutions in Singapore (approximately 35%); and (4) the baseline endemic rate of contact lens–related *Fusarium* keratitis in Singapore (approximately 1 to 2 cases per year, or 0.125 cases per month). Table 1 was created from the epidemic curve (Figure 1).

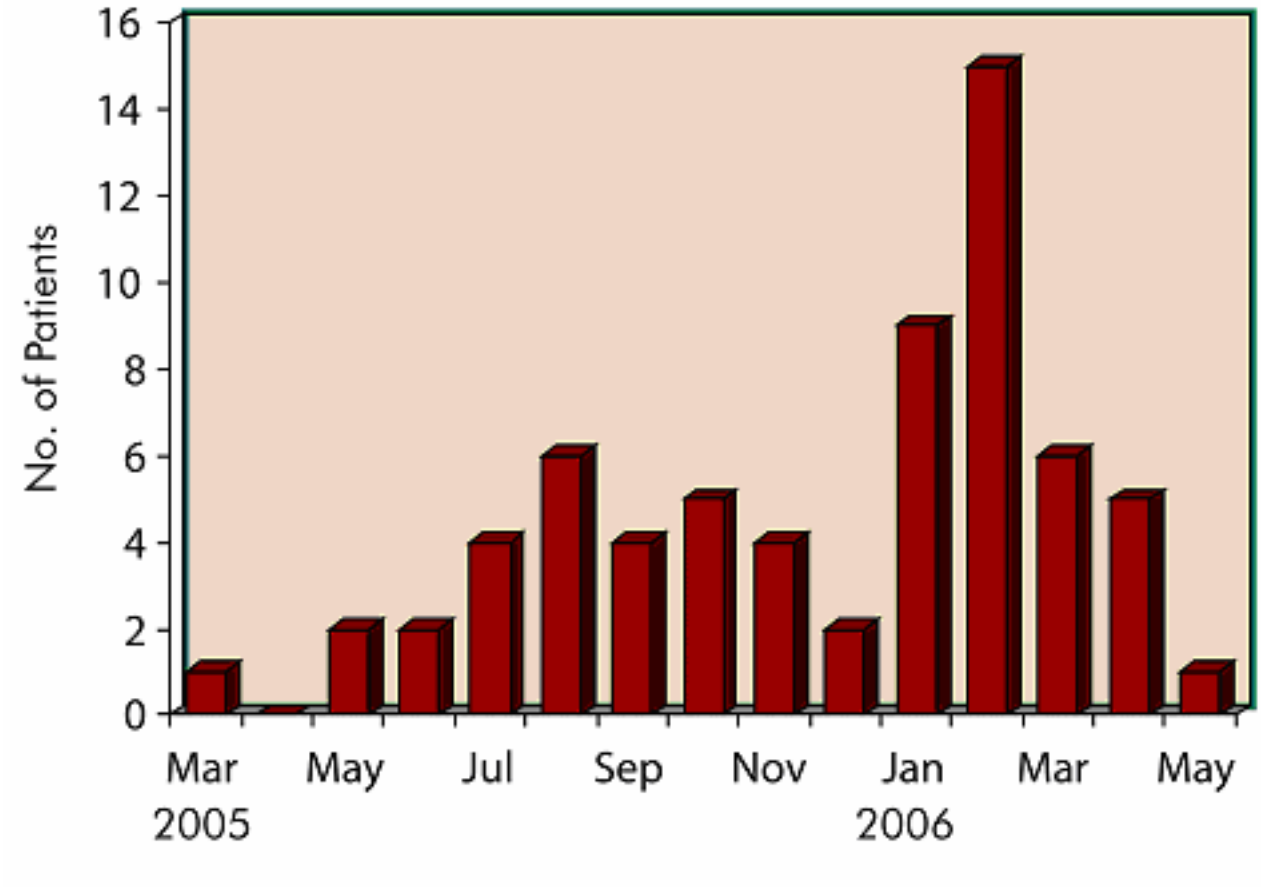

FIGURE 1

Epidemic curve of contact lens–related *Fusarium* keratitis in the Republic of Singapore. Redrawn from *JAMA* 2006;295:2867-2873.

Of the 66 total cases of contact lens–related *Fusarium* keratitis in the Singapore outbreak, 62 patients had used a ReNu brand contact lens solution and one patient had used the Complete brand (Advanced Medical Optics, Santa Ana, California); for the remaining 3, the brand of contact lens solution used could not be determined. Of the 62 patients who had used a ReNu brand product, 42 had used RML, 6 had used ReNu MultiPlus, 11 had used an unspecified ReNu solution, and the remaining 3 had used more than one solution, including an unspecified ReNu solution. Neither the epidemic curve nor the published data indicated the specific solution(s) used by each of the 66 individual patients.

