

1 MINUTES OF THE TELECONFERENCE

2 OF THE PQRI PSD MASS BALANCE WORKING GROUP ON

3 29 APRIL 2005

4 **I. PARTICIPANTS**

5
6 Terry Tougas (Boehringer Ingelheim), Co-Chair Ken Furnkranz (FDA)
7 Bruce Wyka (Schering-Plough), Co-Chair Rik Lostritto (FDA)
8 Dave Christopher (Schering-Plough) Lana Lyapustina (IPAC-RS)
9 Paul Curry (USP, Solvay) Jolyon Mitchell (Trudell Medical)
10 Bill Doub (FDA) Brian Rogers (FDA)
11 Helen Strickland (GlaxoSmithKline)

12 **II. OPENING**

13 Mr. Wyka welcomed the participants. Dr. Lyapustina reminded the Working Group of the
14 competition guidelines and cautioned against any reference to commercially sensitive subjects.
15 The objectives of the teleconference were: (i) to review the comparison of the April 2005 and
16 November 2004 mass balance (MB) proposals and (ii) to consider next steps.

17 **III. DISCUSSION**

18 Mr. Wyka stated that at the 6 April meeting, it was agreed that the proposal presented at that
19 time by Dr. Lostritto and Dr. Rogers would be evaluated by the statisticians, with the purpose
20 of comparing it to the proposal that the Working Group had drafted in the fall of 2004.

21 Ms. Strickland explained the method of calculation used by the evaluating team, as well as the
22 underlying assumptions and results (see Appendix A). In addition, during the discussion it
23 was clarified that (i) the percents refer to the label claim, not to the target MB; and (ii) USP
24 approach is based on MB calculated as percent of the assay for the batch, rather than as percent
25 of the label claim; this allows to reduce the variability of MB results.

26 Ms. Strickland's analysis demonstrated that the new proposal was significantly more restrictive
27 than the old one.

28 Mr. Wyka stated that it was his understanding that if the new proposal was more restrictive, the
29 group would return to the proposal drafted in the fall for further discussion. Dr. Lostritto
30 replied that (i) he, Dr. Rogers and Dr. Poochikian had never agreed to not consider their or any
31 new proposal regardless of whether it was shown to be more restrictive or not; and (ii) and that
32 there was no consensus of agreement on any proposal.

33 Dr. Lostritto then suggested, on behalf of himself and Drs. Rogers and Poochikian, that the
34 activities of this Working Group be put on hiatus for an indefinite time. He explained that they

35 see no value added in continued circular discussions at this time. He also mentioned the time
36 and resource limitations imposed by the PDUFA related workload, the upcoming move of parts
37 of CDER to White Oak, and FDA/CDER/ONDC's reorganization.

38 Mr. Wyka asked whether the proposed hiatus would end within a pre-specified time; Dr.
39 Lostritto did not feel it would end in the near future because of the uncertainties caused by the
40 move, workload and re-organization.

41 Dr. Tougas proposed that the status of this project and FDA's situation be re-evaluated at a
42 specific time in the future; but Dr. Lostritto declined this proposal. Dr. Tougas explained that
43 the Working Group cannot, by itself, end the project, and an appropriate process would have to
44 be followed. He indicated that this would need to be brought up to the SC and DPTC.

45 Mr. Wyka asked whether Dr. Lostritto could give any specific objections to the previous
46 proposal discussed by the Group. Dr. Lostritto re-stated his observation, shared by Drs. Rogers
47 and Poochikian, that the proposal made on 6 April was justified by the data they see for
48 approved MDI and DPI drug products, NDAs in review, or soon to be submitted NDAs.

49 Dr. Tougas repeated his earlier request that FDA provide the data that is the basis for their
50 proposal to the Working Group for analysis. Another participant commented that either the
51 data FDA sees must be different from the data industry sees or the two parties are looking at the
52 data in different ways. Dr. Lostritto indicated that he would like to provide the data but had no
53 resources to do so. Dr. Lostritto noted however that they see no field alerts or other problems
54 related to mass balance when limited to 85-115%, and that individual companies had not been
55 highlighting mass balance as an issue.

56 Drs. Lostritto and Rogers were asked what criteria they would utilize in the future for assessing
57 Mass Balance, since the committee has not finalized any proposal. They indicated that they
58 would consider to accept the criteria they proposed on 6 April in their individual reviews cases
59 as supported by appropriate data, and could further modify those criteria on a case-by-case
60 basis as needed, to rescale to a different number of units.

