

**ALTERNATIVE APPROACHES FOR ESTIMATING
HEALTH-RELATED QUALITY OF LIFE IMPACTS:**

JUICE PROCESSING REGULATION CASE STUDY

Prepared for:

Committee to Evaluate Measures of Health Benefits
for Environmental, Health, and Safety Regulation
Institute of Medicine
500 Fifth Street, NW
Washington, DC 20001

Prepared by:

Lisa A. Robinson, Independent Consultant
Wilhelmine Miller, Institute of Medicine
Robert Black, Independent Consultant

IOM Committee Advisors:

Alan Garber (Lead)
Judith Wagner

Other Advisors:

Clark Nardinelli, Food and Drug Administration
Sajal Chattopadhyay, Centers for Disease Control and Prevention

**FINAL REPORT
DECEMBER 2005**

PREFACE

This case study was one of three developed to support the work of the Institute of Medicine's Committee to Evaluate Measures of Health Benefits for Environmental, Health, and Safety Regulation. The Committee's summary of this case study, as well as the results of its other investigations and deliberations, is provided in its final report, *Valuing Health in Regulatory Cost-Effectiveness Analysis (2006)*.

This more detailed version of the case study contains additional information that may be of interest to regulatory analysts and other researchers. However, it was largely completed prior to the articulation of the Committee's conclusions and recommendations and thus does not reflect all of the views presented in the Committee's final report.

The case studies were undertaken as a learning experience, to provide the Committee with information on the challenges associated with applying different health-related effectiveness measures in a regulatory context. Due to time and budget limitations, they do not replicate the full complexity and level of detail required for regulatory analysis under current government-wide guidance or under the Committee's final recommendations. The case studies relied extensively on the voluntary efforts of many individuals.

ACKNOWLEDGEMENTS

This case study could not have been completed without the hard work and dedication of a number of volunteers. The Committee is grateful for the extensive efforts of those who assisted in its completion, which contributed enormously to the Committee's understanding of the challenges and opportunities associated with conducting cost-effectiveness analysis in a regulatory context.

Lead authors: Lisa A. Robinson, Independent Consultant; Wilhelmine Miller, Institute of Medicine; Robert Black, Independent Consultant.

IOM Committee advisors: Alan Garber (lead); Judith Wagner.

Other advisors: Clark Nardinelli, Food and Drug Administration; Sajal Chattopadhyay, Centers for Disease Control and Prevention.

Contributors: John Anderson, University of California, San Diego; Barbara Altman, National Center for Health Statistics; Fred Angulo, Centers for Disease Control and Prevention; Lawrence Deyton, M.D., Veteran's Administration; Sherine Gabriel, M.D., Mayo Clinic; Janel Hanmer, University of Wisconsin-Madison; William Lawrence, M.D., Agency for Healthcare Research and Quality; Gwen Wanger, M.D., Beth Israel Deaconess Medical Center.

Expert application of generic indices: *Infectious disease* -- Claire Panosian, M.D., David Geffen School of Medicine, UCLA; David A. Pegues, M.D., David Geffen School of Medicine, UCLA; Matthew Leibowitz, M.D., David Geffen School of Medicine, UCLA; Glenn Mathisen, M.D., Olive View-UCLA Medical Center; Sherwood L. Gorbach, M.D., Tufts New England Medical Center; David R. Snyderman, M.D., Tufts New England Medical Center; Mark Holodniy, M.D., Veteran's Administration Palo Alto Health Care System; Victoria Davey, R.N., M.P.H., U.S. Department of Veterans Affairs. *Rheumatology* -- Lenore Buckley, M.D., Virginia Commonwealth University School of Medicine; Gene G. Hunder, M.D., Mayo Clinic (retired); Eric L. Matteson, M.D., Mayo Clinic College of Medicine; Daniel H. Solomon, M.D., Harvard Medical School; Elizabeth A. Tindall, M.D., Oregon Health and Science University.

TABLE OF CONTENTS

SECTION 1.0: INTRODUCTION	4
SECTION 2.0: FDA ANALYSIS	6
2.1 Cost Analysis	6
2.2 Risk Assessment	7
2.3 Benefit Valuation.....	9
SECTION 3.0: CASE STUDY APPROACH.....	14
3.1 Disease Descriptions	14
3.2 Expert Assignment	17
3.3 Comparison to Normal Health.....	19
3.3.1 Calculation of Weighted Values for Pathogen-Related Illness.....	19
3.3.2 HRQL in the Absence of Pathogen-Related Illness.....	20
SECTION 4.0: RESULTS OF CASE STUDY ANALYSIS	24
4.1 Expert Assignment of Attribute Levels	24
4.2 HRQL With and Without the Condition.....	31
4.3 Calculation of Cost-Effectiveness.....	35
SECTION 5.0: LIMITATIONS.....	38
5.2 Comments from Experts Involved in the HRQL Assessment	38
5.3 Implications of Key Uncertainties	40
REFERENCES	42
APPENDIX A: FDA QWB ASSESSMENT.....	43
APPENDIX B: DOMAIN AND ATTRIBUTE DESCRIPTIONS FOR EACH INDEX	46

SECTION 1.0: INTRODUCTION

The Institute of Medicine's (IOM's) Committee to Evaluate Measures of Health Benefits for Environmental, Health, and Safety Regulation commissioned three case studies as part of its investigations related to the use of cost-effectiveness analysis to assess the impacts of economically significant federal health and safety regulations. These case studies allowed the Committee to explore the application of alternative approaches to estimating health-related quality of life (HRQL) impacts in the regulatory context, and were one of many inputs into its deliberations.

This report provides a detailed account of the Committee's second case study, which addresses the U.S. Food and Drug Administration's (FDA's) 2001 juice processing rule. We selected this regulation as one of the Committee's case studies because it allowed us to examine the effects of applying different measures to both short-lived, acute illnesses and lifelong chronic illnesses. It also provided an example of current agency practices for using monetized HRQL estimates in benefit-cost analysis.

We compared the FDA benefit values to those that result under four generic indices: the EuroQol EQ-5D, the Health Utility Index (HUI) Mark 3, the Standard Form SF-6D, and the Quality of Well-Being (QWB) index. In this case study, we asked clinical experts to match the characteristics of each health outcome to the attribute levels used under each index. We then weighted the results to determine the value of each health effect under each index, based on the surveys of community preferences associated with each of the generic indices. This weighting process arrays the values on a scale anchored at zero and one, where zero corresponds to death and one corresponds to perfect or optimal health.

In the case study, we focus on annual impacts for simplicity and comparability, assessing the change in disease incidence attributable to a single year of the regulatory intervention. The new cases prevented each year will have longer term impacts, however, if the health effect is chronic or long-lived. We take these future year impacts into account, using discounting to reflect the timing of the impacts. Agency regulatory analyses generally take a longer term view and assess the impacts of the rulemaking over a multi-year period as well as on an annual basis.

This case study was developed as a learning experience for the Committee, and provided an opportunity to use the information available to regulatory analysts to develop different effectiveness measures. Due to time and budget limitations, it does not replicate the full complexity of FDA's regulatory analysis. It involves the use of simplified analytic approaches and assumptions and relies largely on mean or median estimates, providing only limited information on the range of possible values and the distribution of impacts across population subgroups. In these and other respects, the case study does not fully adhere to the existing guidelines for regulatory analysis nor to the recommendations developed by the IOM Committee. The lessons learned from this case study are discussed in the Committee's report.

The following sections describe our analytic approach and findings in detail; a summary of this case study is available in Appendix A of the Committee's final report. First, we summarize the original FDA regulatory analysis. Next, we discuss our analytic approach in

detail. The following section presents the results, and the last section then discusses the limitations of our analysis. The appendices provide supplementary information on selected aspects of the analysis.

SECTION 2.0: FDA ANALYSIS

This case study is based on a 2001 juice processing rule developed by FDA to enhance the safe and sanitary processing and import of fruit and vegetable juices. The rule requires processors to apply Hazard Analysis and Critical Control Point (HACCP) principles, which provide a systematic, preventive approach to addressing foodborne illness. It sets a performance standard for reducing microbial pathogens that industry can meet through pasteurization or other treatment methods; the standard is phased-in over a three year period.

These standards are authorized primarily under Section 402 of the Federal Food, Drug and Cosmetic Act, which allows regulation of food that contains hazardous substances. FDA also relies on authority under the Public Health Service Act, which supports regulation of activities that would otherwise allow disease transmission across state lines.

FDA first proposed the juice processing rule in the April 24, 1998 *Federal Register*, and soon after published its detailed preliminary regulatory impact analysis in the May 1, 1998 *Federal Register*. The preliminary analysis addresses both the juice processing rule and a related juice labeling rule, providing detailed discussion of FDA's approach for assessing both costs and benefits. FDA's quantitative analysis considers only the provisions of the two proposed rules. Several other options, that vary in terms of the characteristics of the juice processors covered and the nature of the regulatory requirements (including the "no action" alternative), are discussed qualitatively.

In January 2001, FDA promulgated the final juice processing rule, accompanied by an updated assessment of its costs and benefits. (The related rule on labeling untreated juice was finalized in July 1998 as an interim protective measure.) FDA's analysis of the final rule differs from the proposal due to changes in the methodology and data sources used as well as changes in the regulatory requirements. However, the basic approach for valuing benefits was not altered. The 2001 assessment quantifies the benefits and costs of the final rule only; other regulatory options are again discussed qualitatively.

The following sections briefly summarize FDA's approach for assessing costs, estimating risk reductions, and valuing benefits for the proposed and final rules, based on information in the key FDA documents: the 1998 preliminary regulatory impact analysis and the 2001 preamble to the final rule (FDA 1998, 2001).

2.1 Cost Analysis

To determine the costs of the regulations, FDA first estimated the costs per processing plant for each component of the rulemaking. Varying cost estimates were used depending on current practices, products, production duration, and plant size. FDA then multiplied these estimates by the number of plants nationwide to determine the total costs of the rule. The agency separately estimated the first year costs of rule implementation and the subsequent recurring costs. In its preliminary regulatory analysis, FDA used a probabilistic (Monte Carlo) analysis to address uncertainty in the estimates of the initial costs of installing and using pasteurization

processes. FDA also considered the impact of the rule on small juice processors as required under the Regulatory Flexibility Act as amended by the Small Business Regulatory Enforcement Fairness Act.

In its 2001 analysis of the final rule, FDA indicated that first year costs would range from \$44 to \$58 million. This range reflected uncertainty regarding the costs of pathogen-related controls, which account for more than half the costs of the rule. In the subsequent years of the program, FDA expected costs to total \$23 million annually. Over time, FDA estimated that the present value of these costs (discounted at 7 percent over an infinite time horizon) would be about \$400 million.¹

This estimate may overstate actual costs to some (unknown) extent, since certain types of counterbalancing savings were not included. In the 2001 notice, FDA noted that offsetting cost-savings (such as increased firm goodwill) were not quantified.² Earlier, in the 1998 preliminary analysis, FDA also discussed other cost-savings related to government enforcement, increased firm efficiency, and increased product shelf life.

2.2 Risk Assessment

In its benefit analysis, FDA focused on the health impacts that were most significant in terms of severity and probability of occurrence, considering illnesses associated with four microbial pathogens: *Bacillus cereus*, *Cryptosporidium parvum*, *Escherichia coli* O157:H7, and *Salmonella (non typhi)*.³ The effects of these pathogens include infections that result in gastrointestinal illness and reactive arthritis. Most effects are short-lived, although in a small number of cases the infection may lead to chronic illness or death. FDA categorized these effects in terms of duration (i.e., average days of illness) and severity (i.e., mild, moderate, severe), considering whether the patient is likely to seek medical attention and/or be hospitalized. FDA's severity categories and average duration estimates are summarized in Exhibit 1.

¹ At the time that the FDA analysis was completed, the U.S. Office of Management and Budget (OMB) recommended use of a 7 percent discount rate. This guidance was changed in September 2003, and OMB now recommends that agencies report the results using both 7 and 3 percent rates (OMB 2003) as well as indicate the timing of the undiscounted results.

² Whether such savings are counted on the cost or benefit side of the analysis varies across agencies; FDA included such savings in its discussion of benefits. However, for consistency with other case studies, we consider any savings related to industry compliance or government enforcement as offsets to costs.

³ FDA noted that the benefits of reducing exposure to other pathogens and pesticide residues are not quantified.

Exhibit 1	
TYPES AND DURATIONS OF MICROBIAL HAZARDS IN JUICE	
Endpoint	Duration^{1,2}
<i>Bacillus cereus</i> Mild Moderate Severe Death	0.75 days 1.0 days N/A N/A
<i>Cryptosporidium parvum</i> Mild Moderate Severe Death	9 days 17 days 24 days N/A
<i>Escherichia coli</i> O157:H7 Mild Moderate Severe-acute ³ Severe-chronic ³ Death	5 days 9 days 32 days 26,645 days (73 years) N/A
<i>Salmonella (non typhi)</i> Mild Moderate Severe Reactive arthritis –short-term Reactive arthritis –long-term ⁴ Death	2 days 5 days 17 days 25 days 18,250 days (50 years) N/A
<p>Source: FDA 1998, pp. 24259, 24267.</p> <p>Notes:</p> <p>N/A = not applicable</p> <p>1. Some cases are sequential; e.g., acute cases may be followed by chronic cases and/or death.</p> <p>2. FDA assumed that long-term effects would last from the age at incidence to the end of an average, normal life span (i.e., 77 years). FDA estimated that average age at incidence would be four years for severe, chronic <i>E. coli</i> infections and 27 years for long-term reactive arthritis and other nonfatal effects associated with <i>Salmonella</i> (FDA 1998, pp. 24259, 24295). Otherwise, FDA assumed that the average age of the affected individuals would be the same as the U.S. population average, which was 36 in 2000 (emails from Clark Nardinelli to Lisa Robinson, March 1 and 3, 2005).</p> <p>3. FDA expected that the severe acute and chronic cases associated with <i>E. coli</i> would result in acute hemorrhagic colitis (80 percent of all cases) or acute hemolytic uremic syndrome (20 percent of all cases) (FDA 1998, pp. 24262, 24344).</p> <p>4. FDA expected that the long-term cases of reactive arthritis associated with <i>Salmonella</i> would vary in severity. Of the total, 55.2 percent were expected to involve flares and remissions of pain with periods of wellness, 22.4 percent were expected to involve waxing and waning of pain with no periods of wellness, and 22.4 percent were expected to involve chronic, unremitting pain (FDA 1998, pp 24294-24295).</p>	

As indicated by the exhibit, most of the health effects associated with these pathogens were expected to last for only a few days on average. For these short-lived health effects, FDA assumed that the average age at incidence would be 27 for *Salmonella*-related infections. For the acute endpoints related to other pathogens, FDA assumed that average age at incidence would be the same as the U.S. population average, which was 36 in the year 2000 (Census 2004).