Statistical Analysis

The Poisson distribution was used to estimate the earliest identification of the outbreak. This distribution expresses the probability of the number of events occurring in a fixed period of time if these events occur with a known average rate and are independent of the time since the last event.[6] The probability that a single event occurs within an interval of time is proportional to the duration of the interval. The probability, $Pr(x)$, that there are exactly x cases of contact lens–related *Fusarium* keratitis during an outbreak interval of

duration, D, is $Pr(x) = [e^{-\lambda} \bullet \lambda^{x}] / x!$, where e is Euler's number (the base of Naperian [natural] logarithms, having an approximate value of 2.71828) and λ, the expected number of cases that would have occurred during the same interval if there had not been an outbreak and if the typical local historic endemic rate, R_B (the baseline number of cases per unit time), had still been in effect during that interval, equals $D \bullet R_B$.[6]

TABLE 1. DATA DERIVED FROM EPIDEMIC CURVE

MONTH ENDING	NO. OF NEW CASES IN CURRENT MONTH	CUMULATIVE NO. OF OBSERVED CASES, Σ
3/31/2005	1	1
4/30/2005	0	1
5/31/2005	2	3
6/30/2005	2	5
7/31/2005	4	9
8/31/2005	6	15
9/30/2005	4	19
10/31/2005	5	24
11/30/2005	4	28
12/31/2005	2	30
1/31/2006	9	39
2/28/2006	15	54
3/31/2006	6	60
4/30/2006	5	65
5/31/2006	1	66

The probable cause of the outbreak was determined using sequential unmatched case-control studies, based on Table 2. The probability that any one particular case had used a ReNu brand solution was at least 62/66, and the corresponding probability of nonuse was, at most, 4/66. Multiplying these probabilities by the cumulative number of cases in the epidemic, Σ, yields the theoretical cumulative number of exposed and unexposed cases. This allows calculation of the *P* values using the Fisher exact test, odds ratios, and 95% confidence intervals for each month of the epidemic. An additional analysis was performed using actual whole numbers of cases (instead of probabilistically derived fractional cases), assuming that the first 4 cases had used a non-ReNu brand solution.

NEW PREVENTION STRATEGY

Thermochromic strips (Thermax 8 Level Strips, product No. THE08S-A; Tempil, South Plainfield, New Jersey) were applied to cartons of contact lens solution bottles. Figure 2 shows a control (room temperature) strip and a thermochromic strip that was exposed to 135°F, showing an irreversible color change from white to black up to the 129°F level. These strips are able to measure 8 different temperature levels. The cartons of contact lens solution bottles were then placed in a KitchenAid Superba 27″ Self Clean Thermal oven (US Appliance, Auburn Hills, Michigan) for 1 hour at temperatures ranging from 120°F to 150°F, in 5° increments, measured using a TruTemp thermometer, model 3506 (Taylor Precision Products, Oak Brook, Illinois). The relationship between the oven and strip temperatures was examined using the Pearson correlation coefficient, and the corresponding *P* value was calculated.

TABLE 2. DATA AND CALCULATIONS REQUIRED FOR THE CREATION OF SEQUENTIAL 2X2 TABLES FOR ReNu USE vs *FUSARIUM* KERATITIS

VARIABLE	CASE	CONTROL	TOTAL
ReNu Use	(62/66) • Σ	78,680-[(62/66) • Σ]	78,680 (= 35%•224,800)
ReNu Nonuse	(4/66) • Σ	146,120-[(4/66) • Σ]	146,120 (= 65%•224,800)
Total	Σ	224,800- Σ	224,800

Σ, cumulative number of observed cases.