61 Dr. Lyapustina asked why not have better developed MB criteria in the guidance so that fewer
62 exceptions would be needed and the review time could be reduced. Dr. Rogers explained that
63 this would not result in a substantial times savings because the review time spent on evaluating
64 MB characteristics is much shorter than that spent on reviewing some other parameters and
65 characterization data, such as; DCU, PSD- stage groupings and review of container-closure data

66 Dr. Mitchell proposed that the work of this Group be at least documented in a technical paper
67 so that if somebody wanted to pick up this topic in the future they would know where to start.
68 Dr. Lostritto stated that he and his colleagues cannot agree to have their names on any such
69 paper; he suggested that the minutes of this Working Group provide sufficient documentation
70 on the completed work.

71 At the end of the teleconference, several Working Group members expressed their
72 disappointment; Drs. Lostritto and Rogers thanked Ms. Strickland and other participants for
73 their work.

74 No plans were made for a future teleconference. The participants agreed to finalize by email
75 the minutes of this teleconference and of the 6 April 2005 meeting.

76

Finalized on 28 June 2005

77 **APPENDIX A. EVALUATION OF NOVEMBER 2004 AND APRIL 2005 MB TESTS.**

78

79 **Introduction**

80

81 A new proposal was offered at the April face to face meeting of the PQRI Mass Balance
82 Working Group by Drs. Rogers and Lostritto. This proposal was discussed at that
83 meeting and it was agreed that a sub-group would perform a statistical evaluation. It
84 was agreed that the performance of this new proposal would be compared to the
85 November 2004 proposal. The agreed criterion for further considering this new scheme
86 was whether it was no more 'stringent' than the November 2004 proposal. In the
87 evaluation that follows this was evaluated based on a comparison of the Type I error
88 rate of the proposed schemes and variants i.e. the probability of rejecting a 'good'
89 batch.

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91 **Results and Discussion**

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93 **Evaluation based on 5 Units**

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95 Table 1 describes the April 2005 proposed Mass Balance requirements and Table 2
96 describes November 2004 three-tier proposal for ease of comparison.

97

98 In general, the April 2005 proposal requires a minimum of four of five mass balance
99 results to be within $T_{MB} \pm 15\%$ ¹ with only one result is outside $T_{MB} \pm 15\%$ but within T_{MB}
100 $\pm 20\%$. However, when four of five Mass Balance results are within $T_{MB} \pm 15\%$ and one
101 result is outside $T_{MB} \pm 20\%$, then a retest of the unit whose MB is outside $T_{MB} \pm 20\%$ is
102 allowed. When the retest result is outside $T_{MB} \pm X\%$ (where $X=15$ or 20%) it is deemed
103 that a mass balance failure has occurred and expanded investigation is performed to
104 disposition the batch.

105

¹ Here, all percents refer to the label claim.

106 The three-tier November 2004 proposal requires that the mass balance result of an
107 individual unit be within $T_{MB} \pm 15\%$ and it allows a maximum of two retests per unit while
108 following the published laboratory investigation methodology recommended in the PQRI
109 Working Group's GCIP paper prior to concluding that a mass balance failure has
110 occurred and OOS investigation is initiated.

111

112 Table 3 provides the probability of passing the November 2004 three-tier criteria as
113 applied to 5 units and the probability of passing the April 2005 Mass Balance criteria
114 using a retest limit of $T_{MB} \pm 15\%$ and $T_{MB} \pm 20\%$. The probability of passing was
115 computed for populations where the total variation (product variation and measurement
116 variation) of the mass balance measurements are 2, 4, 5, 6, 7, 7.5, 8, 9, 10 and 12.5%
117 and for mass balance population means where the average mass balance is on Target
118 and where the average mass balance is off target by 1, 2, 3, 4 or 5%. Tables 4 to 6
119 provide general information on how the probability of passing was computed for the
120 April 2005 proposal with retest limits of $\pm 15\%$ and the November 2004 three-tier
121 proposal with limits of $T_{MB} \pm 15\%$.