For all of the longer term health effects, FDA assumed that the impacts will be lifelong. FDA used the U.S. average life expectancy (77 years) in assessing the duration of these conditions. The long-term effects include severe, chronic infections associated with *E. coli*, which FDA assumed would begin, on average, at age four. For cases of long-term reactive arthritis, FDA assumed that they would begin, on average, at age 27. For fatal cases, FDA assumed that the average affected individual would die at age 36, and would have otherwise lived with certainty until age 77.⁴

The longer term health conditions vary in their impacts. For severe, acute and chronic infections associated with *E. coli*, FDA estimated that the infection would lead to acute hemorrhagic colitis in 80 percent of the cases, or acute hemolytic uremic syndrome (HUS) in 20 percent of all cases. For long-term reactive arthritis, FDA expected that the cases would vary in severity; more than half were expected to involve periods of wellness, while the remainder were expected to result in more constant problems.

To estimate the number of cases averted by the regulations, FDA first determined the number of reported confirmed cases of each type, based on data from nine apple and orange juice outbreaks that occurred between 1992 and 2000. FDA then applied multipliers to these estimates to adjust for underreporting. (FDA assessed uncertainty in the estimates of underreporting in its preliminary 1998 analysis). In its analysis for the final 2001 juice processing rule, FDA netted out the effects of the earlier labeling rule from its results, and then estimated the likely effectiveness of the processing rule in preventing the remaining cases.

2.3 Benefit Valuation

To determine the value of averting these health effects, FDA considered: (1) the utility loss associated with the symptoms, (2) the utility loss associated with changes in functional status, and (3) the societal costs associated with medical treatment.⁵ FDA developed estimates for the two categories of utility loss by applying the QWB index to calculate quality adjusted life days (QALDs) for survivors. Utility losses for fatal cases were valued using estimates of the value of statistical life (VSL), rather than by adding estimates of life years lost to the QWB results for nonfatal effects.⁶

⁴ For comparability to the original FDA results, we use the FDA approach to assessing life expectancy in this case study, which uses a single average value. The other IOM case studies provide examples of an alternative (and preferable) approach that uses estimates of conditional survival rates, that take into account the likelihood of dying at each year of age.

⁵ We use the term “utility” in this section as it is used in the FDA analysis. Welfare economists apply this term when discussing the level of individual satisfaction or well-being. However, the QWB and other HRQL indices are consistent with the tenets underlying utility theory only under very restrictive assumptions.

⁶ The value of statistical life refers to the value of small changes in mortality risk spread throughout a large population; e.g., an 1 in 10,000 change in an individual’s risk of preventable mortality. It is the sum of what individuals are willing and able to pay to for risk reductions that total one statistical life, not the value of saving the life of an identifiable individual.

To value nonfatal cases, FDA staff first reviewed the QWB symptom/problem codes (that describe different types and severities of pain and discomfort) and functional status codes (that address changes in mobility as well as the ability to pursue other physical activities and to engage in social activities) and applied the relevant codes to each of the health endpoints of concern. The specific codes selected by FDA staff are provided in Appendix A of this report. FDA then weighted these results to determine the combined effects of these attributes on HRQL. As discussed in more detail in Section 3.3, this weighting process places the values on a scale anchored at zero and one, where zero corresponds to death and one corresponds to perfect or optimal health. FDA then multiplied the weighted values by the duration of each health condition to determine the QALDs associated with each averted case. FDA then multiplied the QALD results by the number of cases avoided to determine the utility losses averted by the rule.

FDA valued a QALD in perfect health at \$630, and used the QALD results for each nonfatal health endpoint to adjust this value downwards to reflect the decrement in health attributable to each condition. The starting point for this dollar value was FDA's VSL estimate (\$5,000,000 per fatality avoided), which FDA annualized at a seven percent discount rate to estimate the value of a statistical life year (VSLY) at \$230,000. FDA then divided the VSLY estimate by 365 days to determine the value of a day in perfect health (i.e., \$630).⁷ For nonfatal cases, FDA added the avoided medical costs of illness to the monetized value of averted QALD losses to estimate the total dollar value of benefits per case. FDA then added the VSL estimates for fatal cases to the values for nonfatal cases to determine the overall benefits of the regulations.

The per case values used in FDA's analysis are provided in Exhibit 2 below. As indicated by the exhibit, the monetized HRQL impacts are greater than medical costs in all cases, often by significant amounts. The values for fatal cases are far larger than the values for nonfatal cases, and the values for chronic or long-term nonfatal cases are larger than the values for short-term effects often by two or more orders of magnitude.

⁷ In other words, if a day with the illness resulted in a 60 percent loss in the quality of life (as measured by the QWB), then the value of that daily loss would be \$378 ($\630×60 percent).

Exhibit 2				
FDA ESTIMATES OF PER CASE VALUES (dollar year not reported)				
Endpoint	Utility Losses for Survivors (QALDs)	Value of Utility Losses (monetized QALDs)	Medical Costs	Total Monetary Value
<i>B. cereus</i>				
Mild	0.4	\$300	\$0	\$300
Moderate	0.5	300	100	400
Severe	0	0	0	0
Death	N/A	5,000,000	N/A	5,000,000
<i>C. parvum</i>				
Mild	3.6	\$2,300	\$0	\$2,000
Moderate	6.7	4,200	400	5,000
Severe	14.7	9,300	8,300	18,000
Death	N/A	5,000,000	N/A	5,000,000
<i>E. coli</i> O157:H7				
Mild	2.8	\$1,800	\$0	\$2,000
Moderate	5.3	3,300	200	4,000
Severe-acute	27.8	17,200	16,000	33,000
Severe-chronic	11,907.7	995,700	225,000	1,221,000
Death	N/A	5,000,000	N/A	5,000,000
<i>Salmonella (non typhi)</i>				
Mild	1.1	\$700	\$200	\$1,000
Moderate	2.6	1,600	800	2,000
Severe	10.6	6,700	9,100	16,000
Reactive arthritis –short-term	10.8	6,800	100	7,000
Reactive arthritis –long-term	5,223.2	970,000	5,860	976,000
Death	N/A	5,000,000	N/A	5,000,000
Source: FDA 1998, pp. 24261 and 24267				
Notes:				
Utility losses for nonfatal cases were valued at \$630 per QALD; fatal effects were valued at \$5,000,000 per case.				
Dollar values were rounded to nearest \$100 in source document; other discrepancies in values were not discussed.				
FDA discounted long-term effects at a 7 percent rate.				

The results of FDA’s benefit analysis for the final rule are summarized in Exhibit 3. As indicated by the exhibit, FDA estimated that the majority of the cases avoided would be mild, but that the dollar value of the overall benefits would be determined largely by the effects of averting long-term cases of reactive arthritis. On an annual basis, the benefit estimates totaled \$151 million. Over the long run, FDA estimated that monetized benefits would total about \$2 billion (discounted at a seven percent annual rate over an infinite time horizon).

Exhibit 3		
FDA ESTIMATES OF ANNUAL QUANTIFIED AND MONETIZED BENEFITS (dollar year not reported)		
Endpoint	Avoided Incidence (cases/year)	Monetary Value (QALD losses + medical costs)
<i>B. cereus</i>		
Mild	340	\$102,000
Moderate	<0.1	---
Severe	0.3	---
Death	<u>0</u>	<u>---</u>
Subtotal	340	\$102,000
<i>C. parvum</i>		
Mild	2,890	\$5,780,000
Moderate	290	1,450,000
Severe	20	360,000
Death	<u>1</u>	<u>5,000,000</u>
Subtotal	3,200	\$12,590,000
<i>E. coli</i> O157:H7		
Mild	95	\$190,000
Moderate	60	240,000
Severe-acute	5	165,000
Severe-chronic	10	12,210,000
Death	<u><0.1</u>	<u>---</u>
Subtotal	160	\$12,805,000
<i>Salmonella (non typhi)</i>		
Mild	1,590	\$1,590,000
Moderate	730	1,460,000
Severe	20	320,000
Reactive arthritis –short-term	50	350,000
Reactive arthritis –long-term	120	117,120,000
Death	<u>1</u>	<u>5,000,000</u>
Subtotal	2,340	\$125,840,000
Monetized Total	6,040	\$151,337,000
Source: FDA 2001, pp. 6183-6184		
Note:		
Detailed estimates of incidence do not add to total cases in source document, due to largely to deliberate double counting of cases that begin as acute and become chronic or long-term.		
FDA discounted estimates of long-term effects at seven percent.		

As indicated by the exhibit, FDA estimated that benefits would total about \$151 million on an annual basis, compared to recurring costs of \$23 million. Hence the results of the analysis indicate that monetized net benefits (benefits minus recurring costs) would equal approximately

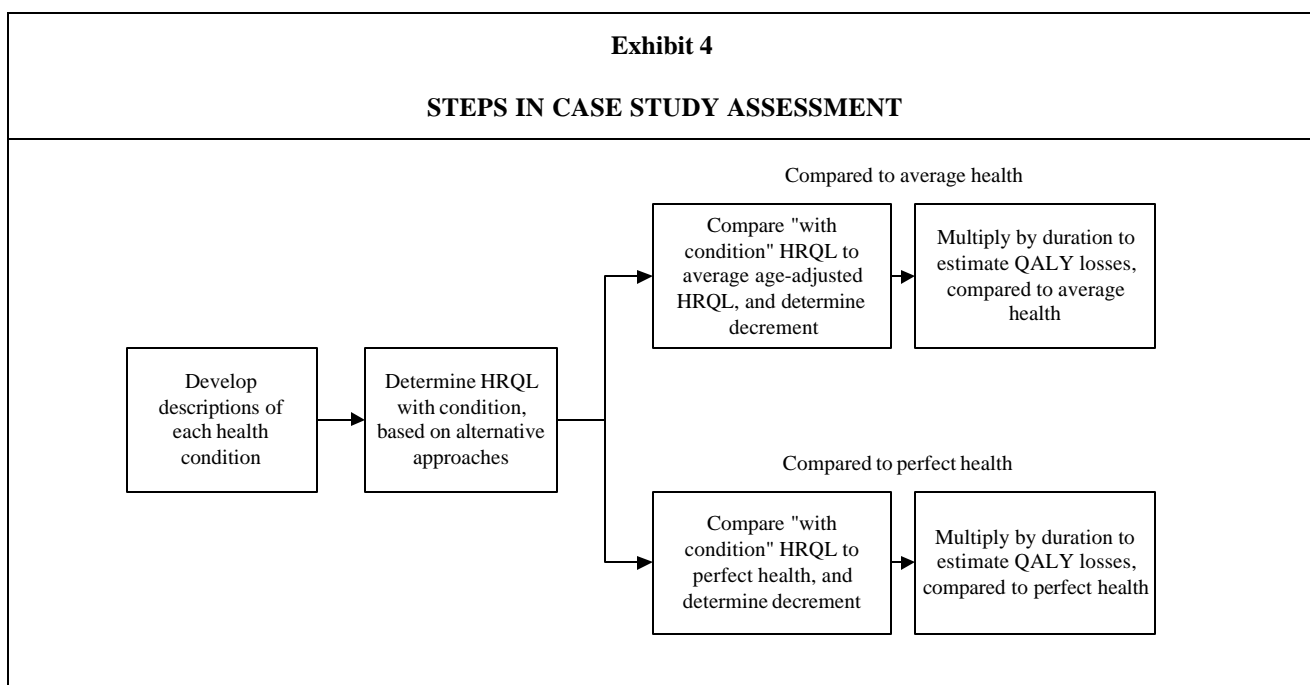
\$128 million per year.⁸ Over the long run, the present value of these net benefits totaled \$1.6 billion using a seven percent discount rate. As noted earlier, certain costs and savings as well as other possible health effects (such as those related to exposure to other pathogens and contaminants such as pesticides) were not included in these quantified estimates.

⁸ FDA's calculation excluded first year costs, which were estimated as \$44 to \$58 million, the mid-point of which is equivalent to roughly \$5 million per year if annualized at a seven percent discount rate.

SECTION 3.0: CASE STUDY APPROACH

To estimate the gains in HRQL and longevity attributable to the juice processing rule under different approaches, the IOM case study team followed a process that included three major components. First, we developed descriptions of each pathogen-related illness based on the materials provided by FDA. Second, we asked clinical medical experts to determine the attribute levels that best match the likely impacts of each illness, as defined under each of the four generic HRQL indices considered. Third, we weighted the resulting values under each index (based on the survey of community preferences associated with each index) to estimate the total HRQL impact of each health condition. We then determined the difference between HRQL with and without the illness under two scenarios: one compared to average population health (adjusted for age), and one compared to perfect health. We then multiplied the resulting decrement by the expected duration of each illness, taking longevity into account. In this analysis, we use the FDA approach for expressing impacts as QALDs, but then convert our results to the more commonly used measure of quality adjusted life years (QALYs).

This process is illustrated in Exhibit 4. These steps are discussed in more detail below.



3.1 Disease Descriptions

The first step in the case study analysis involved developing disease descriptions that could be scored under the alternative HRQL approaches. For consistency with the FDA analysis, we based these descriptions solely on information provided by FDA (especially two detailed appendices to the 1998 preliminary regulatory impact analysis) and did not update them to reflect more recent information. Developing these descriptions requiring addressing several complex issues.

First, we were uncertain about the appropriate level of detail to include in the descriptions, and lacked the time and resources needed to address this concern through formal pre-testing of the definitions. Our goal was to enable the experts to understand, and distinguish between, the different FDA endpoints (listed in Exhibit 1 above) without providing an overwhelming amount of information, since these experts presumably have a good understanding of the health effects from their medical training and experience. Second, we wanted to avoid using language in the descriptions that could prejudice the assignment of the attributes under each index; e.g., that indicates functional limitations or other HRQL impacts. We found it hard to avoid this language completely because in some cases it was part of the characteristics FDA used to distinguish between the endpoints. For example, FDA distinguishes between different types of long-term reactive arthritis based in part on the pain experienced, and pain is one of the domains covered by the indices.