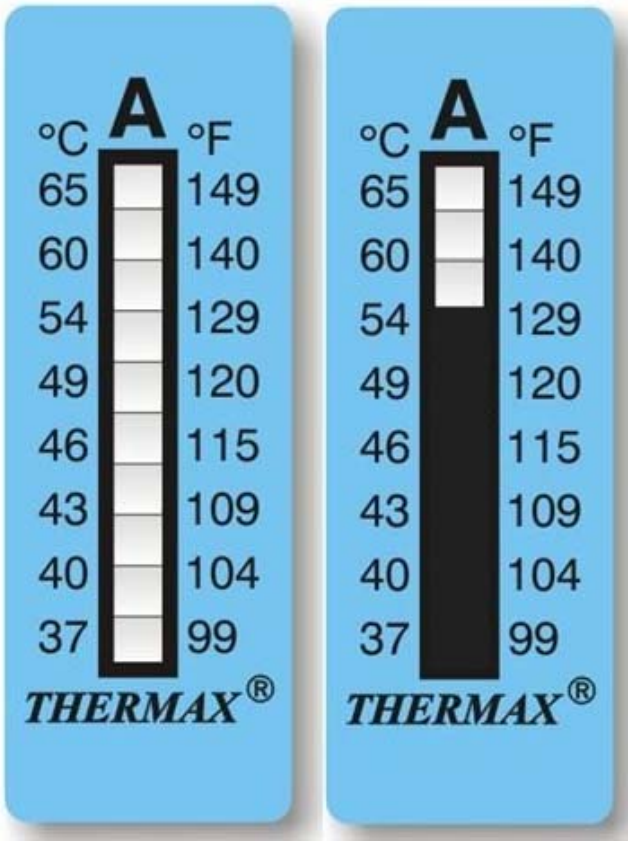

FIGURE 2

Thermochromic strips. Left, Control (room temperature) strip. Right, Strip exposed to 135ºF, showing color change from white to black up to the 129ºF level.

RESULTS

FDA DOCUMENTS

The 1997 contact lens guidance document stated that every 10°C increase in storage temperature would decrease the shelf life by a factor of 2.[1] In its application for clearance to market RML (FDA K033854), B&L asserted that it was substantially equivalent to, among others, their current product, ReNu MultiPlus, even though it contained 2 major ingredients not found in other soft contact lens solutions currently on the market: the bisbiguanide antimicrobial agent, alexidine dihydrochloride, and polyquaternium-10, a moisture-retaining polysaccharide that holds water close to the contact lens surface.[2,3] As previously reported,[7,9] B&L was cited in FDA Form 483 for inadequacies in temperature control in the production, storage, and transport of their products (Observations 8,12a/b; 1 in addendum). Additional analysis revealed that B&L had violated FDA regulations by (1) not reporting Asian cases of *Fusarium* keratitis to the FDA (Observation 4a); (2) not reporting their withdrawal of the RML solution from the Asian markets to the FDA (Observation 5); and (3) not performing biocidal testing on samples associated with Asian cases of *Fusarium* keratitis (Observation 9a).[8]

ANALYSIS OF THE SINGAPORE OUTBREAK

Earliest Identification of the Outbreak

The Poisson distribution calculates the probability that the observed number of cases of contact lens–related *Fusarium* keratitis was merely a chance variation from the expected number. Table 3 shows that by May 31, 2005, the probability of observing 3 or more cases by chance alone (when only .375 cases were expected) was .0067. Typically, one is interested in ascertaining not the specific value of *Pr*(x), but the probability of observing x or more cases, in this instance designated $Pr(x \geq \Sigma)$ (Table 3, column 6), where $Pr(x \geq \Sigma) = 1- \{Pr(0) + Pr(1) + Pr(2) + \ldots + Pr(x-1)\}$. This term, which is subtracted from 1, can be obtained using the Poisson function of Microsoft Office Excel 2003 (Microsoft Corporation, Redmond, Washington), by entering the value of x-1 for "x" (the number of events [observed number of cases]), the value of λ for "mean" (the expected number of cases), and "TRUE" for "cumulative," designating the cumulative Poisson probability.

TABLE 3. CALCULATION OF POISSON PROBABILITIES

MONTH ENDING	DURATION OF OUTBREAK, D (MONTHS)	NO. OF NEW CASES IN CURRENT MONTH	CUMULATIVE NO. OF OBSERVED CASES, Σ	EXPECTED NO. OF CASES (λ = 0.125 • D)	POISSON PROBABILITY, $Pr(x \geq \Sigma)$*
3/31/2005	1	1	1	0.125	.1175
4/30/2005	2	0	1	0.250	.2212
5/31/2005	3	2	3	0.375	.0067
6/30/2005	4	2	5	0.500	1.72×10^{-4}
7/31/2005	5	4	9	0.625	2.3×10^{-8}
8/31/2005	6	6	15	0.750	5.0×10^{-15}

*Probability of observing x or more cases.