122

123 As indicated in Table 3 for a product whose total variation is 5% and whose average
124 mass balance is on Target, 99.9999% of the batches would meet the November 2004
125 Three-Tier criteria, whereas, 99.9926 and 99.9927% would meet the April 2005 $T_{MB} \pm$
126 $X\%$ where $X=15$ or $X=20\%$, respectively. This implies that for any of the three criteria
127 less than 1 out of 1000 'good' batches would indicate inadequate mass balance that
128 would result in an OOS investigation.

129

130 Another example, for a product whose total variation is 7.5% and whose average mass
131 balance is off Target by 5%, 99.5714% of the batches would meet the November 2004
132 Three-Tier criteria, whereas, 91.8260 and 92.3846% would meet the April 2005 $T_{MB} \pm$
133 $X\%$ where $X=15$ or $X=20\%$, respectively. This implies that approximately 82 out of 1000
134 'good' batches for either of the April 2005 criteria and only 4 batches for the November
135 2004 three-tier criteria would indicate inadequate mass balance that would result in an
136 OOS investigation.

137

138 The difference in the number of batches that indicate inadequate mass balance by the
139 measurement is minimal when the total variation is less than 5%. However, when the
140 total variation is greater than 5% there is a significant difference in the number of 'good'
141 batches that are deemed to exhibit inadequate mass balance. In general, it was
142 observed that both variants of the April proposal have a higher Type I error rate than the
143 previous November 2004 proposal.

144

145 Evaluation based on 10 Units

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147 Some preliminary work was done for evaluating the April 2005 proposal applied to 10
148 units. Unlike the November 2004 proposal, the April 2005 proposal cannot be directly
149 and simply scaled to any number of units, either for evaluation or for implementation.

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151

152 **Conclusions**

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154 Evaluation based on 5 Units

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156 With respect to the November 2004 evaluation criterion, this analysis demonstrates that
157 the April proposal is more 'stringent' and would result in a higher Type I error rate
158 particularly at variabilities typical of the MB determination.

159

160 The April 2005 proposal elevates mass balance in a CI determination to a redundant
161 specification as opposed to a run qualification in the November 2004 proposal. The
162 April 2005 Mass Balance proposal assesses the performance of the drug product and
163 the analytical method collectively. Whereas, the November 2004 Mass Balance
164 proposal allows adequate assessment of the performance of the analytical method
165 before assessing the performance of the drug product via the independent assessment
166 of each individual Mass Balance result. The independent assessment of each Mass
167 Balance results permits the appropriate implementation of the GCIP investigation
168 method (i.e., the Decision Tree) to be applied.

169

170 Inherently, the total variation for a mass balance measurement is greater than the total
171 variation in the emitted dose measurement because the measurement error of the
172 cascade impaction method is greater than the measurement error of the emitted dose
173 test. This implies that the assessment of the mass balance measurement would result
174 in declaring a batch unacceptable when the emitted dose measurement would result in
175 declaring the batch acceptable. Coupling this with the probability of meeting the April
176 2005 and November 2004 criteria, applying the April 2005 criteria would increase the

177 number of false indications of failures when compared to the November 2004 criteria
178 when the total variation is greater than 5%. As indicated by the IPAC-RS database, the
179 typical total variation (standard deviation) for the mass balance measurement was
180 7.6%. This value is consistent with typical variability of HPLC assays and the
181 complexity and number of measurements required to obtain a CI mass balance
182 determination.

183

184 Evaluation based on 10 Units

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186 Preliminary assessment of the April 2005 proposal indicates that it will likely be much
187 more difficult to implement this proposal to accommodate increased testing, which is
188 counter to the general direction FDA is moving to minimize penalties for increased
189 testing to better determine consumer product quality. This represents a step backward
190 in light of FDA's Pharmaceutical Quality for the 21st Century initiative.

191

192 **Table 1. Mass Balance Specification Proposed by FDA on April 6, 2005**

193

Single MB results X_i generated from each of 5 units.

If 5/5 $X_i \in [T_{MB-15}, T_{MB+15}]$ then MB test is acceptable. Testing complete.

If 4/5 $X_i \in [T_{MB-15}, T_{MB+15}]$ and 5/5 $X_1 \in [T_{MB-20}, T_{MB+20}]$ then MB test is acceptable.

If 4/5 $X_i \in [T_{MB-15}, T_{MB+15}]$ and 1/5 $X_i \notin [T_{MB-20}, T_{MB+20}]$, then unit whose MB result is outside $[T_{MB-20}, T_{MB+20}]$ is retested.