Finally, the FDA definitions of the health endpoints are for statistical (or “average”) cases rather than for individual, identifiable patients, and cover time periods over which HRQL impacts may vary.⁹ Hence we needed to encourage the experts to consider the average patient with each pathogen-related illness and to assess the expected average impact of the illness over time.¹⁰ In some cases, we used information provided in the FDA analysis to split the endpoints into subcategories, to better distinguish between differences in the likely impacts. More specifically, for severe (acute and chronic) cases of *E. coli*, we distinguished between cases resulting in acute hemorrhagic colitis (80 percent of all cases) and HUS (20 percent). For the *Salmonella*-related long-term cases of reactive arthritis, we distinguished between cases expected to involve flares and remissions of pain with periods of wellness (55.2 percent), cases expected to involve waxing and waning of pain with no periods of wellness (22.4 percent), and cases expected to involve chronic, unremitting pain (22.4 percent).

The resulting disease descriptions are provided in Exhibit 5 below.¹¹ These descriptions cover 13 categories of infections that address the FDA endpoints with one or more than one case averted (see Exhibit 3), splitting the severe cases associated with *E. coli* into the subcategories described above. In addition, they cover four *Salmonella*-related reactive arthritis endpoints, splitting the long-term cases into subcategories depending on severity.

⁹ “Statistical cases” refers to two inter-related aspects of the risk assessment often used to support regulatory analysis: (1) it reflects predicted changes in the risks of incurring an illness throughout a large population, and (2) the particular individuals likely to be affected are not identifiable.

¹⁰ An alternative, and perhaps preferable, approach would be to develop a longitudinal disease model that identifies the different phases of illness, their duration, and probability of occurrence, and to ask the experts to assign attribute levels to each phase. However, the development of such models is extremely difficult and would require substantially more time and resources than were available for this case study.

¹¹ These descriptions were developed by the case study team in consultation with Fred Angulo, Centers for Disease Control and Prevention, Dr. Lawrence Deyton, Veteran’s Administration, Dr. William Lawrence, Agency for Healthcare Research and Quality, and Dr. Gwen Wanger, Beth Israel Deaconess Medical Center.

Exhibit 5

DISEASE DESCRIPTIONS PROVIDED TO CLINICAL EXPERTS

Infections

1. Diarrhea and abdominal cramping resulting from ingestion of *Bacillus cereus*, expected to last approximately one day and to not require medical attention.

2. Watery diarrhea, nausea, vomiting, abdominal pain, and cramping resulting from ingestion of *Cryptosporidium parvum*, expected to last slightly more than one week and to not require medical attention.

3. Watery diarrhea, nausea, vomiting, abdominal pain, and cramping resulting from ingestion of *Cryptosporidium parvum*, expected to last between two and three weeks and to require medical attention but not hospitalization.

4. Watery diarrhea, nausea, vomiting, abdominal pain, and cramping resulting from ingestion of *Cryptosporidium parvum*, expected to last about three weeks and to require medical attention and hospitalization.

5. Diarrhea, abdominal pain, and nausea resulting from the ingestion of *Escherichia coli* O157:H7, expected to last less than one week and to not require medical attention.

6. Diarrhea, abdominal pain, nausea, muscle pain and dehydration, resulting from the ingestion of *Escherichia coli* O157:H7, expected to last slightly more than one week and to require medical attention but not hospitalization.

7. Diarrhea, abdominal pain, nausea, muscle pain and dehydration resulting from the ingestion of *Escherichia coli* O157:H7, expected to last roughly one month and to require medical attention and hospitalization. Will result in acute hemorrhagic colitis.

8. Diarrhea, abdominal pain, nausea, muscle pain and dehydration resulting from the ingestion of *Escherichia coli* O157:H7, expected to last roughly one month and to require medical attention and hospitalization. Will result in acute hemolytic uremic syndrome.

9. Diarrhea, abdominal pain, nausea, muscle pain and dehydration resulting from the ingestion of *Escherichia coli* O157:H7, expected to last for the individual's remaining life span and to require medical attention and hospitalization. Will result in acute hemorrhagic colitis.

10. Diarrhea, abdominal pain, nausea, muscle pain and dehydration resulting from the ingestion of *Escherichia coli* O157:H7, expected to last for the individual's remaining life span and to require medical attention and hospitalization. Will result in acute hemolytic uremic syndrome.

11. Diarrhea, nausea, vomiting, fever and headache resulting from ingestion of *Salmonella (non-typhi)*, expected to last a couple days and to not require medical attention.

12. Diarrhea, nausea, vomiting, fever and headache resulting from ingestion of *Salmonella (non-typhi)*, expected to last less than one week and to require medical attention but not hospitalization.

13. Diarrhea, nausea, vomiting, fever and headache resulting from ingestion of *Salmonella (non-typhi)*, expected to last slightly more than two weeks and to require medical attention and hospitalization.

Reactive arthritis from Salmonella (non-typhi.)

14. Short-term -- joint pain, stiffness, redness, or swelling resulting from a previous infection, generally resolves within four months, often within less than one month.

15. Long-term -- joint pain, stiffness, redness, or swelling resulting from a previous infection, typically lasting throughout the individual's remaining life span. Involves some flares and remissions as well as periods of wellness.

16. Long-term -- joint pain, stiffness, redness, or swelling resulting from a previous infection, typically lasting throughout the individual's remaining life span. Pain waxes and wanes with no periods of wellness.

17. Long-term -- joint pain, stiffness, redness, or swelling resulting from a previous infection, typically lasting throughout the individual's remaining life span. Pain is chronic and unremitting.

3.2 Expert Assignment

The next step involved asking clinical experts to identify the domain attributes associated with these conditions under each of the HRQL indices. These domains reflect the different aspects of HRQL considered under each index, and are provided in Appendix B of this report.

To identify experts to participate in this process, we worked through the case study team’s professional contacts. We identified eight infectious disease specialists and five rheumatologists, as listed in Exhibit 6.¹²

Exhibit 6	
CLINICAL EXPERTS	
Infectious Disease	Rheumatology
<ol style="list-style-type: none"> 1. Claire Panosian, M.D., David Geffen School of Medicine, UCLA 2. David A. Pegues, M.D., David Geffen School of Medicine, UCLA 3. Matthew Leibowitz, M.D., David Geffen School of Medicine, UCLA 4. Glenn Mathisen, M.D., Olive View-UCLA Medical Center 5. Sherwood L. Gorbach, M.D., Tufts New England Medical Center 6. David R. Snyderman, M.D., Tufts New England Medical Center 7. Mark Holodniy, M.D., Veteran’s Administration Palo Alto Health Care System 8. Victoria Davey, R.N., M.P.H., U.S. Department of Veterans Affairs 	<ol style="list-style-type: none"> 1. Lenore Buckley, M.D., Virginia Commonwealth University School of Medicine 2. Gene G. Hunder, M.D., Mayo Clinic (retired) 3. Eric L. Matteson, M.D., Mayo Clinic College of Medicine 4. Daniel H. Solomon, M.D., Harvard Medical School 5. Elizabeth A. Tindall, M.D., Oregon Health and Science University

Members of the case study team contacted each expert by phone to describe the project and determine whether the expert was interested and available to participate. We then sent a package of materials to each expert that included a cover letter providing detailed instructions, sheets defining the attributes within each domain for each index, and tables containing the disease descriptions (from Exhibit 5) that included space to fill in the relevant attribute levels for each domain. A copy of the cover letter sent to each expert appears below. The domains and attribute levels for each index are provided in Appendix B.

¹² Note that we selected these experts based largely on the extent and relevance of their clinical expertise and their willingness to participate in this assessment on short notice. As discussed later in the section on limitations, ideally we would have considered other criteria such as including a range of subspecialties and geographic locations, since these considerations are likely to affect the characteristics of the patients seen and conditions examined. Judith Wagner and Dr. Sherine Gabriel (of Mayo Clinic) identified and recruited many of the experts.

Exhibit 7
INSTRUCTIONS SENT TO CLINICAL EXPERTS

February 1, 2005

Dear _____,

Thank you for agreeing to participate in the development of a case study for the IOM's *Committee to Evaluate Measures of Health Benefits for Environmental, Health, and Safety Regulation*. In collaboration with economists and public health experts at CDC, we are converting a regulatory impact analysis developed by the Food and Drug Administration for a rule promulgated in 2001 governing the commercial processing of fruit juices into a cost-effectiveness analysis using different metrics to value the health benefits estimated to result from improved food safety. One of the health benefits claimed for the "Juice" rule is a nation-wide reduction of food-borne infections. The case study is attempting to measure the impacts on health-related quality of life (HRQL) from these expected reductions in the incidence of infection. For purposes of comparability, our analysis is based on the information available to the FDA at the time it developed its regulatory impact assessment, and hence excludes some more recent evidence on the pathogens likely to be present in juice products. [*The case study is attempting to measure the impacts on health-related quality of life (HRQL) from these expected reductions in the incidence of infection, including reductions in cases of reactive arthritis following a salmonella infection.*]

We seek your help in measuring the impact on HRQL of several acute and chronic infections from food borne pathogens [*of reactive arthritis – a rare but sometimes serious outcome of food-borne infections*—as measured by four commonly used survey instruments. These health status instruments are

- the EuroQol 5D scale (EQ-5D);
- the Quality of Well-Being scale (QWB);
- the Short Form 6D scale (SF-6D); and
- the Health Utilities Index (HUI3).

The first step in this process is locating a group of "typical" cases of several types of infections of differing levels of severity according to the various categories or domains listed in each of the four instruments. The domains and descriptors for all possible states within every domain for each of these (HRQL) instruments are listed in attachments. [*The first step in this process is locating a group of "typical" cases of reactive arthritis resulting from infection according to the various categories listed in each of the four instruments. Tables 1-4 describe the domains and descriptors for all possible states within every domain for each of these (HRQL) instruments.*]

For this task, we are asking you, as a member of our panel of experts in infectious diseases, to put yourself in the place of a "typical" patient who might fall into each of the 13 disease or case descriptions presented in the attached tables and assess how such a patient might locate him- or herself within each domain for each of the four instruments. [*For this task, we are asking you, as a member of our panel of experts in rheumatology, to put yourself in the place of a "typical" patient who might fall into each of the four categories of reactive arthritis described in Tables 1-4 and assess how such a patient might locate him- or herself within each domain for each of the four instruments.*] Take into account how the patient might feel on an average day if the condition were expected to last for about the amount of time indicated in the case description.

Please fill in Tables 1 through 4 to classify the case descriptions according to the criteria given in Tables 5 through 8 for the corresponding instrument. When you are finished, please return them to me, preferably by filling out the attached Excel spreadsheets electronically and emailing them back. You will also receive this letter and attachments in hard copy format and you are welcome to fill out the tables by hand and send them back in the self-addressed pre-paid envelope provided if that is more convenient.

Once we have received yours and your colleagues' answers for each of the four instruments, we will be able to apply HRQL weights (on a scale from 0 to 1, where 0 is death and 1 is perfect health) associated with the set of responses across all domains for a given case. The weights for each type of instrument come from community-based samples that have either been published or supplied to us by researchers. This final step will allow us to assess the loss in health-related quality of life in terms of quality-adjusted years of life predicted by each of the four instruments.

We would appreciate receiving your completed tables by February 11, 2005. If you have any questions, please contact me by phone (202-334-1359); fax (202) 334-2862 or email wmiller@nas.edu. Additionally, if you have comments on how this process might be revised if we were to repeat it or other reactions to this expert assessment exercise, please forward them along with the tables. With your permission, I would like to call you at your convenience for a short debriefing interview after you have completed the assessment.

Again, thank you very much for your time and for contributing your invaluable expertise to the development of this case study. We expect to have a draft version of the case study completed by April 2005 and we will be glad to send you the results of the expert assessment exercise at that time and a copy of the final IOM report with the completed case studies once it is published. Your contribution will be acknowledged in the IOM report. If you have any questions about this project or about this specific task, please do not hesitate to contact me.

Sincerely,

Wilhelmine Miller, M.S., Ph.D.

Attachments

Note: regular text represents letter sent to infectious disease experts, *italicized* sentences represent changes incorporated into version sent to rheumatologists. Actual letter was printed on IOM letterhead.

Once the experts completed and returned the tables, we incorporated them into an Excel spreadsheet model used to assess the HRQL impacts associated with the regulations, as discussed in more detail below.¹³ Due to the limited time and resources available, we did not attempt to work with the experts to ensure that they had a thorough or common understanding of the materials describing the health endpoints, the domain attributes, and the task itself. Nor did we attempt to resolve any inconsistencies either within the responses of an individual expert or across the responses from different experts, and we used simplifying assumptions in some cases.¹⁴ The implications of this simple, abbreviated expert elicitation process, as well as comments on the process received from the experts themselves, are discussed in the limitations section of this report.

3.3 Comparison to Normal Health

After receiving the expert data, we determined the weighted values for the HRQL impacts and compared these values to estimates of HRQL without the pathogen-related illness. These steps are summarized below.

3.3.1 Calculation of Weighted Values for Pathogen-Related Illness

The domain attributes identified through the expert judgment process described above provide descriptive information on the HRQL impacts of the health condition; for example, on the extent to which the condition limits mobility. To determine the value of these attributes (i.e., individuals' relative ranking of these effects, or their willingness to trade-off perfect health against these impacts), we weighted the attributes using the estimates of community preferences associated with each index. This process results in weighted values arrayed on a scale anchored at zero and one scale, where zero corresponds to death and one corresponds to perfect or optimal health.¹⁵ The sources of the weights were as follows.

- EQ-5D: These attributes were valued based on community weights from a representative U.S. national sample, based on time trade-off research (Shaw et al., 2005). The spreadsheet used to calculate weighted values was provided by Dr. William Lawrence, Agency for Healthcare Research and Quality (AHRQ).
- HUI Mark 3: The attributes were weighted using a multiattribute utility function based on a community sample of residents in Ontario, Canada (Feeny et. al, 2002, Table 3).
- SF-6D: For this index, the community weights are derived from a national probability sample in the United Kingdom (Brazier and Roberts, 2004, p. 42).

¹³ These spreadsheets were developed by Committee consultant Robert Black, with assistance from Janel Hanmer, University of Wisconsin-Madison.