Earliest Identification of the Probable Cause of the Outbreak

Table 4 uses the Fisher exact test to examine the statistical significance of the relationship between the use of a ReNu brand solution and the development of *Fusarium* keratitis. The *P* value on May 31, 2005, was .0429, indicating that the *Fusarium* rate was statistically significantly higher for ReNu brand users than for non-ReNu brand users. In Table 5, the odds ratios and 95% CIs (calculated using a +0.5 continuity correction) are shown. By June 30, 2005, the lower limit of the 95% CI first rose above 1.0, reaching 1.15. The analysis shown in Table 6 used whole numbers of cases instead of probabilistically derived fractional cases and assumes that the first 4 cases had been exposed to a non-ReNu brand solution. By August 31, 2005, the lower limit of the 95% CI was above 1.0, at 1.60. Table 7 is a summary of the statistical tests as of August 31, 2005.

TABLE 4. *P* VALUES BY FISHER EXACT TEST (USING THEORETICAL FRACTIONAL CASES)

MONTH ENDING	NO. OF NEW CASES IN CURRENT MONTH	CUMULATIVE NO. OF OBSERVED CASES, Σ	NO. THAT USED ReNu = (62/66) • Σ	NO. THAT DID NOT USE ReNu = (4/66) • Σ	*P* VALUE (FISHER EXACT TEST)
3/31/2005	1	1	0.94	0.06	.35
4/30/2005	0	1	0.94	0.06	.35
5/31/2005	2	3	2.82	0.18	.0429
6/30/2005	2	5	4.70	0.30	.0053
7/31/2005	4	9	8.45	0.55	.0014
8/31/2005	6	15	14.09	0.91	4.18×10^{-6}

TABLE 5. ODDS RATIOS AND 95% CONFIDENCE INTERVALS, USING THEORETICAL FRACTIONAL CASES (CALCULATED USING A +0.5 CONTINUITY CORRECTION)

MONTH ENDING	NO. OF NEW CASES IN CURRENT MONTH	CUMULATIVE NO. OF OBSERVED CASES, Σ	NO. THAT USED ReNu = (62/66) • Σ	NO. THAT DID NOT USE ReNu = (4/66) • Σ	ODDS RATIO	95% CI
3/31/2005	1	1	0.94	0.06	4.77	0.22-104.3
4/30/2005	0	1	0.94	0.06	4.77	0.22-104.6
5/31/2005	2	3	2.82	0.18	9.04	0.67-122.4
6/30/2005	2	5	4.70	0.30	12.0	1.15-126.0
7/31/2005	4	9	8.45	0.55	15.9	2.1-120.6
8/31/2005	6	15	14.09	0.91	19.2	3.4-108.4

TABLE 6. ODDS RATIOS AND 95% CONFIDENCE INTERVALS (ASSUMING THAT THE FIRST FOUR CASES HAD USED A NON-ReNu BRAND CONTACT LENS SOLUTION)

MONTH ENDING	NO. OF NEW CASES IN CURRENT MONTH	CUMULATIVE NO. OF OBSERVED CASES, Σ	NO. THAT USED ReNu	NO. THAT DID NOT USE ReNu	ODDS RATIO	95% CI
3/31/2005	1	1	0	1	0.00	—
4/30/2005	0	1	0	1	0.00	—
5/31/2005	2	3	0	3	0.00	—
6/30/2005	2	5	1	4	0.62	0.10-3.93
7/31/2005	4	9	5	4	2.27	0.65-7.89
8/31/2005	6	15	11	4	4.75	1.60-14.12

TABLE 7. SUMMARY OF STATISTICAL TESTS AS OF AUGUST 31, 2005, SHOWING WITH EXTREMELY HIGH PROBABILITIES THAT AN OUTBREAK WAS PRESENT AND ITS CAUSE WAS A RENU BRAND CONTACT LENS SOLUTION

QUESTION	STATISTICAL TEST	RESULT
Outbreak?	Poisson distribution	$Pr = 5.0\times10^{-15}$
ReNu?	Fisher exact test	$P = 4.18\times10^{-6}$
ReNu?	Odds ratio 95% CI (theoretical)	19.2 3.4-108.3
ReNu?	Odds ratio 95% CI ("biased")	4.75 1.60-14.12

CI, confidence interval; *P*, *P* value; *Pr*, probability.

NEW PREVENTION STRATEGY

Table 8 shows the relationship between the temperature of the oven and the temperature indicated by the thermochromic strip. The Pearson correlation coefficient was .971, and the corresponding *P* value was .0003.

TABLE 8. RELATIONSHIP BETWEEN OVEN AND THERMOCHROMIC STRIP TEMPERATURES IN DEGREES FAHRENHEIT*

OVEN (°F)	STRIP (°F)
120	120
125	120
130	129
135	129
140	140
145	140
150	149

*The Pearson correlation coefficient was .971, and the corresponding *P* value was .0003.