If 3/5 $X_i \in [T_{MB-15}, T_{MB+15}]$, then MB test failure observed, perform OOS investigation.

If 2/5 $X_i \in [T_{MB-15}, T_{MB+15}]$, then MB test failure observed, perform OOS investigation.

If 1/5 $X_i \in [T_{MB-15}, T_{MB+15}]$, then MB test failure observed, perform OOS investigation.

If 0/5 $X_i \in [T_{MB-15}, T_{MB+15}]$, then MB test failure observed, perform OOS investigation.

RETEST OPTION 1 WITH $\pm 15\%$ LIMITS.

If 1/1 $X_1 \in [T_{MB-15}, T_{MB+15}]$, then MB test passes. Testing complete.

If 1/1 $X_i \notin [T_{MB-15}, T_{MB+15}]$, then MB test failure observed, perform OOS investigation.

RETEST OPTION 2 WITH $\pm 20\%$ LIMITS

If 1/1 $X_1 \in [T_{MB-20}, T_{MB+20}]$, then MB test passes. Testing complete.

If 1/1 $X_i \notin [T_{MB-20}, T_{MB+20}]$, then MB test failure observed, perform OOS investigation.

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196 **Table 2. Mass Balance Procedure for November 2004 Three Tier Test**

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Tier 1:

MB result X_i generated from unit.

If $X_i \in [T_{MB-15}, T_{MB+15}]$, then MB result is acceptable. Testing complete. Tier 1 Pass.

If $X_i \notin [T_{MB-15}, T_{MB+15}]$, then MB result not acceptable. Perform Tier 2 testing.

Tier 2:

MB result X_i generated from same unit.

If $X_i \in [T_{MB-15}, T_{MB+15}]$, then MB result is acceptable. Testing complete. Tier 2 Pass.

If $X_i \notin [T_{MB-15}, T_{MB+15}]$, then MB result not acceptable. Perform Tier 3 testing.

Tier 3:

MB result X_i generated from same unit.

If $X_i \in [T_{MB-15}, T_{MB+15}]$, then MB result is acceptable. Testing complete. Tier 3 Pass.

If $X_i \notin [T_{MB-15}, T_{MB+15}]$, then MB test failure observed. Perform OOS Investigation.

198 **Table 3. Probability of Passing**

Population Standard Deviation	Proposal 5 Units	Population Mean On Target	Population Mean TMB ± 1	Population Mean TMB ± 2	Population Mean TMB ± 3	Population Mean TMB ± 4	Population Mean TMB ± 5
2	Nov04 (3-Tier)	100.0000	100.0000	100.0000	100.0000	100.0000	100.0000
	April05($\pm 15\%$)	100.0000	100.0000	100.0000	100.0000	100.0000	99.9999
	April05($\pm 20\%$)	100.0000	100.0000	100.0000	100.0000	100.0000	99.9999
4	Nov04 (3-Tier)	99.9999	99.9999	99.9999	99.9999	99.9999	99.9998
	April05($\pm 15\%$)	99.9999	99.9999	99.9996	99.9981	99.9911	99.9616
	April05($\pm 20\%$)	99.9999	99.9999	99.9996	99.9981	99.9911	99.9619
5	Nov04 (3-Tier)	99.9999	99.9999	99.9999	99.9997	99.9986	99.9940
	April05($\pm 15\%$)	99.9926	99.9894	99.9748	99.9299	99.8055	99.4902
	April05($\pm 20\%$)	99.9927	99.9895	99.9752	99.9312	99.8098	99.5034
6	Nov04 (3-Tier)	99.9990	99.9987	99.9973	99.9930	99.9800	99.9439
	April05($\pm 15\%$)	99.8444	99.8123	99.6945	99.4208	98.8541	97.7679
	April05($\pm 20\%$)	99.8492	99.8183	99.7055	99.4441	98.9050	97.8752
7	Nov04 (3-Tier)	99.9834	99.9805	99.9698	99.9436	99.8845	99.7565
	April05($\pm 15\%$)	98.9724	98.8586	98.4800	97.7239	96.4034	94.2643
	April05($\pm 20\%$)	99.0247	98.9181	98.5637	97.8574	96.6250	94.6297
7.5	Nov04 (3-Tier)	99.9529	99.9466	99.9246	99.8750	99.7729	99.5714
	April05($\pm 15\%$)	97.9671	97.7967	97.2457	96.1977	94.4683	91.8260
	April05($\pm 20\%$)	98.0874	97.9291	97.4177	96.4451	94.8400	92.3846
10	Nov04 (3-Tier)	98.8129	98.7607	98.5954	98.2903	97.7986	97.0505
	April05($\pm 15\%$)	84.7442	84.3552	83.1748	81.1676	78.2903	74.5117
	April05($\pm 20\%$)	85.8736	85.5123	84.4144	82.5423	79.8474	76.2886
12.5	Nov04 (3-Tier)	94.0522	93.9388	93.5916	92.9898	92.0991	90.8725
	April05($\pm 15\%$)	63.0344	62.6813	61.6261	59.8830	57.4787	54.4570
	April05($\pm 20\%$)	65.3548	65.0144	63.9961	62.3095	59.9743	57.0247