¹⁴ Specifically, under the QWB, two experts provided more than one response for the symptom/problem complex. We used the response that led to the highest decrement in quality of life in both cases.

¹⁵ Values less than zero are possible in cases where multiple domains are assessed at the lowest attribute level.

- **QWB:** The community weights used to value these attributes are based on a 1974-1975 survey of 866 San Diego residents (Kaplan and Anderson (1988), as presented in Patrick and Erickson (1993), pp. 389-391).

As discussed below, we compared the resulting values to both age-adjusted average health and to perfect or optimal health. For perfect health, the comparison was straight-forward; we simply used the estimates from experts for each condition, valued using the approaches noted above. For the comparison to average health, the calculation was more complex. Many researchers believe that individuals responding to these sorts of questionnaires implicitly compare the condition to perfect health, rather than to average health for an individual of a given age. The case study team discussed several approaches for anchoring the expert responses in average age-adjusted health; e.g., by providing information on the domain attributes likely to be associated with typical health at selected years of age. However, we determined that these approaches were too complex to implement in the sort of simple expert process used for this case study. Instead, we adjusted the condition-specific HRQL results proportionately when comparing them to normal health.¹⁶

More specifically, when comparing the pathogen-related illness to average health, we multiply the weighted HRQL value for the condition by the mean population HRQL for the same age, then use the adjusted result in our analysis. For example, if the “initial” HRQL score for a particular health condition (such as reactive arthritis) is 0.8, we assumed that it represented 80 percent of perfect health (a value of 1.0). If average population HRQL is 0.9 for the same age, the “adjusted” HRQL score for that condition (in comparison to average health) would be 0.72 ($0.8 * 0.9$). Under our sensitivity analysis, where the comparison is to perfect health rather than to average age-adjusted health, we simply use the value of 0.8 to represent HRQL with the condition. This is equivalent to assuming that each expert was comparing the condition to perfect health, and, if they had instead compared to age-adjusted average health, the HRQL with the condition would reflect the same proportionate reduction. We recognize that this is a somewhat imperfect approach to addressing this issue, but it seemed to be the most pragmatic option for the case study.

3.3.2 HRQL in the Absence of Pathogen-Related Illness

As noted above, in our base case analysis (i.e., our best estimates), we compared the HRQL values for these pathogen-related illnesses to the population average HRQL for individuals of the same age. This approach is likely to provide a relatively realistic assessment of the impacts of the rule, because affected individuals are likely to be in less than perfect health for reasons other than the pathogen exposure. In sensitivity analysis, we also compared the “with condition” HRQL estimates to a value of 1.0. This latter comparison is equivalent to assuming that, in the absence of the pathogen-related illness, the affected individuals would be in perfect or optimal health throughout their life span.

¹⁶ This approach is based on a suggestion from Judith Wagner and discussions with Dennis Fryback, Alan Garber, Marthe Gold, and Emmett Keeler.

These age-adjusted estimates of average population health use the same community weights noted above, and were based on unpublished analyses from the following sources.¹⁷

- EQ-5D: Dr. William Lawrence, AHRQ, estimated average HRQL by age and gender, based on 2001 data from the Medical Expenditure Panel Survey (MEPS) that includes roughly 19,000 – 20,000 surveys provided by 22,500 eligible respondents. Estimates were provided by gender and age, divided into 10-year age groups beginning with ages 20-29 and ending at ages 80-89.¹⁸
- HUI Mark 3: Average HRQL was estimated by age and sex by Barbara Altman, National Center for Health Statistics (NCHS), based on 2002 data from the Joint U.S.-Canada Survey of Health, which included a U.S. sample of roughly 5,000 individuals. Estimates were provided by gender and age, divided into 10-year groups ranging from ages 20-29 to ages 70-79, plus values for ages 80-85.¹⁹
- SF-6D: Average HRQL was estimated by age and gender by Janel Hanmer, University of Wisconsin-Madison, based on 2001 data from MEPS.²⁰ Estimates were provided by gender and age, divided into 10-year age groups beginning with ages 20-29 and ending at ages 80-89.²¹
- QWB: John Anderson, University of California – San Diego, provided estimates of average HRQL by age and gender, divided into 10-year age groups beginning with ages 20-29 and ending at ages 80-89, based on U.S. National Health Interview Survey data for the year 2001.²²

These analyses were missing average health estimates for the very young and the very old, hence we assumed the following:

- For ages 0 to 9, average health would equal perfect health (a value of 1.0).
- For ages 10 to 19, average health would be the mid-point between perfect health and the values estimated for ages 20 to 29.
- For elderly individuals, average health would remain constant at the value reported for the eldest age group.

¹⁷ Updated estimates for the EQ-5D, SF-6D, and QWB are available in Hanmer et al., forthcoming.

¹⁸ Email from William Lawrence to Wilhelmine Miller, November 9, 2004.

¹⁹ Email from Barbara Altman to Wilhelmine Miller, January 7, 2005. (The survey data are available at <http://www.statcan.ca/start.html>.)

²⁰ MEPS includes survey responses for the SF-12, which were converted SF-6D values based on the same research as used to weight our results for the SF-6D (Brazier and Roberts, 2004).

²¹ Email from Janel Hanmer to Wilhelmine Miller, January 24, 2005.

²² Email from Janel Hanmer to Lisa Robinson, April 21, 2005.

For each index, the values were provided separately for males and females. We weighted the gender-specific values by the proportion of males and females of each age in the U.S. population as of the year 2000, to determine population averages (Census 2004).

These assumptions primarily affect the analysis of those health endpoints that occur among children or that are lifelong. Only one health endpoint is expected to typically begin in childhood; severe, chronic cases associated with *E. coli* are expected to begin, on average, at age 4. The average health assumptions for elderly individuals affect the estimates of life-long impacts of chronic *E. coli* cases and *Salmonella*-related long-term reactive arthritis, as well as the estimates of for cases of preventable mortality. Otherwise, the effects are short-lived and the average person affected is a young to middle-aged adult.

In Exhibit 8, we provide the estimates of average population health used in this analysis for selected ages, for males and females combined. These estimates for specific ages are provided for illustrative purposes; the case study calculations used the full range of estimates across all ages as described above. The source documents cited provide information on the confidence intervals associated with the gender-specific estimates and on the uncertainty associated with each generic instrument and its set of community weights.

Exhibit 8				
HRQL IN THE ABSENCE OF PATHOGEN-RELATED ILLNESS				
	Age 20	Age 40	Age 60	Age 80
<i>Mean Population Index Value (base case)</i>				
EQ-5D	0.921	0.875	0.825	0.746
HUI-3	0.908	0.880	0.822	0.694
SF-6D	0.844	0.821	0.800	0.733
QWB	0.822	0.800	0.737	0.651
<i>Perfect Health (sensitivity analysis)</i>				
All indices	1.0	1.0	1.0	1.0
<p>Notes: Estimates are preliminary; see Hamner et al. (forthcoming) for updated estimates for the EQ-5D, SF-6D, and QWB. See sources below for information on the confidence intervals related to each of these estimates. Additional uncertainty related to the generic instruments and their valuation surveys is discussed in the references describing their development. Sources: EQ-5D: Unpublished analysis by William Lawrence, November 9, 2004 HUI-3: Unpublished analysis by Barbara Altman, January 7, 2005. SF-6D: Unpublished analysis by Janel Hanmer, January 24, 2005. QWB: Unpublished analysis by John Anderson, April 21, 2005.</p>				

As is evident from the exhibit, the estimates of average population health vary. This variation reflects several factors, including the differences in: (1) the data sources used to assess

health attributes; (2) the sources of community weights used to value these attributes; and, (3) the indices themselves. In combination, these factors generally lead to the highest average HRQL estimates under the EQ-5D and the lowest under the QWB; however, this relationship varies by age group. As expected, the average population HRQL declines with age under each index.

These estimates of average population health may overstate “without condition” HRQL for some individuals potentially affected by pathogens in juice. The FDA analysis and more recent studies suggest that infections may be more common and/or more severe in individuals with suppressed immune systems. We were not, however, able to quantify the extent to which such individuals will be disproportionately affected, nor were we able to determine the extent to which the gains in HRQL or longevity might differ across those with and without immune deficiencies.²³ The effects on such vulnerable sub-populations instead must be discussed qualitatively.

²³ The FDA estimates of the probability and severity of illness reflect the distribution of cases across individuals with and without compromised immune systems. However, these estimates are averages and are not disaggregated to indicate the distribution of the impacts across these subgroups. (Email from Clark Nardinelli to Lisa Robinson, April 15, 2005).

SECTION 4.0: RESULTS OF CASE STUDY ANALYSIS

In the following sections, we first report the results of the expert assignment process, and the HRQL estimates that result, for each pathogen-related illness. We next discuss the estimates of total QALD (and QALY) losses averted by the rule under varying assumptions regarding health in the absence of the illness, and compare these results to net regulatory costs as well as to the results of the original FDA benefits analysis.

4.1 Expert Assignment of Attribute Levels

As discussed in Section 3.2, we asked clinical experts to determine the attribute levels that best match the likely impacts each of the health endpoints assessed in this case study, under four generic HRQL indices (the EQ-5D, HUI-3, SF-6D, and QWB). Below, we summarize the attributes identified for each health endpoint under each index considered by the experts.²⁴ These assessments address only the nonfatal endpoints; the “with condition” weighted value for fatal endpoints is “zero” under all of these indices, as discussed later in this section.

In Exhibit 9, we summarize the attributes identified by the experts under the EQ-5D for each endpoint of concern. These endpoints are numbered for ease of reference to Exhibit 5, which contains the detailed descriptions provided to the clinical experts. For each domain, we provide the median attribute score, as well as the maximum and minimum score reported by the experts.²⁵ For example, for mild cases resulting from exposure to *B. cereus*, the median mobility score across the experts was a value of 1.0 (“no problems”). The lowest mobility score reported was also 1.0, while the highest score assigned by one or more experts was 2.0 (“some problems”). The definitions of the attributes corresponding to each score can be found in Appendix B, Exhibit B-1.

²⁴ These results are based on completed assessments from eight infectious disease experts and five rheumatologists.

²⁵ Due to the small number of experts involved, we use the median rather than the mean as our estimate of central tendency.

Exhibit 9					
EXPERT ASSIGNMENT OF ATTRIBUTES FOR NONFATAL ENDPOINTS: EQ-5D					
(median (min, max))					
Endpoint	Domain Attributes				
	Mobility	Self-Care	Usual Activities	Pain/Discomfort	Anxiety/Depression
1. <i>B. cereus</i> , mild	1.0 (1,2)	1.0 (1,2)	2.0 (1,2)	2.0 (1,2)	1.0 (1,2)
2. <i>C. parvum</i> , mild	1.5 (1,2)	1.0 (1,2)	2.0 (2,3)	2.0 (2,2)	1.5 (1,2)
3. <i>C. parvum</i> , moderate	2.0 (1,3)	1.0 (1,2)	2.0 (2,3)	2.0 (2,3)	2.0 (1,3)
4. <i>C. parvum</i> , severe	2.0 (2,3)	2.0 (2,3)	3.0 (2,3)	2.0 (2,3)	2.0 (2,3)
5. <i>E. coli</i> , mild	2.0 (1,2)	1.0 (1,2)	2.0 (2,3)	2.0 (2,2)	2.0 (1,2)
6. <i>E. coli</i> , moderate	2.0 (1,3)	1.5 (1,2)	2.0 (2,3)	2.0 (2,3)	2.0 (1,2)
7. <i>E. coli</i> , severe-acute, with colitis	2.5 (2,3)	2.0 (2,2)	3.0 (2,3)	3.0 (2,3)	2.0 (2,3)
8. <i>E. coli</i> , severe-acute, with HUS	3.0 (2,3)	3.0 (2,3)	3.0 (3,3)	3.0 (2,3)	3.0 (2,3)
9. <i>E. coli</i> , severe-chronic, with colitis	3.0 (2,3)	3.0 (1,3)	3.0 (2,3)	3.0 (1,3)	3.0 (2,3)
10. <i>E. coli</i> , severe-chronic, with HUS	3.0 (2,3)	3.0 (1,3)	3.0 (2,3)	3.0 (1,3)	3.0 (3,3)
11. <i>Salmonella</i> , mild	1.5 (1,2)	1.0 (1,2)	2.0 (1,3)	2.0 (1,3)	1.0 (1,2)
12. <i>Salmonella</i> , moderate	2.0 (1,2)	1.5 (1,2)	2.0 (2,3)	2.0 (2,3)	2.0 (1,2)
13. <i>Salmonella</i> , severe	2.0 (2,3)	2.0 (2,3)	3.0 (2,3)	2.0 (2,3)	2.0 (2,3)
14. <i>Salmonella</i> , short-term reactive arthritis	2.0 (1,2)	1.0 (1,2)	2.0 (1,2)	2.0 (2,2)	2.0 (1,2)
15. <i>Salmonella</i> , long-term reactive arthritis, flares and remissions with some wellness	2.0 (2,2)	2.0 (1,2)	2.0 (1,2)	2.0 (2,3)	2.0 (1,2)
16. <i>Salmonella</i> , long-term reactive arthritis, waxes and wanes with no wellness	2.0 (2,2)	2.0 (1,2)	2.0 (1,3)	2.0 (2,3)	2.0 (1,2)
17. <i>Salmonella</i> , long-term reactive arthritis, chronic and unremitting	2.0 (2,2)	2.0 (2,2)	2.0 (2,3)	2.0 (2,3)	2.0 (2,3)

Notes:
Attributes corresponding to above scores are listed in Appendix B, Exhibit B-1.

The EQ-5D allows a choice of three attributes within each domain, with lower values indicating fewer problems. As indicated by the median scores in the exhibit, cases of increasing severity often have similar scores. Where the scores vary, they generally follow the expected pattern, in that the attribute levels for severe cases usually indicate greater problems than the levels assigned to mild cases. As discussed earlier, the experts were asked to assess the impact of an average case over time. The range between the minimum and maximum values for each attribute suggest, however, that the experts vary in their assessments of the degree of problems imposed. For example, severe-chronic *E. coli* infections with colitis (endpoint 9) may have anywhere from no effect on pain (attribute level of one) to severe pain (a level of three), according to the experts.