DISCUSSION

In 2004, prior to the release of RML, Leung and coworkers[11] studied the effects of storage temperature on the efficacy of 4 multipurpose contact lens solutions. They noted that the antimicrobial activity toward *Pseudomonas aeruginosa* was adversely affected by higher (30°C [86°F]), lower (4°C [39°F]), or fluctuating temperatures or by the presence of air in the bottle. Similarly, Bullock and associates[7,9] recently noted that when exposed to prolonged temperature elevation (60°C [140°F] for 4 weeks), RML loses its in vitro fungistatic activity, due to antimicrobial failure, to a much greater extent than other products and that improper temperature control of RML may have contributed to the *Fusarium* keratitis epidemic of 2004-2006. Since then, questions have arisen as to whether the *Fusarium* keratitis epidemic could have been prevented, mitigated, or recognized earlier.

Root cause analysis is a problem-solving technique designed to identify key factors in the causation of catastrophic events. It is based on the supposition that preventing future such events is best accomplished by correcting or eliminating as many of their varied causes as possible.[12,13] In the past, this method has been used to analyze the sinking of the RMS *Titanic*,[14] the destruction of the *Challenger*[15,16] space shuttle, and the meltdown of the Chernobyl[17] nuclear reactor, showing that the causes of these disasters went far beyond icebergs, frozen O-rings, and flawed graphite control rods, to include a variety of physical, human, and organizational failures.

A limited tripartite root cause analysis was performed concerning the ReNu-related *Fusarium* keratitis epidemic and included (1) a review of specific FDA documents; (2) a theoretical retrospective statistical analysis of the Singapore outbreak; and (3) the investigation of a new prevention strategy.

The packaging of RML clearly stated "Store at room temperature." The 1997 FDA guidance document clearly predicted elevated temperature–related solution instability.[1] As previously reported by Bullock and associates,[7,9] B&L was cited for inadequacies in temperature control in the production, storage, and transport of their products.

On May 19, 2004, the FDA gave official clearance for B&L to market RML.[2] In this document (FDA K033854), B&L had claimed that RML was substantially equivalent to, among others, their current product, ReNu MultiPlus, despite the fact that it contained 2 major ingredients that had never before been used in a commercially marketed soft contact lens solution[3]: the bisbiguanide antimicrobial agent, alexidine dihydrochloride (previously used in mouthwashes for the treatment of gingivitis and dental plaque[18]) and polyquaternium-10, a moisture-retaining polysaccharide that holds water close to the contact lens surface (previously used in hair care products for reducing static electricity and enhancing the appearance and texture of hair[19]). Polyquaternium-10 is a weakly cationic cellulose derivative that serves as a nutritive media which may facilitate fungal growth, especially at decreasing antimicrobial levels.[20] These 2 new major ingredients may have been essential components of this disaster: the antimicrobial agent, alexidine dihydrochloride, may be thermally labile, and polyquaternium-10 may have served as a nutritive source for the *Fusarium* organisms.

Additional analysis of Form 483 also documented B&L's failure to report to the FDA cases of *Fusarium* keratitis in Hong Kong and Singapore, not reporting to the FDA the removal of RML from the Asian markets, and not performing biocidal testing on samples associated with Asian cases of *Fusarium* keratitis.

A detailed retrospective statistical analysis of the outbreak in Singapore was performed. The specific publication was selected because it represented the best early published data available to epidemiological researchers.[10] The epidemic curve provided the time distribution of the 66 cases. Additional data showed that 62 of the 66 cases had definitely used a ReNu brand product, one had not,

and the other 3 were uncertain of the brand that they had used. Because the most conservative analysis was selected, it was assumed that 4 of the 66 patients had not used a ReNu brand. In addition, it was reported that there were approximately 224,800 (presumably, multipurpose solution utilizing) contact lens wearers in Singapore. Since the ReNu brand had approximately 35% of the market share in Singapore, this number would serve as a proxy[20] for the proportion of ReNu users in the control group, allowing an approximate "back of the envelope" calculation of the odds ratios and 95% CIs for this unmatched case-control study.[21] The last piece of data required was the historic baseline endemic rate of contact lens–related *Fusarium* keratitis in Singapore, reported as "no more than 1-2 cases" per year[10] or .125 cases per month. For this theoretical study, it was assumed that all cases were immediately tabulated upon diagnosis. A new system in Singapore to report rare diseases would have made this assumption a reality.

