1. Introduction

The CP-X.X <INN> drug substance commercial manufacturing process was validated at Site A. The process was validated at a scale of XXX kg ± XX% (XXX to XXX kg) of <starting input material> (Site A Validation Campaign), and the final milling step was validated at Site B.

The drug substance is prepared via X chemical steps (Steps 1 through 3) with a final form setting recrystallization (Step X). Process validation was performed for all X steps of the drug substance manufacturing process.

Critical in-process controls, drug substance intermediates release acceptance limits, and drug substance release acceptance limits were utilized as process validation acceptance criteria.

2. Site A Validation Campaign Results

2.1 Drug Substance Process Validation Batches (Site A)

Three consecutive drug substance batches were manufactured successfully in accordance with the commercial manufacturing process. A summary of the drug substance validation batches is shown in the table below.

Table 1. Drug Substance Process Validation Batches Manufactured at Site A

	Drug Substance Batch Number		Drug Substance Batch Size[a] (kg)
Date of Manufacture	Amgen Batch Number	Site A Batch Number	
DD Mon YYYY	XXXXXXXXXX	XX-XXX-XXXX	XXX.X
DD Mon YYYY	XXXXXXXXXX	XX-XXX-XXXX	XXX.X
DD Mon YYYY	XXXXXXXXXX	XX-XXX-XXXX	XXX.X

[a] Batch size is the actual off-loaded weight of the drug substance.

2.2 Step 1 Process Validation

Step 1 involves the synthesis of [intermediate name] from [starting material 1] and [starting material 2]. The three [intermediate name] validation batches are presented in the table below.

Table 2. Step 1 Process Validation Batches

Date of Manufacture	starting material 1 Batch Number	Step 1 Manufacturing Scale (kg of starting material 1)	Intermediate Batch Number	Intermediate Batch Size (kg)[a]
DD Mon YYYY	XX-XXX-XXXX	XXX.X	XX-XXX-XXXX	XXX.X

DD Mon YYYY	XX-XXX-XXXX	XXX.X	XX-XXX-XXXX	XXX.X
DD Mon YYYY	XX-XXX-XXXX	XXX.X	XX-XXX-XXXX	XXX.X

[a] Batch size is the actual off-loaded weight of the drug substance intermediate.

Process validation of Step 1 demonstrated acceptable and consistent performance. The step yield, in-process control data, and drug substance intermediate release test results are within the defined acceptance criteria as show in the tables below.

Table 3. Step 1 Yield

Performance Indicator	Intermediate Batch Number		
	XX-XXX-XXXX	XX-XXX-XXXX	XX-XXX-XXXX
Yield %	XX	XX	XX

Table 4. Step 1 In-Process Control Data

Performance Indicator	Acceptance Criteria	Classification	Intermediate Batch Number		
			XX-XXX-XXXX	XX-XXX-XXXX	XX-XXX-XXXX
Residual water content (w/w%)	≤ X.XX	Non-critical	X.XX	X.XX	X.XX
Reaction conversion: residual starting material 1 by HPLC (Step Aa) (LC area %)	≤ X.X	Non-critical	X.X	X.X	X.X
Reaction conversion: residual starting material 1 Chloride Intermediate derivatized as intermediate adduct by HPLC (Step Ab) (LC area%)	≤ X.X	Non-critical	X.X	X.X	X.X
End of drying by LOD (Step Ac) (w/w%)	≤ X.X	Non-critical	X.X	X.X	X.X
intermediate content by HPLC (Step Ac) (LC area%)	≤ X.X	Non-critical	X.X	X.X	X.X
intermediate Dimer by HPLC (LC area %)	≤ X.X	Non-critical	Not detected[a]	Not detected[a]	Not detected[a]

[a] The Quantification Limit of the HPLC method is 0.05%.

Table 5. Step 1 DS Release Testing Results

		DS Batch Number		
Performance Indicator	Acceptance Criteria	XX-XXX-XXXX	XX-XXX-XXXX	XX-XXX-XXXX
Appearance	White to off-white, to red, to orange, to brown solid	Off-white solid	Off-white solid	Orange solid
ID by HPLC	Conforms to standard	Conforms	Conforms	Conforms
Assay by HPLC (as is) (w/w%)	XX.X to XXX.X	XX.X	XXX.X	XX.X
Organic Impurities by HPLC (area %)				
Impurity A	≤ X.X	X.XX	X.XX	X.XX
Intermediate Dimer (Impurity B)	≤ X.X	< X.XX	< X.XX	< X.XX
Single Unspecified Impurity	≤ X.XX	X.XX	--	--
		X.XX	X.XX	X.XX
		X.XX	X.XX	--
Total Impurities	≤ X.X	X.XX	X.XX	X.XX

2.3 Step 2 Process Validation

Step 2 involves the synthesis of intermediate 2 from starting material 2. Process validation of step 2 demonstrated acceptable and consistent performance. Because of the quantity of starting material 2 produced in Step 1, four validation lots of intermediate 2 were manufactured. The 4 intermediate 2 validation batches are presented in the table below.