In Exhibit 10, we summarize the attributes identified by the experts under the HUI Mark 3 for each endpoint of concern, following the same format as used to present the EQ-5D results.

The definitions of the attributes corresponding to each score can be found in Appendix B, Exhibit B-2.

Exhibit 10								
EXPERT ASSIGNMENT OF ATTRIBUTES FOR NONFATAL ENDPOINTS: HUI-3								
(median (min, max))								
Endpoint	Domain Attributes							
	Vision	Hearing	Speech	Ambulation	Dexterity	Emotion	Cognition	Pain
1. <i>B. cereus</i> , mild	1.0 (1,1)	1.0 (1,1)	1.0 (1,1)	1.5 (1,2)	1.0 (1,1)	2.0 (1,3)	1.0 (1,2)	3.0 (2,4)
2. <i>C. parvum</i> , mild	1.0 (1,1)	1.0 (1,1)	1.0 (1,1)	2.0 (1,2)	1.0 (1,1)	3.0 (2,4)	1.0 (1,2)	3.0 (2,4)
3. <i>C. parvum</i> , moderate	1.0 (1,1)	1.0 (1,1)	1.0 (1,1)	2.0 (2,4)	1.0 (1,1)	3.0 (2,4)	1.5 (1,2)	3.0 (2,4)
4. <i>C. parvum</i> , severe	1.0 (1,1)	1.0 (1,1)	1.0 (1,2)	3.0 (2,5)	1.0 (1,2)	3.5 (3,4)	2.0 (1,4)	4.0 (2,4)
5. <i>E. coli</i> , mild	1.0 (1,1)	1.0 (1,1)	1.0 (1,1)	1.5 (1,2)	1.0 (1,1)	3.0 (1,3)	1.0 (1,2)	3.0 (2,4)
6. <i>E. coli</i> , moderate	1.0 (1,1)	1.0 (1,1)	1.0 (1,1)	2.0 (1,2)	1.0 (1,1)	3.0 (2,4)	2.0 (1,2)	3.5 (2,5)
7. <i>E. coli</i> , severe-acute, with colitis	1.0 (1,1)	1.0 (1,1)	1.0 (1,2)	4.0 (2,5)	1.0 (1,2)	4.0 (3,4)	3.0 (1,4)	4.0 (3,5)
8. <i>E. coli</i> , severe-acute, with HUS	1.0 (1,4)	1.0 (1,2)	1.0 (1,3)	4.0 (2,6)	1.0 (1,4)	4.0 (3,4)	4.0 (2,5)	4.5 (4,5)
9. <i>E. coli</i> , severe-chronic, with colitis	1.0 (1,1)	1.0 (1,2)	1.0 (1,3)	4.0 (2,5)	1.0 (1,2)	4.0 (3,5)	4.0 (3,5)	4.5 (2,5)
10. <i>E. coli</i> , severe-chronic, with HUS	1.0 (1,5)	1.0 (1,4)	1.0 (1,3)	4.5 (2,6)	1.0 (1,4)	4.0 (4,5)	4.0 (3,6)	4.5 (3,5)
11. <i>Salmonella</i> , mild	1.0 (1,1)	1.0 (1,1)	1.0 (1,1)	1.5 (1,2)	1.0 (1,1)	2.0 (1,3)	1.5 (1,2)	2.5 (1,4)
12. <i>Salmonella</i> , moderate	1.0 (1,1)	1.0 (1,1)	1.0 (1,1)	2.0 (1,2)	1.0 (1,1)	3.0 (2,4)	1.5 (1,2)	3.0 (2,5)
13. <i>Salmonella</i> , severe	1.0 (1,1)	1.0 (1,1)	1.0 (1,2)	3.0 (1,5)	1.0 (1,2)	3.0 (2,4)	2.0 (1,4)	4.0 (2,5)
14. <i>Salmonella</i> , short-term reactive arthritis	1.0 (1,1)	1.0 (1,1)	1.0 (1,1)	2.0 (1,2)	1.0 (1,2)	2.0 (1,2)	1.0 (1,1)	2.0 (2,4)
15. <i>Salmonella</i> , long-term reactive arthritis, flares and remissions with some wellness	1.0 (1,2)	1.0 (1,1)	1.0 (1,1)	2.0 (2,3)	2.0 (1,3)	3.0 (1,3)	1.0 (1,2)	3.0 (2,4)
16. <i>Salmonella</i> , long-term reactive arthritis, waxes and wanes with no wellness	1.0 (1,2)	1.0 (1,1)	1.0 (1,1)	2.0 (2,4)	2.0 (1,3)	3.0 (1,4)	1.0 (1,2)	4.0 (2,4)
17. <i>Salmonella</i> , long-term reactive arthritis, chronic and unremitting	1.0 (1,2)	1.0 (1,1)	1.0 (1,2)	2.0 (2,5)	2.0 (1,4)	3.0 (2,5)	1.0 (1,3)	4.0 (3,5)
Notes: Attributes corresponding to above scores are listed in Appendix B, Exhibit B-2.								

The HUI-3 allows five to six choices within each domain, with lower values again indicating fewer problems. As demonstrated by the exhibit, the experts expect that these pathogen-related illnesses generally will not lead to limitations under some of the domains, such

as vision or hearing. The median scores suggest that cases of increasing severity often have similar attributes; where differences exist they generally follow the expected pattern of increasing scores for cases of greater severity. The experts vary in their assessments of the average attributes associated with each pathogen-related illness over time, as indicated by the range between the minimum and maximum values. For example, severe-chronic *E. coli* infections with colitis (endpoint 9) may have anywhere from mild to moderate pain that does not affect activities (attribute level of two) to severe pain that prevents involvement in activities (a level of five), according to the experts.

In Exhibit 11, we summarize the attributes identified by the experts under the SF-6D for each of the endpoints. The definitions of the attributes corresponding to each score can be found in Appendix B, Exhibit B-3.

Exhibit 11						
EXPERT ASSIGNMENT OF ATTRIBUTES FOR NONFATAL ENDPOINTS:SF-6D						
(median (min, max))						
Endpoint	Domain Attributes					
	Physical Functioning	Role Limitations	Social Functioning	Pain	Mental Health	Vitality
1. <i>B. cereus</i> , mild	1.0 (1,3)	2.0 (1,4)	2.0 (1,4)	2.0 (1,4)	2.0 (1,2)	2.5 (1,4)
2. <i>C. parvum</i> , mild	2.0 (2,3)	2.0 (1,4)	3.0 (2,5)	2.5 (2,4)	2.0 (1,3)	3.0 (2,5)
3. <i>C. parvum</i> , moderate	3.0 (2,3)	2.0 (2,4)	4.0 (2,5)	3.0 (2,4)	3.0 (2,4)	3.5 (2,5)
4. <i>C. parvum</i> , severe	3.0 (3,3)	2.5 (2,4)	5.0 (4,5)	4.0 (3,5)	3.5 (3,5)	4.0 (3,5)
5. <i>E. coli</i> , mild	2.0 (2,3)	2.0 (2,4)	3.0 (2,4)	3.0 (2,4)	3.0 (1,3)	3.5 (2,5)
6. <i>E. coli</i> , moderate	2.5 (2,3)	2.0 (2,4)	4.0 (3,5)	3.5 (3,4)	2.5 (2,4)	3.5 (2,5)
7. <i>E. coli</i> , severe-acute, with colitis	3.0 (3,3)	2.5 (2,4)	5.0 (4,5)	5.0 (4,5)	3.5 (3,5)	4.5 (4,5)
8. <i>E. coli</i> , severe-acute, with HUS	3.0 (3,3)	2.5 (2,4)	5.0 (4,5)	5.0 (4,5)	4.5 (3,5)	5.0 (4,5)
9. <i>E. coli</i> , severe-chronic, with colitis	3.0 (2,3)	4.0 (2,4)	5.0 (3,5)	5.0 (2,5)	5.0 (4,5)	5.0 (3,5)
10. <i>E. coli</i> , severe-chronic, with HUS	3.0 (2,3)	4.0 (2,4)	5.0 (3,5)	5.0 (2,5)	5.0 (4,5)	5.0 (4,5)
11. <i>Salmonella</i> , mild	2.0 (2,3)	2.0 (1,4)	3.0 (2,4)	3.0 (2,4)	2.0 (1,3)	3.0 (2,4)
12. <i>Salmonella</i> , moderate	2.5 (2,3)	2.5 (2,4)	3.5 (2,4)	3.5 (3,4)	2.5 (2,3)	3.0 (2,4)
13. <i>Salmonella</i> , severe	3.0 (3,3)	2.5 (2,4)	5.0 (3,5)	4.5 (3,5)	3.0 (3,5)	4.0 (3,5)
14. <i>Salmonella</i> , short-term reactive arthritis	1.0 (1,3)	1.0 (1,2)	2.0 (1,4)	2.0 (1,3)	2.0 (2,2)	2.0 (2,3)
15. <i>Salmonella</i> , long-term reactive arthritis, flares and remissions with some wellness	2.0 (2,3)	2.0 (1,4)	3.0 (2,3)	3.0 (2,3)	3.0 (1,3)	3.0 (2,4)
16. <i>Salmonella</i> , long-term reactive arthritis, waxes and wanes with no wellness	3.0 (2,3)	4.0 (1,4)	3.0 (2,5)	4.0 (2,4)	3.0 (1,4)	3.0 (3,4)
17. <i>Salmonella</i> , long-term reactive arthritis, chronic and unremitting	3.0 (2,3)	4.0 (1,4)	4.0 (3,5)	5.0 (3,5)	4.0 (2,5)	4.0 (3,5)
Notes: Attributes corresponding to above scores are listed in Appendix B, Exhibit B-3.						

The SF-6D allows three to six attribute choices within each domain, with lower values indicating fewer problems. The median scores suggest that cases of greater severity generally have increasing scores, as expected. As with the other indices, the experts vary in their assessments of the average attribute levels associated with each illness over time, as indicated by the range between the minimum and maximum scores. For example, severe-chronic *E. coli* infections with colitis (endpoint 9) may, on average, have anywhere from pain that interferes with normal work a little (attribute level of two) to extreme pain that interferes a lot with normal work (a level of five), according to the experts.

In Exhibit 12 below, we summarize the attributes identified by the experts under the QWB. The definitions of the attributes corresponding to each score can be found in Appendix B, Exhibit B-4. Note that the three scales under this index are the inverse of the others, in that increasing values indicate fewer limitations, hence the numeric value reported as the “minimum” (in terms of the degree of problems) is larger than the “maximum.” In addition, the QWB symptom/problem complex describes 23 different combinations of disease manifestations and diagnoses, rather than rankings within functional domains, hence all of the codes provided by the experts are listed in that column.

Exhibit 12				
EXPERT ASSIGNMENT OF ATTRIBUTES FOR NONFATAL ENDPOINTS: QWB (median (min, max)) ¹				
Endpoint	Domain Attributes			
	Mobility Scale	Physical Activity Scale	Social Activity Scale	Symptom/ Problem Complex ²
1. <i>B. cereus</i> , mild	4.0 (5,4)	4.0 (4,2)	4.0 (5,2)	9
2. <i>C. parvum</i> , mild	4.0 (5,2)	2.5 (4,2)	3.0 (4,2)	9
3. <i>C. parvum</i> , moderate	3.5 (5,2)	2.0 (4,2)	3.0 (4,2)	9
4. <i>C. parvum</i> , severe	1.0 (4,1)	2.0 (2,1)	2.0 (3,1)	9
5. <i>E. coli</i> , mild	4.0 (5,4)	3.0 (4,1)	3.0 (4,2)	9
6. <i>E. coli</i> , moderate	4.0 (5,2)	2.0 (4,1)	3.0 (4,2)	8,9
7. <i>E. coli</i> , severe-acute, with colitis	1.0 (4,1)	1.0 (2,1)	2.0 (3,1)	8, 9
8. <i>E. coli</i> , severe-acute, with HUS	1.0 (1,1)	1.0 (2,1)	1.0 (2,1)	2, 8, 9
9. <i>E. coli</i> , severe-chronic, with colitis	1.0 (5,1)	1.0 (2,1)	1.0 (4,1)	8,9,23
10. <i>E. coli</i> , severe-chronic, with HUS	1.0 (5,1)	1.0 (2,1)	1.0 (3,1)	2,8,9,10
11. <i>Salmonella</i> , mild	4.0 (5,4)	2.0 (4,1)	3.5 (4,2)	9
12. <i>Salmonella</i> , moderate	4.0 (5,2)	2.0 (4,1)	3.0 (4,2)	9
13. <i>Salmonella</i> , severe	1.0 (1,1)	1.0 (2,1)	2.0 (2,1)	9
14. <i>Salmonella</i> , short-term reactive arthritis	4.0 (5,1)	2.0 (4,1)	5.0 (5,3)	7, 9, 10, 16, 19, 22
15. <i>Salmonella</i> , long-term reactive arthritis, flares and remissions with some wellness	3.0 (5,1)	2.0 (2,1)	4.0 (5,3)	7,10,19
16. <i>Salmonella</i> , long-term reactive arthritis, waxes and wanes with no wellness	2.0 (5,1)	2.0 (2,2)	3.0 (5,2)	6,7,10,19
17. <i>Salmonella</i> , long-term reactive arthritis, chronic and unremitting	2.0 (5,2)	2.0 (2,1)	3.0 (5,1)	6,7,10,19

Notes:
Attributes corresponding to above scores are listed in Appendix B, Exhibit B-4.
1. The three QWB scales are the inverse of the other indices, in that lower attribute scores reflect increasing severity (i.e., a value of “5” indicates no limitation). Hence the minimum attribute value is a number that is greater than the maximum value.
2. The symptom/problem complex differs from the other scales in that the attribute scores reflect a combination of impacts rather than a ranking. Hence we report all of the codes provided by the experts. (Two experts reported more than one code, so we used the code that yielded the greatest decrement in estimated HRQL in our calculations.)

Under the three QWB scales, there is a choice of four or five attribute values, with increasing values indicating fewer problems. While the median scores are somewhat similar across endpoints of increasing severity, in general more severe cases have lower scores, as expected. Again, the experts vary in their assessments of the average attributes associated with each illness over time. For example, the severe-chronic *E. coli* infection with colitis (endpoint 9) may lead to no limitations on mobility (an attribute level of five) or to hospitalization (a level of one), according to the experts. The symptom/problem complex codes are generally consistent with the description of the illness. For example, the most often used code for the infections is

nine, which describes various characteristics of gastrointestinal illness such as loose bowel movements.