The earliest identification of the Singapore outbreak was determined using the Poisson distribution. This distribution, discovered by Siméon-Denis Poisson, was first published in his 1837 treatise *Recherches sur la probabilié des jugements en matières criminelles et matière civile* (Research on the Probability of Judgments in Criminal and Civil Matters), in which it was initially applied to jury deliberations.[6] This distribution can also be used to model discrete rare events that take place during a given interval of time. In the present study, it was used to calculate the probability that the cumulative number of observed cases of *Fusarium* keratitis in Singapore, Σ, was merely a chance variation from the expected number, λ. Table 3 shows that by May 31, 2005, the observed number of cases, three, exceeded the expected number, .375, with a Poisson probability of .0067, thus indicating a probable outbreak.

Using the Fisher exact test (Table 4), which examines the statistical significance of the relationship between the use of a ReNu brand solution and the development of *Fusarium* keratitis, the *P* value on May 31, 2005, was .0429, indicating that the *Fusarium* keratitis rate was statistically significantly higher for ReNu users than for non-ReNu users. The data for Table 4 were derived from Table 2, where theoretical fractional cases and controls were probabilistically calculated. These same data were used in Table 5, where the odds ratios and 95% CIs were calculated, again using theoretical fractional numbers of cases and controls. By June 30, 2005, the lower limit of the 95% CI first rose above 1.0, reaching 1.15. Therefore, by June 30, 2005, the cause of the outbreak could have been attributed with 95% confidence to the ReNu brand solutions.

One possible criticism of the data in Tables 4 and 5 is that they were derived "after the fact," that is, at the termination of the epidemic when it was ultimately determined that at least 62 of the 66 patients had used a ReNu brand solution. Yet, the fractions 62/66 and 4/66 were applied from the beginning of the analysis to sort the cases to ReNu use or nonuse. This analysis is still reasonable, since most of the patients had used ReNu. (It was later revealed that the first 13 patients had all, in fact, used RML.[20]) However, in order to overcome this criticism, an additional analysis was performed in Table 6, in which actual whole numbers of cases and controls were used, rather than the probabilistically derived fractional ones. To bias in favor of ReNu, the first 4 cases were assigned to non-ReNu-using status. Thus, by "front-loading" the non-ReNu-using cases, it would now take longer for the actual ReNu-using cases to outweigh the non-ReNu cases and reach statistical significance. However, by August 31, 2005, there were 11 cases assumed to have used ReNu and 4 non-ReNu cases, giving an odds ratio of 4.75, with a 95% CI of 1.60 to 14.12. Thus, in doing this most conservative analysis, by August 31, 2005, at the latest, by using the available data,[10] ReNu would have been implicated as the probable cause of the outbreak, since the lower limit of the 95% CI was above 1.0, at 1.60.

Table 7 is a summary of the statistical data as of August 31, 2005. These show, with extremely high probabilities, that (1) an outbreak was present and (2) its probable cause was the ReNu brand contact lens solution. Since RML was not withdrawn from the world market until May 15, 2006 (at least 8½ months later), it is obvious that many of the cases of blindness in Singapore and around the world could, theoretically, have been prevented if all of the ReNu brand solutions had been removed from the world market on or before August 31, 2005. Further investigation would later have identified RML specifically as the culprit, and the other ReNu product(s) could have then been reintroduced to the market.

Another question that has arisen is whether or not any controls were being implemented for thermal protection of these solutions.[9(p127)] This question stimulated the following investigation. Thermochromism is the ability of a substance to change color due to a change in temperature[22] and is the scientific basis of the once popular "mood ring."[23] Thermochromic paper was invented by the NCR Corporation in Dayton, Ohio, for use in printing cash register receipts.[24] When heated, a microencapsulated dye reacts with an acid and irreversibly shifts to a colored form, typically black. Thermax strips (Tempil, South Plainfield, New Jersey) are a temperature indication technology, commercially available for more than 15 years; the strips change color irreversibly from white to black upon exposure to heat. They are accurate to within ±2% of the rated temperature (Pramathesh Desai, Tempil, personal communication, February 27, 2009). When these strips were applied to cartons of bottles of contact lens solution that were then heated, the strips changed color irreversibly, thus indicating heat exposure. The present experimental study demonstrated a high degree of correlation between the temperature indicated by the strip and the oven temperature (measured using a thermometer) to which the contact lens solution bottles had been exposed. (The Pearson correlation coefficient was .971, and the corresponding *P* value was .0003.) Had this safety feature been applied to cartons of solution bottles of B&L's RML, this would have provided a warning that the bottles may be unsafe. Monothermic labels (Figure 3) indicate exposure to just one temperature (Series 21 Tempilabel, TLL-21-100 to TLL-21-140; Tempil, South Plainfield, New Jersey) and cost $217.30 per 1,000 labels (Pramathesh Desai, Tempil, personal communication, March 23, 2009). If a monothermic label, sensitive to a temperature determined to be just below the failure threshold temperature of RML, had been applied to the outer surface of each 12-count carton of bottles, then the additional cost of this safety feature would have been only 1.8 cents per bottle. While even a brief exposure to elevated temperature will produce a color change in the thermochromic label, and prolonged temperature exposure may be required to inactivate the antimicrobial agent, alexidine, it would have been best to err on the side of safety and discard thermally exposed bottles rather than risk *Fusarium* keratitis.

