

Preliminary Results of the Animal Study Comparing the Vero Cell DNA Oral and IM Uptake Efficiency

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Vaccine Cell Substrates 2004

Previously Merck Proposed that the WHO 10 ng limit be Adjusted by the 10^4 Difference in Uptake Efficiency Between IM and Oral Routes



WHO's 10 ng limit not applicable to oral vaccines



$10 \text{ ng Parenteral limit}$
 $\times 10^4 \text{ Factor for Parenteral/Oral Uptake}$

 $= 100 \mu\text{g DNA Proposed Safety Limit}$



RotaTeq® is under $100 \mu\text{g DNA}$

Last Year Merck Proposed to Develop Further Empirical Data Supporting the $\geq 10^4$ Difference in Uptake Efficiency

Administer
100 μ g Vero Cell DNA to Rats

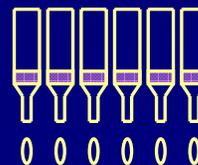


Perform Necropsies 1, 2, 3, & 7 Days Post-Dose

GI Tract	IM	Lymph Nodes
1. Tongue	17. Quadriceps	20. Mesenteric
2. Oral Muc.	18. Hamstrings	21. Inguinal
3. Pharynx Muc.	19. Skin	22. Iliac
4. Proximal Esophagus		
5. Distal Esophagus		
6. Glandular Stomach		
7. Non-gland. Stomach		
8. Proximal Duodenum	23. Blood	29. Liver
9. Distal Duodenum	24. Kidneys	30. Ovaries
10. Proximal Jejunum	25. Heart	31. Lungs
11. Middle Jejunum	26. Thymus	32. Brain
12. Distal Jejunum	27. Spleen	33. Muscle
13. Ileum	28. Testes	34. Skin
14. Cecum		
15. Middle Colon		
16. Terminal Colon		

Other Tissues

Perform
QPCR Analyses

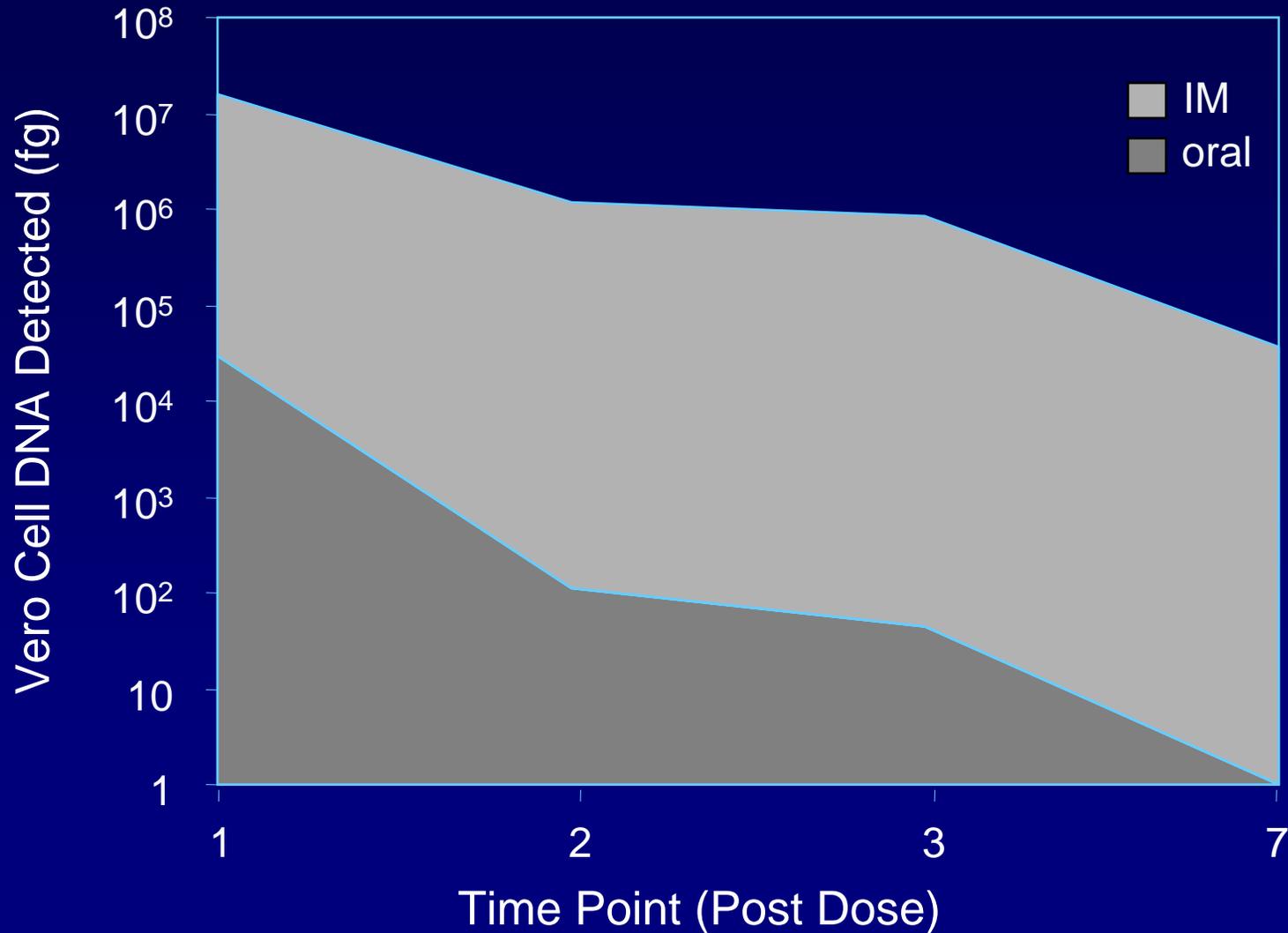


Extract
DNA

A Simple Formula is Used to Translate the QPCR Results to Amount of DNA per Tissue

$$\frac{\text{fg of AGM DNA}}{\mu\text{g of Rat DNA}} \times \frac{\mu\text{g of Rat DNA}}{\text{mg of Tissue}} \times \text{Tissue Wt} = \text{fg of AGM DNA in the Tissue}$$

Preliminary Results of Vero Cell DNA IM vs. Oral Uptake Study Confirms Oral Route is Less Efficient than the IM Route



Adjustment of the WHO 10 ng Limit by the Difference in Uptake Efficiency Between IM and Oral Routes

Day(s) Post-Dose	IM vs. Oral Ratio			Adjusted Res DNA Safety Limit (μg)
	F	M	GM	
2-7	147	1.1×10^6	13437	134
7	$>1.5 \times 10^4$	$>8.6 \times 10^4$	$>3.6 \times 10^4$	>360

Factors to Consider When Adjusting the WHO 10 ng Limit by the Difference in IM and Oral Uptake Efficiency

- Study results imply new adjusted residual DNA safety limit will be ~100 μg using AUC comparison 2-7 days post-dose.