In Exhibit 13, we use the weighting formulae for each index (derived from the community-based valuation surveys discussed in Section 3.3) to value the attributes assigned by the experts. The results indicate HRQL with each condition (not the decrement from normal health) proportionate to perfect health, on a scale anchored at zero and one. (Comparisons to average age-specific health are discussed in the following section.) This exhibit excludes the fatal endpoints, which have a value of zero under the “with condition” scenario under all indices.

Exhibit 13				
HRQL WITH PATHOGEN-RELATED ILLNESS				
Endpoint	Case Study Expert assignment (median)			
	EQ-5D	HUI-3	SF-6D	QWB
1. <i>B. cereus</i> , mild	0.816	0.760	0.737	0.587
2. <i>C. parvum</i> , mild	0.773	0.618	0.675	0.527
3. <i>C. parvum</i> , moderate	0.738	0.495	0.555	0.527
4. <i>C. parvum</i> , severe	0.437	0.346	0.472	0.491
5. <i>E. coli</i> , mild	0.738	0.641	0.654	0.557
6. <i>E. coli</i> , moderate	0.643	0.501	0.560	0.556
7. <i>E. coli</i> , severe-acute, with colitis	0.156	0.104	0.434	0.482
8. <i>E. coli</i> , severe-acute, with HUS	(0.109)	0.038	0.366	0.437
9. <i>E. coli</i> , severe-chronic, with colitis	(0.109)	(0.076)	0.356	0.437
10. <i>E. coli</i> , severe-chronic, with HUS	(0.109)	(0.096)	0.345	0.437
11. <i>Salmonella</i> , mild	0.797	0.711	0.692	0.527
12. <i>Salmonella</i> , moderate	0.603	0.579	0.568	0.527
13. <i>Salmonella</i> , severe	0.437	0.305	0.464	0.482
14. <i>Salmonella</i> , short-term reactive arthritis	0.708	0.734	0.800	0.641
15. <i>Salmonella</i> , long-term reactive arthritis, flares and remissions with some wellness	0.597	0.556	0.692	0.558
16. <i>Salmonella</i> , long-term reactive arthritis, waxes and wanes with no wellness	0.597	0.422	0.526	0.518
17. <i>Salmonella</i> , long-term reactive arthritis, chronic and unremitting	0.597	0.226	0.394	0.518
Notes: Values in parenthesis are negative, reflecting the weighted value of attributes assessed at their lowest levels (e.g., “severe” limitations).				

As indicated by this exhibit, the attribute levels identified by the experts result in median HRQL values that decrease with the increasing severity of the illness, as expected, in some cases

dropping below zero. However, the difference between perfect health (a value of 1.0) and health with the illness varies across indices. For mild cases, the EQ-5D generally results in the values closest to perfect health, while the QWB results in the lowest values, but this pattern is not constant across the different pathogen-related illnesses.

4.2 HRQL With and Without the Condition

The next step in the analysis involves estimating the HRQL losses averted by FDA’s juice processing rule. This step includes: (1) determining the decrement from normal health for each condition; (2) multiplying the decrement by the duration of each condition, to estimate the quality adjusted life days (QALDs) lost; and (3) multiplying the per case values by the number of cases averted by the rule. The assumptions used for average age at incidence, duration, and number of cases avoided annually are the same as those used in the FDA analysis (discussed in Section 2.0), and are summarized in Exhibit 14 for ease of reference.

Exhibit 14			
FDA ASSUMPTIONS FOR AVERAGE AGE, DURATION, AND CASES AVERTED			
Endpoint	Age at Incidence	Duration (days)	Cases Averted (annual)
1. <i>B. cereus</i> , mild	36	0.75	340
2. <i>C. parvum</i> , mild	36	9	2,890
3. <i>C. parvum</i> , moderate	36	17	290
4. <i>C. parvum</i> , severe	36	24	20
5. <i>E. coli</i> , mild	36	5	95
6. <i>E. coli</i> , moderate	36	9	60
7. <i>E. coli</i> , severe-acute, with colitis	36	32	4
8. <i>E. coli</i> , severe-acute, with HUS	36	32	1
9. <i>E. coli</i> , severe-chronic, with colitis	4	26,645 ¹	8
10. <i>E. coli</i> , severe-chronic, with HUS	4	26,645 ¹	2
11. <i>Salmonella</i> , mild	27	2	1,590
12. <i>Salmonella</i> , moderate	27	5	730
13. <i>Salmonella</i> , severe	27	17	20
14. <i>Salmonella</i> , short-term reactive arthritis	27	25	50
15. <i>Salmonella</i> , long-term reactive arthritis, flares and remissions with some wellness	27	18,250 ²	66
16. <i>Salmonella</i> , long-term reactive arthritis, waxes and wanes with no wellness	27	18,250 ²	27
17. <i>Salmonella</i> , long-term reactive arthritis, chronic and unremitting	27	18,250 ²	27
18. Preventable mortality	36	14,965 ³	2
Notes:			
1. Assumed to begin at age four and last through the remaining life span; i.e., until 77 years of age.			
2. Assumed to begin at age 27 and last through the remaining life span; i.e., until 77 years of age.			
3. Assumed to occur at age 36, compared to an average life expectancy of 77 years.			

Exhibit 15 provides estimates of the total losses averted by the rule, converting the estimates of daily losses (QALDs) into the more commonly used yearly estimates (QALYs). These results reflect our base case scenario, where we assume that normal health (in the absence of the condition) would equal average age-adjusted health for the U.S. population. We present the results discounted at both of the rates recommended in current government-wide guidance (three and seven percent) in determining the present value of the long-term effects (see OMB 2003). As discussed in Section 3.3.1, we assume that the expert assignment implicitly involved comparison to perfect health, and that the decrement from average health would represent the same proportional reduction. We exclude FDA's QWB results from this exhibit, because FDA did not compare their results to an average health scenario.

Exhibit 15									
TOTAL QALY LOSSES COMPARED TO AVERAGE AGE-ADJUSTED HEALTH (all cases, median HRQL estimates)									
Endpoint	EQ-5D		HUI-3		SF-6D		QWB		Discount rate
	3 percent	7 percent	3 percent	7 percent	3 percent	7 percent	3 percent	7 percent	
1. <i>B. cereus</i> , mild	0.2	0.2	0.2	0.2	0.2	0.2	0.3	0.3	
2. <i>C. parvum</i> , mild	15	15	25	25	19	19	27	27	
3. <i>C. parvum</i> , moderate	3.2	3.2	6.2	6.2	5.0	5.0	5.0	5.0	
4. <i>C. parvum</i> , severe	0.7	0.7	0.8	0.8	0.6	0.6	0.5	0.5	
5. <i>E. coli</i> , mild	0.3	0.3	0.4	0.4	0.4	0.4	0.5	0.5	
6. <i>E. coli</i> , moderate	0.5	0.5	0.7	0.7	0.5	0.5	0.5	0.5	
7. <i>E. coli</i> , severe-acute, with colitis	0.3	0.3	0.3	0.3	0.2	0.2	0.1	0.1	
8. <i>E. coli</i> , severe-acute, with hemolytic uremic syndrome	0.1	0.1	0.1	0.1	0.0	0.0	0.0	0.0	
9. <i>E. coli</i> , severe-chronic, with colitis	242	120	234	116	134	67	108	53	
10. <i>E. coli</i> , severe-chronic, with hemolytic uremic syndrome	61	30	60	30	34	17	27	13	
11. <i>Salmonella</i> , mild	1.6	1.6	2.3	2.3	2.3	2.3	3.3	3.3	
12. <i>Salmonella</i> , moderate	3.7	3.7	3.8	3.8	3.7	3.7	3.8	3.8	
13. <i>Salmonella</i> , severe	0.5	0.5	0.6	0.6	0.4	0.4	0.4	0.4	
14. <i>Salmonella</i> , short-term reactive arthritis	0.9	0.9	0.8	0.8	0.6	0.6	1.0	1.0	
15. <i>Salmonella</i> , long-term reactive arthritis, flares and remissions with some wellness	601	327	663	360	432	233	574	313	
16. <i>Salmonella</i> , long-term reactive arthritis, waxes and wanes with no wellness	246	134	353	192	272	147	256	140	
17. <i>Salmonella</i> , long-term reactive arthritis, chronic and unremitting	246	134	472	257	348	187	256	140	
18. Preventable mortality	41	23	40	23	38	22	35	20	
Total	1,463	794	1,864	1,019	1,293	706	1,298	721	

Notes:
Assumes that in the absence of illness, health status would equal the average for the U.S. population in the same age group.
Represents HRQL decrement per case multiplied by duration and by number of new cases averted annually.
Detail may not add to total due to rounding.

This exhibit indicates that the health effects that lead to the largest HRQL decrements (see Exhibit 13) are not necessarily the health effects that account for the largest proportion of the benefits of the rule. When adjusted for duration and number of cases averted, preventing long-term reactive arthritis (endpoints 15 through 17) accounts for the largest share of the overall benefits across all of the indices, although the exact proportion varies by index; FDA’s original

analysis was also dominated by the results for this endpoint. In total, the HUI-3 leads to the largest estimate of QALY losses when compared to average health.

Although the severe cases of *E. coli* infections generally lead to the largest decrement in HRQL, the rule averts relatively few such cases. Hence, while the impact of averting these severe *E. coli* cases is greater than the impact of averting the large numbers of mild cases, the overall impact of the severe *E. coli* cases is less significant than the impact of averting long-term cases of reactive arthritis.

Because the weighted HRQL results for severe *E. coli* infections are less than zero under the EQ-5D and HUI-3 (see Exhibit 13), the estimates of QALY losses are greater than the actual (discounted) duration of the illness. For example, at the age of incidence (age 4), we assume that average HRQL without the illness is 1.0, and find that the HRQL with the illness is *negative* 0.109 under the EQ-5D, for a *decrement* of 1.109 from average health. If we multiply this decrement by 365 days to reflect the impacts of the first year of the illness (1.109×365), the QALDs lost total 405, exceeding the number of days in the year.

For preventable mortality, the estimates vary because the calculations compare a “with condition” value of zero to the age-specific estimates of average population health reported in Exhibit 8. Because the QWB results in the lowest estimates of average health over time, it also results in the lowest estimates of QALY losses for fatal cases.

Discounting the long-term impacts at a three percent annual rate, rather than at seven percent, increases the present value of the results, as expected. The relatively large difference in the results occurs because the three percent rate increases the contribution of the long-term impacts to the total present value, since it discounts future impacts by a smaller amount. The undiscounted results are even larger (ranging from 2,514 to 3,686 QALYs when compared to average health), because in this case the long-term impacts are not discounted to reflect their timing.

Exhibit 16 summarizes these estimates and compares them to the estimates for our sensitivity analysis, where we assume perfect health (a value of 1.0) in the absence of the illness. This comparison is likely to overstate the actual impact of the rule, because the affected individuals are not likely to be in perfect health throughout their life span in the absence of exposure to the juice-related pathogens. However, we include this perfect health comparison since it is often found in the literature and underlies the original FDA approach.

Exhibit 16						
SENSITIVITY ANALYSIS OF QALY LOSSES COMPARED TO AVERAGE AND PERFECT HEALTH						
Scenario	Discount Rate	Case Study Expert Assessment (median)				FDA QWB Results
		EQ-5D	HUI-3	SF-6D	QWB	
Total QALY losses compared to <u>average</u> age-adjusted health	3 percent	1,463	1,864	1,293	1,298	N/A
	7 percent	794	1,019	706	721	
Total QALY losses compared to <u>perfect</u> health	3 percent	1,659	2,121	1,563	1,700	888*
	7 percent	882	1,136	843	924	

Notes:
N/A = not reported in FDA analysis (FDA 2001).
* Adds life years lost for fatal cases to FDA's QALY estimate for nonfatal cases.

This exhibit indicates that comparison to perfect health increases the estimates of QALY losses across the different indices, as expected. The overall results continue to be dominated by the estimates for long-term reactive arthritis. Because the difference between average health and perfect health increases with age (see Exhibit 8), the use of a perfect health comparison has the largest impact on those health conditions that have life long effects.

The differences between the expert assignment and the original FDA assessment for the QWB appear to stem largely from the selection of different attributes. While FDA uses a set of QWB attributes that is organized somewhat differently than the list we provided to the clinical experts (see Appendix A compared to Appendix B, Exhibit B-4), the weights used are based on the same community valuation survey results as used in our analysis (see Ross 1988). Information from QWB researchers indicates that the weighted results should be the same regardless of which QWB list of attributes is used.²⁶

4.3 Calculation of Cost-Effectiveness

Our final step involved developing cost-effectiveness ratios based on different measures of effectiveness. In these calculations, we use FDA's estimates of annualized regulatory costs and health treatment cost savings. In both cases, FDA applies a discount rate of seven percent. While we were able to re-calculate the estimate of regulatory costs to reflect a three percent discount rate, we lacked the data necessary to re-calculate the estimates of medical cost savings. Thus we use the same estimates of medical cost savings under both discounting scenarios, which is likely to understate these savings under the three percent scenario by an unknown amount. In addition, the FDA estimates include medical expenditures only and do not include the other types of health treatment cost savings recommended for inclusion in these calculations (see Gold

²⁶ Email communications between Robert Kaplan and Wilhelmine Miller, March 20, 2005.

et al., 1996). Hence the net costs used in these ratios are higher than they would be due to limitations in the health care cost-savings estimates.

In Exhibit 17, we first report the costs per life saved and per life year saved, discounted at three and seven percent. The cost estimate in each of these calculations includes compliance costs only, including both recurring costs and the annualized value of the initial costs.²⁷ Medical cost savings are not considered. We then report the ratios that result under each of the alternative approaches to estimating QALY losses; in this case, we net out the medical costs savings from the regulatory costs. In all cases, this exhibit indicates the QALY losses calculated as a decrement from average population health.

