Determining Reliability Requirements and Testing Costs in the Early Stages of Single Use Medical Product Development

Fritz Eubanks, Ph.D., CRE

Battelle Medical Devices & Diagnostics

07.12.2010

The System Engineer’s Question

“We’re working on a single use auto-injector for patient use at home. It needs to be 95% reliable. I’m putting together the verification test plan. How many do I need to test to verify device reliability?”

The Project Manager’s Question

“I’m putting together the verification test budget, and funds are pretty tight. How much is this reliability testing going to cost?”

“Oh, and by the way, marketing says none of these things can fail.”

Structuring the Requirement

- Basic reliability information
  - Measure of success/failure
    - 95%
  - Definition of success/failure
    - Actuate, deploy, dispense, and retract within 5 seconds
  - Range of normal operating conditions
    - Home use
  - Interval of performance
    - 5 second follow 2 years of refrigerated storage

Structuring the Requirement

- Reliability Requirement
  - The product shall deliver the proper dose to the patient within 5 seconds of actuation with a probability of at least 95% when used in an environmentally controlled interior space with temperature of 15-35°C, humidity of 10-95% RH, and atmospheric pressure of 14.7-10.3 psia following storage at 2-5°C for no more than 2 years.

- Verification Testing Context
  - 95 successes out of every 100 devices tested
  - Devices either pass by completing all required actions, or they fail
  - Devices are production equivalent
  - Analysis of verification test results same as analysis of sample testing from production lots

Reliability of Single Use Devices

- Binary result – success/failure
  - Constant failure rate assumption not applicable
    - Only applies to continuous variables
  - Can't do 100% acceptance testing
  - Requires statistics of population proportions

$$R = p = \frac{X}{n}$$

    - Where X = # of successes, n = sample size
  - Normal distribution assumption applicable when $np > 10$ and $n(1-p) > 10$
    - At $p = 0.95$, $n > 200$
  - Binomial distribution tables required when $np < 10$ or $n(1-p) < 10$

- Need to account for sampling errors

Sampling Errors - Confidence

- Type I error: rejecting a good batch
  - 1 - P(type I error) = 1 - α = level of confidence
  - Sample 200 units, #successes = 190 $\rightarrow$ p = 95%
    - LCL = 92% with 95% confidence

- Verification testing context
  - Falsely conclude that verification test failed
    - Implication: investigation and more testing = $

Sampling Errors - Power

- Type II error: accepting a bad batch
  - 1 - P(type II error) = 1 - β = power
  - Sample 200 units, #successes = 190 → p = 95%
    - 23% probability that population success rate is actually 91%
    - Sample 400 units: LCL = 0.93 and $\beta(.91)$ = 6%

- Verification testing context
  - Falsely conclude that verification testing was successful
    - Implication: product released that does not meet requirements = $$$

Confidence, LCL, and Sample Size

- Normal calculation of lower confidence limit
  - Measured reliability (R), confidence (α) and sample size (n) known

$$LCL = R - z_{\alpha}\sqrt{\frac{R(1-R)}{n}}$$

- Our problem: given a reliability goal (R), find n

$$n = R(1-R)\left(\frac{z_{\alpha}}{(R-LCL)}\right)^{2}$$

- What do we do about confidence and LCL?

Confidence, LCL, and Sample Size

- What lower confidence limit of reliability is acceptable at the desired statistical confidence level?
  - Calculate sample sizes for combinations confidence and LCL

R = 95%			
	LCL		
Confidence	94%	93%	92%
99%	2,571	643	286
98%	2,003	501	223
97%	1,680	420	187
96%	1,456	364	162
95%	1,285	321	143
94%	1,148	287	128
93%	1,035	259	115
92%	938	234	104
91%	854	213	95
90%	780	195	87

Estimating Costs

- Verification testing cost
  - Higher sample size = higher costs

$$Part\ Cost = n * (Part\ cost)$$

$$Testing\ Cost = \frac{n}{(Testing\ Rate)} * \left[(Labor\ rate) + (Facility\ rate)\right]$$

$$Total\ Cost = Part\ Cost + Testing\ Cost + Equipment\ Cost$$

Estimating Costs

- Compute the reliability verification testing costs using previous sample size calculations

Part cost =	$200		
Testing rate =	6 /hour		
Labor rate =	$100 /hour		
Fixture cost =	$5000		
Facility rate =	$75 /hour		
	LCL		
Confidence	94%	93%	92%
99%	$594,107	$152,277	$70,456
98%	$464,134	$119,784	$56,015
97%	$390,059	$101,265	$47,784
96%	$338,627	$88,407	$42,070
95%	$299,510	$78,627	$37,723
94%	$268,135	$70,784	$34,237
93%	$242,080	$64,270	$31,342
92%	$219,903	$58,726	$28,878
91%	$200,679	$53,920	$26,742
90%	$183,779	$49,695	$24,864

