

Table of Contents

1	Introduction	7
1.1	Regulatory Framework on Comparability.....	7
1.2	Issues with rAAV Comparability	8
1.3	Purpose and Scope	8
1.4	Structure of the Guide.....	9
2	rAAV Gene Therapy Manufacturing Processes	11
2.1	Introduction	11
2.2	Process Understanding.....	12
2.3	Process Parameters	29
2.4	Trending.....	29
2.5	Sampling and QC.....	29
2.6	Biosafety	29
3	Analytical Techniques.....	31
3.1	Introduction	31
3.2	Compendial Tests	31
3.3	Biosafety	32
3.4	Identity and Integrity.....	36
3.5	Capsid Protein Ratio	37
3.6	Aggregation.....	38
3.7	Vector Genome Titer	39
3.8	Bioactivity and Potency	39
3.9	Product-Related Purity/Impurities	41
3.10	Process-Related Impurities.....	45
4	Comparability	47
4.1	Objective of Comparability	49
4.2	Process and Product Understanding and Risk Assessment.....	52
4.3	Changes Requiring Comparability Studies	53
4.4	Strategies for Analytical Comparability	64
4.5	Preclinical or Clinical Comparability.....	71
5	Appendix 1 – Case Studies	73
5.1	Introduction	73
5.2	Facility Change/Process Transfer (Clinical and Commercial Phases).....	73
5.3	Adherent to Suspension (Pre-Clinical and Clinical).....	74
5.4	Bioreactor Model Change (Pre-Clinical and Clinical).....	76
6	Appendix 2 – References	81
7	Appendix 3 – Glossary.....	93
7.1	Acronyms and Abbreviations	93