Exhibit 17								
COST-EFFECTIVENESS RATIOS								
	3 percent discount rate				7 percent discount rate			
Averted preventable deaths	2 deaths				2 deaths			
Averted life year losses	47 years				27 years			
Regulatory compliance costs	\$26 million				\$28 million			
<i>Compliance Cost per Fatality Averted</i>	\$13 million				\$14 million			
<i>Compliance Cost per Life Year Gained</i>	\$560,000				\$1.0 million			
	EQ-5D	HUI-3	SF-6D	QWB	EQ-5D	HUI-3	SF-6D	QWB
Averted QALY losses	1,500 QALYs	1,900 QALYs	1,300 QALYs	1,300 QALYs	790 QALYs	1,000 QALYs	700 QALYs	720 QALYs
Regulatory compliance costs, net of health treatment savings	\$22.0 million				\$23.4 million			
<i>Health Benefits Only Ratio</i>	\$16,000 per QALY	\$13,000 per QALY	\$18,000 per QALY	\$18,000 per QALY	\$29,000 per QALY	\$23,000 per QALY	\$33,000 per QALY	\$32,000 per QALY
Notes:								
Reflects new incidence averted by a single year of full implementation of the rule, dollar year not reported.								
Assumes that, without the pathogen-related illness, health status will be the same as the average for the U.S. population in the same age group.								
Rounded to two significant figures; calculations are based on unrounded results.								

²⁷ Annualization spreads initial costs over the estimated lifetime of the investment, similar to the process of determining loan payments (with an interest rate that equals the discount rate). In this case, we annualize the costs over 20 years.

This exhibit indicates that the costs per life saved and per life-year saved are relatively high, because this rule averts only two cases of preventable mortality per year. Once we add in the impacts of the nonfatal effects, as well as the medical cost savings, the ratios result in much smaller values. In general, the HUI-3 leads to the lowest costs per QALY, and the SF-6D leads to the highest, and the SF-6D and QWB results are very similar. Because a higher discount rate leads to lower future year QALY values, the costs per QALY are higher under a seven percent discount rate than under the three percent rate. All of these ratios would show lower costs per QALY if the results of our sensitivity analysis were used, because the comparison to perfect health increases the estimates of QALY gains.

We also calculated cost-effectiveness based on FDA's QWB estimates, which compare to perfect health and are discounted at seven percent. If we add in the effects of preventable mortality (which were not included in FDA's QALY estimates) to FDA's estimates for nonfatal effects, the result is a value of \$26,000 per QALY. While somewhat higher than the above results that compare to average health, this estimate is within the same range that would result if we calculated the costs per QALY using the estimates (from Exhibit 16) that compare to perfect health.

SECTION 5.0: LIMITATIONS

This case study was prepared as a learning exercise for the IOM Committee to Evaluate Measures of Health Benefits for Environmental, Health, and Safety Regulation, and as such lacks some of the detail and complexity that would be required in an actual regulatory analysis. Perhaps most importantly, current guidance (OMB 2003) requires substantial assessment of uncertainty, while this case study largely relies on mean or median estimates and includes only limited sensitivity analysis. The existing guidelines for regulatory analysis require agencies to discuss qualitatively the main uncertainties in the calculations, use sensitivity analysis to assess the effects of changes in the approach on the resulting estimates, and/or develop formal probabilistic analysis of uncertainty using simulation models and/or expert judgment.²⁸ The OMB guidance also emphasizes the importance of providing information on impacts that cannot be quantified or that can be quantified in physical terms but not assigned a value. In addition, the Committee did not assess the distribution of the effects of this regulation, which is also required under the OMB guidelines and other administrative and legal authorities.

In this section, we briefly discuss the sources of uncertainty most directly related to our application of the four HRQL indices. We first discuss the comments received from the experts involved in the assignment of the attribute levels, and then discuss other key areas of uncertainty.

5.2 Comments from Experts Involved in the HRQL Assessment²⁹

Between one day and four weeks following receipt of the experts' results, we held scheduled phone interviews with 11 of the 13 clinicians who sent in assignments. Eight infectious disease experts completed the assessments, and seven completed debriefing interviews. Five rheumatologists completed the assessments and four completed interviews.

In conversations lasting from 10 to 30 minutes (most took about 15 minutes, which was the time for a call we requested), we first asked the clinicians open-ended questions, beginning with their overall impression of the task they were asked to complete, their mental model when characterizing a typical patient for a particular scenario (literally, what they had in mind as they assigned the attributes to each condition), and whether they took into account the HRQL impacts of possible co-morbidities or only thought only about the condition described in the scenario. Other questions elicited their views on the domain attributes, the clarity of the instructions, and how the expert assignment process might be improved; we also asked them to estimate the time they spent on the assignments.

In many respects the comments of the experts assessing the two different sets of conditions were quite similar. The complexity of the exercise was perceived to be greater for reactive arthritis, in part because of the relatively long course of the disease, its dynamic or cyclical nature, and potentially transient symptoms, which had to be reduced to a single average location (i.e., the selection of a single attribute description) on each of the four indices' domain

²⁸ As of January, 2005, formal probabilistic analysis is required for all rules with impacts that exceed \$1 billion annually, but the juice processing rule would not exceed this threshold.

²⁹ Wilhelmine Miller conducted these interviews.

scales. One expert noted that reactive arthritis has a less predictable course than rheumatoid arthritis. Several experts emphasized that unlike most other arthritic conditions, most patients with reactive arthritis recovered without symptoms. In contrast, only one of the infectious disease experts found the task difficult, noting that many of the scenarios were very similar and difficult to distinguish using the information we provided. The rheumatology experts reported spending between 15 minutes and one hour assessing the four scenarios, while the infectious disease experts reported spending anywhere from 30 minutes to two hours (1 hour 20 minutes, on average) assessing the 13 scenarios.

The experts in both specialties envisioned the “typical patient with the condition” as an otherwise healthy person “between 20 and 50” or “a young adult of school or working age in good health.” Several mentioned that *E. coli* was most likely to affect young children. Neither set of experts tended to think about co-morbidities in patients with these conditions, other than the impacts specifically mentioned in the scenarios. At the same time, the experts uniformly identified their standard for comparison as “average health for age” rather than “perfect health.” One possible explanation for this apparent contradiction is that the experts do not expect to see noticeable decrements in average health (compared to perfect health) in the age range they considered. This is somewhat consistent with the data we use on average population health, which shows more rapidly increasing declines in health in more advanced years. As a result, the expert assignment may reflect a comparison to a “without illness” health status that is somewhere between our perfect and average health scenarios at the average age at incidence, but that does not reflect the larger declines in average population health that occur after age 50.

Most of the experts volunteered that the scenarios were informative and clinically accurate from their experience. Negative comments on the scenarios from two infectious disease specialists indicated that the scenarios were often too similar to distinguish in the assignment of attributes; a third would have liked more diagnostic and treatment information, particularly for the hospitalization scenarios.

Many experts commented on the instruments’ domains as “not all that helpful,” “not sensitive to severity differences,” or “not enough distinctions on some scales.” A few marked on their forms that the QWB mobility scale was particularly confusing and did not contain appropriate alternatives. (It should be noted, however, that the QWB assignment form given to the experts was a greatly condensed version of the full investigator-administered questionnaire and, unlike the category descriptions for the other three instruments, is not verbatim from the user-validated survey form.) One clinician felt that the exercise left the assessors “on their own with the instruments,” without adequate guidance in applying them.

Several experts observed that anxiety/depression, mental, or emotional status varies widely among patients with foodborne infections, and that it was difficult to assign a typical classification for this domain. Several also noted that the categories were not well suited to these types of conditions, and a few mentioned the HUI-3 as containing irrelevant categories. Several experts used the vision category on the HUI-3 to note temporary visual impairments with some infections. One expert recommended using a disease-specific index rather than generic instruments. A rheumatologist, however, commented that there was no established way to measure HRQL for reactive arthritis patients, whose experience differs from that of patients with

other forms of arthritis, and was gratified that this assignment was asking specifically about reactive arthritis.

Finally, several experts were concerned that asking clinical experts to act as proxies for patients in assessing HRQL was likely to introduce “noise” into the valuation of these conditions both because “its hard not to personalize – how would I respond?” and because the variability in responses among real patients cannot be captured by a small number of experts characterizing the “typical” patient. One physician commented that future expert elicitations could be improved by asking “thought leaders” in a field to nominate expert assessors.

5.3 Implications of Key Uncertainties

This analysis is subject to a number of uncertainties. Many of these uncertainties relate to the information used in the original FDA regulatory analysis and to the construction of the individual generic indices, and are discussed in the sources referenced in this case study. In particular, FDA’s risk assessment is subject to significant uncertainty because of the need to adjust for underreporting of foodborne disease, as noted in the FDA documents. Full exploration of the uncertainties that arise when extrapolating from data for a relatively small number of juice-related outbreaks is beyond the scope of this case study, however.³⁰

Below, we focus on the key uncertainties in the analyses conducted by the case study team and the implications for our comparison of the results across the indices. We are uncertain about the direction or magnitude of the bias resulting from these considerations; more research would be needed to determine the significance of these effects.

First, available evidence suggests that descriptive information on the HRQL impacts of illness differs when elicited from clinical experts rather than from patients. As noted in the previous section, experts may have a view of the limitations imposed that differs from the view of their patients. Because this case study involved assessing “average” cases of each illness, rather than individual patients, it also requires a complex thought process that takes into consideration the full range of each expert’s experiences. This cognitive process may be especially difficult when addressing those illnesses that are rare or that have long lasting or highly variable impacts. The experts definition of “average” also be affected by the population from which they draw their patients and by their subspecialties, arguing for the use of experts who represent a variety of subspecialties and geographic areas.

In addition, different populations were surveyed in developing the community weights and the estimates of average population health across indices. Hence some of the variation in our results may reflect differences in the data sources used rather than solely reflecting differences in the indices themselves. The estimates of the decrement in HRQL also may be overstated if a significant portion of those affected by these pathogen-related illnesses are in less good health than the general population; for example, due to immune system problems. For these individuals,

³⁰ For example, relatively rare events (such as the severe infections) can be difficult to predict when the available data are limited.

the difference between the “with pathogen-related illness” and “without pathogen-related illness” attribute values may be different than estimated in our analysis.

Finally, it is difficult to define the baseline used in the experts’ determination of attribute values. The experts’ assumptions regarding the definition of “average” health are likely to vary, and are inextricably linked with assumptions regarding the age of the affected individuals. In addition, at times it may be difficult to separate the characteristics associated with a particular disease state from characteristics that may be associated with other aspects of a patient’s health. Our assumption that the attribute values provided by the experts reflect decrements from perfect health, and that the decrements from average health are proportional to the decrements provided by the experts, introduces additional uncertainty into the findings.

REFERENCES

- Brazier, John E., and Jennifer Roberts. 2004. "The Estimation of a Preference Based Measure of Health from the SF-12." *Medical Care*. Vol. 42, No. 9.
- Gold, Marthe E., Joanna E. Siegel, Louise B. Russell, and Milton C. Weinstein (eds). 1996. *Cost-Effectiveness in Health and Medicine*. New York: Oxford University Press.
- Feeney, David, William Furlong, George W. Torrance, Charles H. Goldsmith, Zenglong Zhu, Sonja DePauw, Margaret Denton, and Michael Boyle. 2002. "MultiAttribute and Single-Attribute Utility Functions for the Health Utilities Index Mark 3 System." *Medical Care*, Vol. 40, No. 2, pp 113-128.
- Hanmer, Janel, William F. Lawrence, John P. Anderson, Robert M. Kaplan, Dennis G. Fryback. 2005. "Report of Population Norms for the Non-Institutionalized U.S. Adult Population for Seven Health Related Quality of Life Scores." Unpublished manuscript.
- Patrick, Donald L., and Pennifer Erickson. 1993. *Health Status and Health Policy: Allocating Resources to Health Care*. New York: Oxford University Press.
- Ross, Scott. 1988. "Appendix D: Review of the Health Status Index Literature." In *Estimating the Value of Consumers' Loss from Foods Violating the FD&C Act*. J. Mauskopf et al, eds. Prepared for the U.S. Food and Drug Administration.
- Shaw, James W., Jeffrey A. Johnson, and Stephen Joel Coons. 2005. "US Valuation of the EQ-5D Health States: Development and Testing of the D1 Valuation Model." *Medical Care*. Vol. 43. No. 5, pp. 203-220.
- U.S. Census Bureau. June 14, 2004. "Table 1: Annual Estimates of the Population by Sex and Five-Year Age Groups for the United States: April 1, 2000 to July 1, 2003" (NC-EST2003-01).
- U.S. Food and Drug Administration (FDA). January 19, 2001. "Hazard Analysis and Critical Control Point (HAACP); Procedures for the Safe and Sanitary Processing of Juice; Final Rule." *Federal Register*. Washington, D.C.: U.S. Government Printing Office. pp. 6138 - 6202.
- U.S. Food and Drug Administration (FDA). May 1, 1998. "Preliminary Regulatory Impact Analysis and Initial Regulatory Flexibility Analysis of the Proposed Rules to Ensure the Safety of Juice and Juice Products; Proposed Rule." *Federal Register*. Washington, D.C.: U.S. Government Printing Office. pp. 24254-24352.
- U.S. Office of Management and Budget (OMB). September 17, 2003. *Circular A-4, Regulatory Analysis*.

APPENDIX A: FDA QWB ASSESSMENT

Excerpt from: FDA (1998), pp. 24259-24360 [*italicized notes added*]. The QWB attribute descriptions and weights used by FDA and reported in the tables below are in a different format than those used in our expert assignment (see Section 3.3 and Exhibit B-4). These differences reflect alternative approaches to aggregating the domain attributes, but the same community valuation survey underlies the preference weights in both cases.

2. Description of Health Effects and Symptoms of Microbial Hazards in Juice

In order to quantify the loss (disutility) that individuals experience from becoming ill, the pain, suffering, and mobility loss must be scaled. Tables 3, 4, and 5 represent the outcome of one type of scaling of these effects. Individuals who become ill experience different levels of functional status in terms of mobility, ability to do other physical activity, and ability to engage in social activities. The “Functional Status Code” column in Table 3 represents the status code which correlates with the categories of severity for each hazard. Individuals who become ill also experience additional disutility due to the symptoms of the illness. The “Symptom/Problem Complex Code” column represents the symptom/problem complex codes which correlate with the categories of severity for each hazard. Descriptions of the functional status and symptom/problem complex codes are given in Tables 4 and 5. FDA requests comment on this scaling model.