Table 4. Probability Computations for Mass Balance Proposal using $\pm 15\%$ Retest Limits

Outcome	Outcome Description	Probability Terms	Probability of a Single Occurrence in Terms of Limits given a Normal Distribution (μ, σ^2)	Probability of Occurrence Over Entire Sample Space	
1	$P\{5/5 \in [T_{MB}-15, T_{MB}+15]\}$	$P\{X \in [T_{MB}-15, T_{MB}+15]\} = P_{w15}$	$(P_{w15})^5$	P_1	
2	$P\{4/5 \in [T_{MB}-15, T_{MB}+15]\}$	$P\{X \in [T_{MB}-20, T_{MB}-15]\} = P_{w5L}$	$(P_{w15})^4(P_{w5L})$	$\binom{5}{4} P_{2a}$	
		$P\{X \in (T_{MB}+15, T_{MB}+20]\} = P_{w5R}$	$(P_{w15})^4(P_{w5R})$	$\binom{5}{4} P_{2b}$	
		$P\{X < T_{MB}-20\} = P_{LT20}$	$P\{X \in [T_{MB}-15, T_{MB}+15]\} = P_{w15}$	$(P_{w15})^4(P_{LT20})(P_{w15})$	$\binom{5}{4} P_{2c1}$
			$P\{X \notin [T_{MB}-15, T_{MB}+15]\} = P_{o15}$	$(P_{w15})^4(P_{LT20})(P_{o15})$	$\binom{5}{4} P_{2c2}$
		$P\{X > T_{MB}+20\} = P_{GT20}$	$P\{X \in [T_{MB}-15, T_{MB}+15]\} = P_{w15}$	$(P_{w15})^4(P_{GT20})(P_{w15})$	$\binom{5}{4} P_{2d1}$
			$P\{X \notin [T_{MB}-15, T_{MB}+15]\} = P_{o15}$	$(P_{w15})^4(P_{GT20})(P_{o15})$	$\binom{5}{4} P_{2d2}$

3	$P\{3/5 \in [T_{MB}-15, T_{MB}+15]\}$	$P\{X \in [T_{MB}-15, T_{MB}+15]\} = P_{w15}$ $P\{X \notin [T_{MB}-15, T_{MB}+15]\} = P_{o15}$	$(P_{w15})^3(P_{o15})^2$	$\binom{5}{3} P_3$
4	$P\{2/5 \in [T_{MB}-15, T_{MB}+15]\}$	$P\{X \in [T_{MB}-15, T_{MB}+15]\} = P_{w15}$ $P\{X \notin [T_{MB}-15, T_{MB}+15]\} = P_{o15}$	$(P_{w15})^2(P_{o15})^3$	$\binom{5}{2} P_4$
5	$P\{1/5 \in [T_{MB}-15, T_{MB}+15]\}$	$P\{X \in [T_{MB}-15, T_{MB}+15]\} = P_{w15}$ $P\{X \notin [T_{MB}-15, T_{MB}+15]\} = P_{o15}$	$(P_{w15})(P_{o15})^4$	$\binom{5}{1} P_5$
6	$P\{0/5 \in [T_{MB}-15, T_{MB}+15]\}$	$P\{X \notin [T_{MB}-15, T_{MB}+15]\} = P_{o15}$	$(P_{o15})^5$	P_6
Sum Over Entire Sample Space				1