Table 6. Step 2 Process Validation Batches

Date of Manufacture	Starting material 2 Batch Number	Step 2 Manufacturing Scale (kg)	Intermediate 2 Batch Number	Intermediate 2 Batch Size (kg)[a]
DD Mon YYYY	XX-XXX-XXXX	XXX.X	XX-XXX-XXXX	XXX.X
DD Mon YYYY	XX-XXX-XXXX	XXX.X	XX-XXX-XXXX	XXX.X
DD Mon YYYY	XX-XXX-XXXX	XXX.X	XX-XXX-XXXX	XXX.X

The step yield, in-process control data, and drug substance intermediate release test results are within the defined acceptance criteria as show in the tables below.

Table 7. Step 2 Yield

Performance Indicator	Intermediate 2 Batch Number			
	XX-XXX-XXXX	XX-XXX-XXXX	XX-XXX-XXXX	XX-XXX-XXXX
Yield %	XX	XX	XX	XX

Step 2 is a very efficient step and routinely has high yields. This resulted in the yield slightly exceeding 100% in the final batch. The results are considered acceptable.

Table 8. Step 2 In-Process Control Data

Performance Indicator	Acceptance Criteria	Classification	Intermediate 2 Batch Number			
			XX-XXX-XXXX	XX-XXX-XXXX	XX-XXX-XXXX	XX-XXX-XXXX
Palladium content (step 2a) (ppm)	≤ XX (corrected for assay)	Critical	< X	< X	< X	X
Reaction conversion (by HPLC, step 2b) (LC area%)	≤ X.XX	Non-critical	< X.XX	< X.XX	< X.XX	< X.XX
End of drying, water content (step 2c) (w/w%)	≤ X.X	Non-critical	X.X	X.X	X.X	X.X

Table 9. Step 2 Intermediate 2 Release Testing Results

		Intermediate 2 Batch Number			
Performance Indicator	Acceptance Criteria	XX-XXX-XXXX	XX-XXX-XXXX	XX-XXX-XXXX	XX-XXX-XXXX
Appearance	White to off-white to light brown solid	Off-white solid	Off-white solid	Off-white solid	Off-white solid
ID by HPLC	Conforms to Standard	Conforms	Conforms	Conforms	Conforms
Assay by HPLC (as-is) (w/w%)	XX.X to XXX.X	XX.X	XX.X	XX.X	XX.X
Organic Impurities by HPLC (area %)					
Impurity A	≤ X.XX	< X.XX	< X.XX	< X.XX	< X.XX
Any single unspecified impurity	≤ X.XX	X.XX (RRT:X.XX)	--	--	--
		< X.XX (RRT:X.XX)	X.XX (RRT:X.XX)	<X.XX (RRT:X.XX)	<X.XX (RRT:X.XX)
		X.XX (RRT:X.XX)	--	--	--
		X.XX (RRT:X.XX)	--	--	--
		X.XX (RRT:X.XX)	--	--	--
Total Impurities	≤ X.X	X.XX	X.XX	X.XX	< X.XX

HPLC = High-performance liquid chromatography; RRT = Relative Retention Time

'--' no impurity detected at RRT

2.4 Step 3 Process Validation

Step 3 involves the synthesis of unfinished <INN> from Intermediate 2. Process validation of step 3 demonstrated acceptable and consistent performance. The 3 validation batches of unfinished <INN> are presented in the table below.

Table 10. Step 3 Process Validation Batches

Date of Manufacture	Intermediate 2 Batch Number	Step 4 Manufacturing Scale (kg)	Unfinished <INN> Batch Number	Unfinished <INN> Batch Size (kg)[a]
DD Mon YYYY	XX-XXX-XXXX	XXX.X	XX-XXX-XXXX	XXX.X
DD Mon YYYY	XX-XXX-XXXX	XXX.X	XX-XXX-XXXX	XXX.X
DD Mon YYYY	XX-XXX-XXXX	XXX.X	XX-XXX-XXXX	XXX.X

[a] Batch size is the actual off-loaded weight of the drug substance intermediate.

The step yield, in-process control data, and drug substance intermediate release test results are within the defined acceptance criteria as shown in the tables below.