TABLE 3.—DESCRIPTION OF HEALTH EFFECTS AND SYMPTOMS OF MICROBIALLY RELATED ILLNESSES IN JUICE

[Italicized estimates added to Table 3 for C. parvum from Table 16 on p. 24267]

Hazard	Severity	Functional Status Code ¹	Symptom/Problem Complex Code ²
E. coli	Mild	L20	8, 12, 13, 29
	Moderate	L19	8, 12, 13, 16, 19, 29, 32
	Severe-acute	(L1 x .2) + (L6 x .8) ³	8, 12, 13, 16, 19, 29, 32
	Severe-chronic	L31	9
Salmonella (non typhi)	Mild	L20	12, 13, 29
	Moderate	L20	12, 13, 29
	Severe	L6	12, 13, 16, 29
	Reactive arthritis	L35, L41, L42, L43 ⁴	19
B. cereus	Mild	L19	12, 13, 29
	Moderate	L19	19 12, 13, 29
	Severe	NA	NA
<i>C. parvum</i>	<i>Mild</i>	<i>L41</i>	<i>12, 13, 29</i>
	<i>Moderate</i>	<i>L41</i>	<i>12, 13, 29</i>
	<i>Severe</i>	<i>L6</i>	<i>12, 13, 29</i>

1 Functional Status Codes are described in Table 4.

2 Symptom/Problem Complex Codes are described in Table 5.

3 The disutilities for two functional status codes were taken for severe cases of E. coli O157:H7 because functional status varies among severe cases of this hazard.

4 Functional Status Code varies, Ref. 10. *[Reference to 1998 Zorn and Klontz analysis reprinted in full as appendix to Federal Register notice.]*

In Table 4, the last column, “Level of Disutility,” represents the degree of departure from perfect functionality. Thus, a person would be functioning at about half capacity if the level was .5 and would be even more diminished at .75. Code L42 is used whenever the mobility, physical activity, and social activity conditions apply and a person is experiencing a symptom described in Table 5. Code L43 is used whenever the mobility, physical activity, and social activity conditions apply and a person is experiencing no symptoms. In Table 5, “Level of Disutility” refers to the amount of pain and suffering such that .03 would be minor pain and suffering relative to .3.

TABLE 4.—DESCRIPTION OF FUNCTIONAL STATUS CODES¹

Function Status Levels	Mobility	Physical Activity	Social Activity	Level of Disutility
L1	In special care unit	In bed or chair	Had help with self-care	.5626
L6	In hospital	In bed or chair	Had help with self-care	.5301
L19	In house	Walked with physical limitations	Performed self-care but not work, school, or housework	.4176
L20	In house	Walked with physical limitations	Limited in work, school, or housework	.4448
L23	In house	Walked without physical limitations	Performed self-care, but not work, school, or housework	.3512
L31	Did not drive, needed help with transportation	Walked without physical limitations	Limited in work, school, or housework	.4087
L35	Drove car and used transportation without help	Walked with physical limitations	Limited in work, school, or housework	.3980
L41	Drove car and used transportation without help	Walked without physical limitations	Did work, school, or housework, but other activities limited	.3145
L42	Drove car and used transportation without help	Walked without physical limitations	Did work, school, or household, and other activities	.2567
L43	Drove car and used transportation without help	Walked without physical limitations	Did work, school, or household, and other activities	.0000

¹ Ref. 4. [Ross 1988]

TABLE 5.—DESCRIPTION OF SYMPTOM/PROBLEM COMPLEX CODES¹

Symptom/Problem Complex	Description	Level of Disutility
8	Itching, bleeding or pain in rectum	.0379
9	Pain in chest, stomach, side, back, or hips	.0382
12	Sick or upset stomach, vomiting, or diarrhea (watery bowel movements)	.0065
13	Fever chills with aching all over and vomiting or diarrhea	.0722
16	Headache, dizziness, or ringing in ears	.0131
19	Pain, stiffness, numbness, or discomfort of neck, hands, feet, arms, legs ankles, or several joints together	.0344
29	General tiredness, weakness, or weight loss	.0027
32	Loss of consciousness such as seizures (fits), fainting, or coma (out cold or knocked out)	.1507

¹ Ref. 4, p. D-14. [Ross 1988]

APPENDIX B: DOMAIN AND ATTRIBUTE DESCRIPTIONS FOR EACH INDEX

Exhibit B-1		
EQ-5D HEALTH STATUS CLASSIFICATION SYSTEM		
Domain	Attribute Level	Description
MOBILITY	1	I have no problems in walking about
	2	I have some problems in walking about
	3	I am confined to bed
SELF-CARE	1	I have no problems with self-care
	2	I have some problems washing or dressing myself
	3	I am unable to wash or dress myself
USUAL ACTIVITIES	1	I have no problems with performing my usual activities (e.g., work, study, housework, family or leisure activities)
	2	I have some problems with performing my usual activities
	3	I am unable to perform my usual activities
PAIN / DISCOMFORT	1	I have no pain or discomfort
	2	I have moderate pain or discomfort
	3	I have extreme pain or discomfort
ANXIETY / DEPRESSION	1	I am not anxious or depressed
	2	I am moderately anxious or depressed
	3	I am extremely anxious or depressed

Exhibit B-2

HEALTH UTILITIES INDEX MARK 3 (HUI3) HEALTH STATUS CLASSIFICATION SYSTEM

Domain	Attribute Level	Description
VISION	1	Able to see well enough to read ordinary newsprint and recognize a friend on the other side of the street, without glasses or contact lenses.
	2	Able to see well enough to read ordinary newsprint and recognize a friend on the other side of the street, but with glasses.
	3	Able to read ordinary newsprint with or without glasses but unable to recognize a friend on the other side of the street, even with glasses.
	4	Able to recognize a friend on the other side of the street with or without glasses but unable to read ordinary newsprint, even with glasses.
	5	Unable to read ordinary newsprint and unable to recognize a friend on the other side of the street, even with glasses.
	6	Unable to see at all.
HEARING	1	Able to hear what is said in a group conversation with at least three other people, without a hearing aid.
	2	Able to hear what is said in a conversation with one other person in a quiet room without a hearing aid, but requires a hearing aid to hear what is said in a group conversation with at least three other people.
	3	Able to hear what is said in a conversation with one other person in a quiet room with a hearing aid, and able to hear what is said in a group conversation with at least three other people, with a hearing aid.
	4	Able to hear what is said in a conversation with one other person in a quiet room, without a hearing aid, but unable to hear what is said in a group conversation with at least three other people even with a hearing aid.
	5	Able to hear what is said in a conversation with one other person in a quiet room with a hearing aid, but unable to hear what is said in a group conversation with at least three other people even with a hearing aid.
	6	Unable to hear at all.
SPEECH	1	Able to be understood completely when speaking with strangers or friends.
	2	Able to be understood partially when speaking with strangers but able to be understood completely when speaking with people who know me well.
	3	Able to be understood partially when speaking with strangers or people who know me well.
	4	Unable to be understood when speaking with strangers but able to be understood partially by people who know me well.
	5	Unable to be understood when speaking to other people (or unable to speak at all).
AMBULATION	1	Able to walk around the neighborhood without difficulty, and without walking equipment.
	2	Able to walk around the neighborhood with difficulty; but does not require walking equipment or the help of another person.
	3	Able to walk around the neighborhood with walking equipment, but without the help of another person.
	4	Able to walk only short distances with walking equipment, and requires a wheelchair to get around the neighborhood.

Exhibit B-2

HEALTH UTILITIES INDEX MARK 3 (HUI3) HEALTH STATUS CLASSIFICATION SYSTEM

	5	Unable to walk alone, even with walking equipment. Able to walk short distances with the help of another person, and requires a wheelchair to get around the neighborhood.
	6	Cannot walk at all.
DEXTERITY	1	Full use of two hands and ten fingers.
	2	Limitations in the use of hands or fingers, but does not require special tools or help of another person.
	3	Limitations in the use of hands or fingers, is independent with use of special tools (does not require the help of another person).
	4	Limitations in the use of hands or fingers, requires the help of another person for some tasks (not independent even with use of special tools).
	5	Limitations in use of hands or fingers, requires the help of another person for most tasks (not independent even with use of special tools).
	6	Limitations in use of hands or fingers, requires the help of another person for all tasks (not independent even with use of special tools).
EMOTION	1	Happy and interested in life.
	2	Somewhat happy.
	3	Somewhat unhappy.
	4	Very unhappy.
	5	So unhappy that life is not worthwhile.
COGNITION	1	Able to remember most things, think clearly and solve day to day problems.
	2	Able to remember most things, but have a little difficulty when trying to think and solve day to day problems.
	3	Somewhat forgetful, but able to think clearly and solve day to day problems.
	4	Somewhat forgetful, and have a little difficulty when trying to think or solve day to day problems.
	5	Very forgetful, and have great difficulty when trying to think or solve day to day problems.
	6	Unable to remember anything at all, and unable to think or solve day to day problems.
PAIN	1	Free of pain and discomfort.
	2	Mild to moderate pain that prevents no activities.
	3	Moderate pain that prevents a few activities.
	4	Moderate to severe pain that prevents some activities.
	5	Severe pain that prevents most activities.

Exhibit B-3

STANDARD FORM 6-D (SF-6D) HEALTH STATUS CLASSIFICATION SYSTEM

Domain	Attribute Level	Description
PHYSICAL FUNCTIONING	1	Your health does not limit you in moderate activities.
	2	Your health limits you a little in moderate activities.
	3	Your health limits you a lot in moderate activities.
ROLE LIMITATIONS	1	You have no problems with your work or other regular daily activities as a result of your physical health or any emotional problems.
	2	You are limited in the kind of work or other activities as a result of your physical health.
	3	You accomplish less than you would like as a result of emotional problems.
	4	You are limited in the kind of work or other activities as a result of your physical health and accomplish less than you would like as a result of emotional problems.
SOCIAL FUNCTIONING	1	Your health limits your social activities none of the time.
	2	Your health limits your social activities a little of the time.
	3	Your health limits your social activities some of the time.
	4	Your health limits your social activities most of the time.
	5	Your health limits your social activities all of the time.
PAIN	1	You have pain that does not interfere with your normal work (both outside the home and housework) at all.
	2	You have pain that interferes with your normal work (both outside the home and housework) a little bit.
	3	You have pain that interferes with your normal work (both outside the home and housework) moderately.
	4	You have pain that interferes with your normal work (both outside the home and housework) quite a bit.
	5	You have pain that interferes with your normal work (both outside the home and housework) extremely.
MENTAL HEALTH	1	You feel downhearted and low none of the time.
	2	You feel downhearted and low a little of the time.
	3	You feel downhearted and low some of the time.
	4	You feel downhearted and low most of the time.
	5	You feel downhearted and low all of the time.
VITALITY	1	You have a lot of energy all of the time.
	2	You have a lot of energy most of the time.
	3	You have a lot of energy some of the time.
	4	You have a lot of energy a little of the time.
	5	You have a lot of energy none of the time.

Exhibit B-4

QUALITY OF WELL-BEING SCALE (QWB) HEALTH STATUS CLASSIFICATION SYSTEM

Domain	Attribute Level	Description
MOBILITY SCALE	5	No limitations for health reasons
	4	Did not drive a car, health related; did not ride in a car as usual for age (younger than 15 years), health related
	3	Did not use public transportation, health related
	2	Had or would have used more help than usual for age to use public transportation, health related
	1	In hospital, health related
PHYSICAL ACTIVITY SCALE	4	No limitations for health reasons
	3	In wheelchair, moved or controlled movement of wheelchair without help from someone else
	2	Had trouble or did not try to lift, stoop, bend over, or use stairs or inclines, health related; limped, used a cane, crutches, or walker, health related; had any other physical limitation in walking; or did not try to walk as far or as fast as others the same age are able, health related
	1	In wheelchair, did not move or control the movement of wheelchair without help from someone else, or in bed, chair, or couch for most or all of the day, health related
SOCIAL ACTIVITY SCALE	5	No limitations for health reasons
	4	Limited in other (e.g., recreational) role activity, health related
	3	Limited in major (primary) role activity, health related
	2	Performed no major role activity, health related, but did perform self-care activities
	1	Performed no major role activity, health related, and did not perform or had more help than usual in performance of one or more self-care activities, health related
SYMPTOM/ PROBLEM COMPLEX	23	Trouble sleeping; intoxication; problems with sexual interest or performance; or excessive worry
	22	No symptoms or problem
	21	Breathing smog or unpleasant air
	20	Wore glasses or contact lenses
	19	Taking medication or staying on a prescribed diet for health reasons
	18	Pain in ear, tooth, jaw, throat, lips, tongue; several missing or crooked permanent teeth-includes wearing bridges or false teeth; stuffy, runny nose; or any trouble hearing-includes wearing a hearing aid
	17	Overweight for age and height or skin defect of face, body, arms, or legs, such as scars, pimples, warts, bruises, or changes in color
	16	Pain or discomfort in one or both eyes (such as burning or itching) or any trouble seeing after correction
	15	Trouble talking, such as lisp, stuttering, hoarseness, or being unable to speak
	14	Burning or itching rash on large areas of face, body, arms, or legs
	13	Headache, or dizziness, or ringing in ears, or spells of feeling hot, or nervous or shaky

Exhibit B-4

QUALITY OF WELL-BEING SCALE (QWB) HEALTH STATUS CLASSIFICATION SYSTEM

	12	Spells of feeling upset, being depressed, or of crying
	11	Cough, wheezing, or shortness of breath, with or without fever, chills, or aching all over
	10	General tiredness, weakness, or weight loss
	9	Sick or upset stomach, vomiting or loose bowel movement, with or without fever, chills, or aching all over
	8	Pain, burning, bleeding, itching, or other difficulty with rectum, bowel movements, or urination (passing water)
	7	Pain, stiffness, weakness, numbness, or other discomfort in chest, stomach (including hernia or rupture), side, neck, back, hips, or any joints or hands, feet, arms, or legs
	6	Any combination of one or more hands, feet, arms, or legs either missing, deformed (crooked), paralyzed (unable to move) or broken-includes wearing artificial limbs or braces
	5	Trouble learning, remembering, or thinking clearly
	4	Pain, bleeding, itching, or discharge (drainage) from sexual organs-does not include normal menstrual (monthly) bleeding
	3	Burn over large areas of face, body, arms, or legs
	2	Loss of consciousness such as seizure (fits), fainting, or coma (out cold or knocked out)
	1	Death

Note:
See Appendix A for attribute descriptions used in FDA assessment.