Table 5. Probability Computations for Single Unit Passing/Failing Mass Balance Limits

IV. O U T C O M E	Outcome Description	Probability Terms	Probability of Single Occurrence
Tier 1 Pass	1 st MB result within $T_{MB} \pm 15\%$.	$P\{X \in [T_{MB}-15, T_{MB}+15]\} = P_{w15}$	$(P_{w15}) = P_{T1pass}$
Tier 2 Pass	1 st MB result outside $T_{MB} \pm 15\%$. 2 nd MB result within $T_{MB} \pm 15\%$.	$P\{X \notin [T_{MB}-15, T_{MB}+15]\} = P_{o15}$ $P\{X \in [T_{MB}-15, T_{MB}+15]\} = P_{w15}$	$(P_{o15})(P_{w15}) = P_{T2pass}$
Tier 3 Pass	1 st MB result outside $T_{MB} \pm 15\%$.. 2 nd MB result outside $T_{MB} \pm 15\%$.. 3 rd MB result within $T_{MB} \pm 15\%$..	$P\{X \notin [T_{MB}-15, T_{MB}+15]\} = P_{o15}$ $P\{X \notin [T_{MB}-15, T_{MB}+15]\} = P_{o15}$ $P\{X \in [T_{MB}-15, T_{MB}+15]\} = P_{w15}$	$(P_{o15})^2(P_{w15}) = P_{T3pass}$
Tier 3 Failure	1 st MB result outside $T_{MB} \pm 15\%$.. 2 nd MB result outside $T_{MB} \pm 15\%$.. 3 rd MB result outside $T_{MB} \pm 15\%$..	$P\{X \notin [T_{MB}-15, T_{MB}+15]\} = P_{o15}$ $P\{X \notin [T_{MB}-15, T_{MB}+15]\} = P_{o15}$ $P\{X \notin [T_{MB}-15, T_{MB}+15]\} = P_{o15}$	$(P_{o15})^3 = P_{T3fail}$

Table 6. Probability Computations for Five Unit MB Test

Outcome	Outcome Description	Probability Terms	Probability of a Single Occurrence in Terms of Limits given a Normal Distribution (μ, σ^2)	Probability of Occurrence Over Sample Space
1	5/5 Units Passing 3-Tier Test	$P_{T1pass} + P_{T2pass} + P_{T3pass} = P_{pass}$	$[(P_{w15}) + (P_{o15}) (P_{w15}) + (P_{o15})^2 (P_{w15})]^5$	P_1
2	4/5 Units Passing 3-Tier Test	$P_{T1pass} + P_{T2pass} + P_{T3pass} = P_{pass}$ $P_{T3fail} = P_{failure}$	$[(P_{w15}) + (P_{o15}) (P_{w15}) + (P_{o15})^2 (P_{w15})]^4 [(P_{o15})^3]^1$	$\binom{5}{4} P_2$
3	3/5 Units Passing 3-Tier Test	$P_{T1pass} + P_{T2pass} + P_{T3pass} = P_{pass}$ $P_{T3fail} = P_{failure}$	$[(P_{w15}) + (P_{o15}) (P_{w15}) + (P_{o15})^2 (P_{w15})]^3 [(P_{o15})^3]^2$	$\binom{5}{3} P_3$
4	2/5 Units Passing 3-Tier Test	$P_{T1pass} + P_{T2pass} + P_{T3pass} = P_{pass}$ $P_{T3fail} = P_{failure}$	$[(P_{w15}) + (P_{o15}) (P_{w15}) + (P_{o15})^2 (P_{w15})]^2 [(P_{o15})^3]^3$	$\binom{5}{2} P_4$
5	1/5 Units Passing 3-Tier Test	$P_{T1pass} + P_{T2pass} + P_{T3pass} = P_{pass}$ $P_{T3fail} = P_{failure}$	$[(P_{w15}) + (P_{o15}) (P_{w15}) + (P_{o15})^2 (P_{w15})] [(P_{o15})^3]^4$	$\binom{5}{1} P_5$
6	0/5 Units Passing 3-Tier Test	$P_{T1pass} + P_{T2pass} + P_{T3pass} = P_{pass}$ $P_{T3fail} = P_{failure}$	$[(P_{o15})^3]^5$	P_6