Table 11. Step 3 Yield

	Unfinished <INN> Batch Number		
Performance Indicator	XX-XXX-XXXX	XX-XXX-XXXX	XX-XXX-XXXX
Yield %	XX	XX	XX

Table 12. Step 3 In-Process Control and Process Parameter Data

			Unfinished <INN> Batch Number		
Performance Indicator	Acceptance Criteria	Classification	XX-XXX-XXXX	XX-XXX-XXXX	XX-XXX-XXXX
Reaction conversion (Intermediate 2 content by HPLC, step 4a) (LC area%)	≤ X.XX	Critical	X.XX	X.XX	X.XX
End of drying, water content (step 4b) (w/w%)	≤ X.X	Non-critical	X.X	X.X	X.X

Table 13. Step 3 Unfinished <INN> Release Testing Results

		Unfinished <INN> Batch Number		
Performance Indicator	Acceptance Criteria	XX-XXX-XXXX	XX-XXX-XXXX	XX-XXX-XXXX
Appearance	White to off-white to yellow to light brown solid	Off-white solid	Off-white solid	Off-white solid
ID by HPLC	Conforms to Standard	Conforms	Conforms	Conforms
Assay by HPLC (as-is) (w/w%)	XX.X to XXX.X	XX.X	XX.X	XX.X
Organic Impurities by HPLC (w/w%)				
Impurity A	≤ X.X	< X.XX	X.XX	X.XX
Impurity B	≤ X.X	< X.XX	< X.XX	< X.XX
Impurity C				
Impurity D	≤ X.X	X.XX	X.XX	X.XX
Individual Unspecified Impurity	≤ X.XX	Not Detected[a]	Not Detected[a]	Not Detected[a]
Total Impurities	≤ X.X	X.X	X.X	X.X

[a] The Quantification Limit of the HPLC method is 0.05%.

2.5 Step X Process Validation

Step X is the milling operation at Site B, which results in the preparation of Finished <INN>. The 3 Finished <INN> validation batches are presented in the table below.

Table 14. Step X Process Validation Batches

Date of Manufacture	Unmilled <INN> Batch Number	Step X Manufacturing Scale (kg)	Finished <INN> Batch Number	Finished <INN> Batch Size (kg)[a]
DD Mon YYYY	XX-XXX-XXXX	XXX.X	XX-XXX-XXXX	XXX.X
DD Mon YYYY	XX-XXX-XXXX	XXX.X	XX-XXX-XXXX	XXX.X
DD Mon YYYY	XX-XXX-XXXX	XXX.X	XX-XXX-XXXX	XXX.X

[a] Batch size is the actual off-loaded weight of the drug substance.

The step yield, in-process control data, and drug substance intermediate release test results are within the defined acceptance criteria as show in the tables below.

Table 15. Step X Yield

Performance Indicator	Finished <INN> Batch Number		
	XX-XXX-XXXX	XX-XXX-XXXX	XX-XXX-XXXX
Yield %	XX.X	XX.X	XX.X

Table 16. Step X In-Process Control Data

Performance Indicator	Acceptance Criteria	Finished <INN> Batch Number		
		XX-XXX-XXXX	XX-XXX-XXXX	XX-XXX-XXXX
In Process Controls (IPCs) – D_{90} Results				
PSD D_{90} Check #1[a]	< XX µm	XX	XX	XX
PSD D_{90} Check #2[a]	< XX µm	XX	XX	XX
PSD D_{90} Check #3[a]	< XX µm	XX	XX	XX

N/A = Not applicable; "PSD" = Particle Size Distribution

[a] The validation study required a PSD sample check at approximately every XX kg of material milled. This resulted in approximately X PSD check points over the course of the milling operation.

Table 17. Step X Release Testing Results

Performance Indicator	Acceptance Criteria	Finished <INN> Batch Number		
		XX-XXX-XXXX	XX-XXX-XXXX	XX-XXX-XXXX
Batch Composite Sample PSD (D_{50})	≤ XX μm	XX	XX	XX
Batch Composite Sample PSD (D_{90})	≤ XX μm	XX	XX	XX

PSD = Particle Size Distribution

2.6 Finished <INN>

Upon completion of milling at Site B, the Finished <INN> drug substance was returned to Site A and tested against final release specifications. All results are within the defined acceptance criteria for the validation batches evaluated.

3. Conclusion

Validation of the commercial <INN> drug substance manufacturing process, at a scale of XXX kg ± XX% of <starting material>, was successfully completed at Site A and Site B. Results obtained for all process validation batches met acceptance criteria and demonstrate that the manufacturing process is capable of consistently producing drug substance that meets pre-defined acceptance criteria.