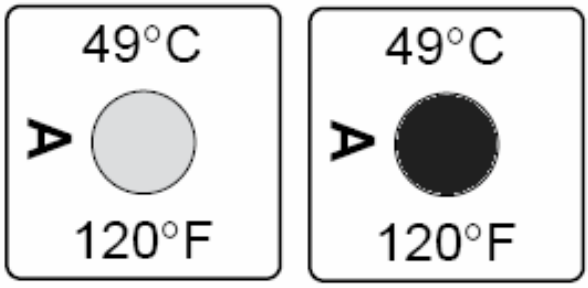

FIGURE 3

Monothermic label. Left, Control (room temperature). Right, Label exposed to 120ºF, showing color change from white to black.

Could the *Fusarium* keratitis epidemic have been prevented? Based on the present analysis, the answer, in the author's opinion, is certainly yes, with much more rigorous oversight by the FDA's approval process, by strict adherence to package instructions and FDA guidelines, by providing temperature-controlled factories, storage areas, and cargo trucks and ships, and by the use of thermochromic labels. Additionally, the FDA needs to mandate much more comprehensive storage time and temperature studies on potentially thermally labile pharmaceuticals. Could the epidemic, and its cause, have been recognized earlier? The answer, in the author's opinion, is, again, yes, by B&L's strict adherence to the FDA's reporting and testing regulations, by a better system of compiling and reporting rare diseases (such as *Fusarium* keratitis) immediately upon diagnosis, and by the application of basic statistical methods to the collected data.

Thus, the lessons learned from a root cause analysis of this pharmacologic catastrophy may help avert or mitigate future epidemics.

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PEER DISCUSSION

DR. EDUARDO C. ALFONSO: This paper addresses the outbreak of *Fusarium* keratitis in contact lens wearers that occurred on a worldwide basis in 2004-2006. The goals of the author were to determine if the outbreak and its cause could have been recognized earlier. It also attempts to delineate a strategy, which could have been used to prevent or contain this epidemic. The author reviewed the 1997 FDA guidelines concerning storage temperatures of contact lens care products that warned about temperature-related solution instability. It also reviewed the 510k (KO33854) document in which Bausch & Lomb claimed that the Renu with MoistureLoc™ was equivalent to Renu Multi-Plus™ even though it contained two new ingredients. These ingredients were alexidine dihydrochloride, which is an antimicrobial antiseptic and polyquaternium-10, which is a polysaccharide wetting agent that helps recoat the contact lens for increased patient comfort. The author references his prior publication that explains how the alexidine dihydrochloride could be destabilized by higher temperatures, thus allowing organisms to grow and feed on the polysaccharide wetting agent polyquartinium-10. In addition, the author reviewed FDA Form 483, which states that Bausch & Lomb did not report to the FDA, as required, cases of Renu-related *Fusarium* keratitis from Hong Kong and Singapore and failed to report the removal of the product from the Asian markets. It also failed to perform biocidal testing on samples associated with Asian cases of *Fusarium* keratitis.

Dr. Bullock undertook epidemiological and statistical analyses on the outbreak of *Fusarium* keratitis in Singapore. With this analysis, it is theorized that the epidemic could have been predicted after recognition of 3, 5, or 15 cases depending upon which statistical method is utilized. He concludes that the epidemic could thus have been predicted 8.5 months before Bausch & Lomb eventually removed the product from the marketplace. In addition, the author presents information on a system using thermochromic labels that can irreversibly change color when exposed to elevated temperatures, thus warning of how elevations in temperature could have destabilized the antiseptic and thus lead to failure in antimicrobial coverage of the multipurpose solution ReNu MoistureLoc™.