Sample Size and Type II Error

- Accounting for type II errors
  - Even if verification test of 321 units yields 305 successes (R = 95%), there is still a 1 in 4 chance that the actual population reliability R′ = 92%

$$\beta(R') = 1 - \Phi\left(\frac{R - R' - z_\alpha \sqrt{\frac{R(1-R)}{n}}}{\sqrt{\frac{R'(1-R')}{n}}}\right) = 1 - \Phi\left(0.663\right) = 0.254$$

  - There is a 1 in 10 chance that R′ = 91%

Sample Size and Type II Error

- What tolerance for type II error (combination of actual reliability in production and probability of realizing that reliability) is acceptable at the desired level of confidence?
  - Can only tolerate 10% chance that reliability is as low as 93%

$$n = \left(\frac{z_\alpha \sqrt{R(1-R)} + z_\beta \sqrt{R'(1-R')}}{(R' - R)} \right)^2 = \left(\frac{1.645\sqrt{0.95(0.05)} + 1.282\sqrt{0.93(0.07)}}{(0.93 - 0.95)} \right)^2 = 1176$$

  - Over 3.5 times the number of test units calculated based on type I error alone

- Question: what does 10% chance of R'=93% really mean?

Estimating Cost of Unreliability

- Type II error cost
  - Higher sample size = lower cost

$$\beta(R') = 1 - \Phi\left(\frac{R - R' - z_\alpha \sqrt{\frac{R(1-R)}{n}}}{\sqrt{\frac{R'(1-R')}{n}}} \right)$$

  - Cost per failure

$$\mathrm{C(failure)} = \sum_{i=1}^{m} \mathrm{P\,(outcome)_i} \times \mathrm{C(outcome)_i}$$

  - Cost of unreliability for population N when R′ < R

$$\mathrm{C(R') = (R - R') \times N \times C(failure)}$$

Estimating Cost of Unreliability

- What tolerance for type II error is acceptable at the desired level of confidence?
  - Calculate probability of type II error for values of

What tolerance for type II error is acceptable at the

R' = 94%			
	LCL		
Confidence	94%	93%	92%
99%	0.085	0.380	0.520
98%	0.131	0.428	0.553
97%	0.167	0.459	0.574
96%	0.199	0.483	0.589
95%	0.227	0.502	0.602
94%	0.253	0.519	0.612
93%	0.276	0.533	0.621
92%	0.298	0.546	0.630
91%	0.319	0.558	0.637
90%	0.339	0.569	0.644

Estimating Cost of Unreliability

- Cost of potential failure outcomes
  - From historical data or risk/benefit estimates

Potential outcome	Probability	Cost
Serious injury	0.0001	$500,000
Moderate injury	0.005	$45,000
Minor injury	0.05	$6000
No injury – returned item	0.94	$500

  - From historical data or risk/benefit estimates
  - Cost per device failure = $1,045
    failure rate = $5,225,000 lost revenue

Estimating Cost of Unreliability

- Impact of Type II Errors

R′ = 94%			
	LCL		
Confidence	94%	93%	92%
99%	$442,514	$1,983,020	$2,714,791
98%	$681,874	$2,235,941	$2,887,849
97%	$873,610	$2,399,667	$2,996,738
96%	$1,038,759	$2,523,768	$3,077,966
95%	$1,186,062	$2,624,967	$3,143,510
94%	$1,320,213	$2,711,089	$3,198,872
93%	$1,444,101	$2,786,469	$3,247,058
92%	$1,559,661	$2,853,771	$3,289,899
91%	$1,668,270	$2,914,762	$3,328,597
90%	$1,770,949	$2,970,675	$3,363,983

- Decision based on
  - Impact of Type II Errors
  - Decision based on

Conclusions

- Represents the probability of releasing a device to production that does not meet reliability requirements
- Cost of unreliability in medical devices can be very high that does not meet reliability requirements

- Cost of unreliability in medical devices can be very high depending on the application

➢ Possible to estimate cost implications of sample size selection
- Requires multi-step trade-off analysis to determine “comfort levels” based on business case
- Cuts down on late project surprises
  - Cost is a great communication tool between SE and

Battelle Medical Devices & Diagnostics

Innovation occurs at the intersection of multiple disciplines

- Contract Medical Device Research & Product Development Company

- Contract Medical Device Research & Product Development Company

A4301 ISO 9001:2000 13485:2003

MDS

1967-2009

217 total

2004, 2008

2002