This paper is an indictment of the inability of a company to prevent and contain a problem with one of its products by not adhering to FDA and manufacturing guidelines. It points out the difficulties of the FDA in monitoring its product approval process and lack of post-marketing product surveillance. In addition, this work points to the inability to minimize damage when a medical product or device is defective. In the United States, we do not have adequate surveillance mechanisms to detect an increase in infections unless voluntary reporting takes place. There is no mandatory reporting mechanisms for contact lens related infections. This presents a problem when considering that there are over 30 million soft contact lens wearers in the United States.[1] The epidemic in the United States did show how the CDC was able to conduct a case control study within one week[1]. The American Journal of Ophthalmology and the Archives of Ophthalmology were willing to expedite publications related to this epidemic in order to alert the ophthalmology profession of the potential dangers of contact lens wear and the use of these products[2, 3]. In addition, the lay media was responsive to request for voluntary dissemination of the problem. I congratulate Dr. Bullock for his excellent work in this subject area and bringing to light very important concepts regarding root cause analyses of this epidemic outbreak. The FDA now has a web-based voluntary incident reporting mechanism for contact lens complications (http://www.fda.gov/cdrh/contactlenses).

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DR. RICHARD K. FORSTER: No conflict of interest. It has been said by many that "we see what we know, but we do not see what we do not know". After this epidemic I tried to look back at cases of fungal keratitis that had presented in the six months or so prior to the epidemic. In our institution, 16% to 18% of all corneal ulcers are due to fungi and we expect them, but we also have noted that there are seasonal fluctuations in the prevalence of this disease. I questioned myself and said, "gee, why didn't I recognize these cases before the published epidemic?" Although Eddie Alfonso did not mention this in his discussion, prior to this epidemic only 3% of our fungal ulcers were seen in patients wearing contact lenses. In contrast, during the epidemic, the incidence of fungal keratitis associated with contact lens wear was closer to 20%, so we perhaps should have recognized this event earlier, but when these cases present sporadically I think by human nature we do not recognize the problem.

DR. MALCOLM R. ING: John, I really appreciate your paper. I wanted your thoughts on particular scenario. Many patients wear contact lenses into swimming pools. This is one of the reasons they actually say "I have to get my lenses so I can go diving" or "I want to go swimming". Does any study show that the common disinfectants used in the better disinfectants for contact lenses are efficient in removing the bacteria that you might find in swimming pools? In other words, this is a preventive kind of question and do you know anything about that subject?

DR. PENNY A. ASBELL: It was a great paper and presentation of the information. I think it leads to a possible role of the American Academy of Ophthalmology in alerting physicians who have a responsibility and a role in letting people know about cases that are unusual or serious infections, or side effects from treatment. They do not really know how to report it and they do not know to whom it should be reported. It must be easy and quick. We have talked about a web based system that is available and should be used when appropriate to alert physicians.

DR. JOHN D. BULLOCK: Thank you very much to all the discussants. I greatly appreciate Dr. Alfonso's insightful primary discussion. Dr. Forster mentioned the difficulty in noticing a difference between 3% versus 20% contact lens wear in his recent patients with *Fusarium* infections. I believe that in my case, I was so inexperienced with fungal keratitis that this is what allowed me to recognize this epidemic. Actually, I had seen only one other patient with *Fusarium* keratitis in my whole career in private practice. This infection occurred in a non-contact lens wearing woman with massive bilateral orbital amyloidosis and exposure keratopathy, who was referred to me for bilateral orbital decompressions. We have two excellent corneal specialists in the Dayton area, so corneal ulcers are typically seen by them.

In early March 2006; however, when I was visiting my former office my antennae immediately went up when I learned that an optometrist whom I had hired 25 years earlier was actually one of the two Dayton *Fusarium* patients. Then he told me that there was another patient, an intensive care unit nurse, who had just come in a few days after his infection, who also had a fungal corneal ulcer. So then I knew that something was awry. Dr. Ronald Warwar and I went on the internet and found the report from Singapore. It turned out that both of Dr. Warwar's patients had grown a *Fusarium* and both patients had used a ReNu^{TM}contact lens solution. Dr. Forster, I guess that when you are being inundated with cases, it is much harder to recognize a pattern.

Concerning Dr. Ing's, comment about the swimming pool and contact lens wear, I think that there are probably a lot of other people in this audience who would be much better qualified to answer that question. The third question was Dr. Asbell's comment about reporting difficulties. I agree with her completely. In an ideal world, you would have a computer in every microbiology or pathology laboratory and every diagnosis would be entered automatically. As I reported in my recent paper in *Cornea* (2008;27:1013-1017), you could know when there was an outbreak versus the routine historical baseline endemic rate for a number of different conditions by using the Poisson distribution. Thank you.