<<**AI/Pen**>>

1. Impact of Extrusion to Drug Product Quality

The prefilled autoinjector/pen (AI/pen) contains a X mg/mL prefilled syringe (PFS) with a staked-in-place needle. Drug product compatibility with the glass syringe primary container closure system was determined by sorption and particulation studies (3.2.P.2.4, Container Closure System [Primary container]) and compatibility was demonstrated for the PFS by comparing product quality before and after extrusion through the syringe (3.2.P.2.6, Compatibility [Primary container]).

Drug product quality was also tested for compatibility after extrusion of product through the syringe using the AI/pen delivery device to identify any additional potential impact from shear stress after extrusion. A change in the distribution of size variants, subvisible particles, and potential chemical modifications are considered the most likely changes in product quality upon extrusion. The analytical methods used in the evaluation are listed in Table 2. Product quality was evaluated at temperatures of 15°C and 25°C (incubated for at least 4 hours). The temperature range exhibits variation in product viscosity and hence different shear forces. The selected conditions support in use compatibility at controlled room temperature (not more than 25°C).

Table 1. Drug Product Quality Parameters Used for Evaluation of Drug Product Compatibility With Prefilled Syringe When Extruded Using the AI/Pen Device

Test Method	Attributes Monitored
Size exclusion HPLC (SE-HPLC)[a]	Size variants
Cation Exchange HPLC (CEX-HPLC)[a]	Deamination
Reduced capillary electrophoresis with sodium dodecyl sulfate (rCE-SDS)[b]	Fragmentation (low and middle molecular weight species) and high molecular weight (HMW)
Subvisible particles by light obscuration (HIAC)[a]	Subvisible particle counts
Micro-flow imaging (MFI)[c]	Subvisible particle counts and morphology

[a] Methods used for commercial release are described in 3.2.S.4.2 (SE-HPLC), 3.2.P.5.2 (CEX-HPLC), and 3.2.P.5.2 (Subvisible Particles).
[b] Method is described in 3.2.P.8.1 (rCE-SDS)
[c] Characterization methods are discussed with in the body of this document

Sample types were compared post-extrusion from the PFS and prefilled AI/pen, with the PFS-extruded samples serving as a control to isolate the impact of AI/Pen extrusion. The extrusion samples were dispensed using either the syringe or AI/Pen at 2 temperatures. Each sample set contained 12 samples.

All test results were concluded to have no adverse product quality impact (Table 3), with no change in size variants as measured by SE-HPLC and rCE-SDS and no change in charge variants as measured by CEX-HPLC. An increase in sub-visible particle count was observed between the PFS and AI/Pen extrusion samples. This behavior may be based on the extrusion rate through the AI/pen and/or analytical method variability as shown by the standard deviation. MFI is able to differentiate between spherical and non-spherical counts. A comparison of non-spherical particle counts detected by MFI and $\geq$ 5 mm, which would not be expected to be due to silicone oil, were comparable across all samples (Table 3). These data provide the basis for concluding no unexpected impact on product quality as a result of extrusion.

Table 2. Results From Evaluation of Drug Product Compatibility With the Glass Syringe Using the Autoinjector/Pen

			PFS Extruded Samples		AI/Pen Extruded Samples	
Method	Quality Attribute		15°C	25°C	15°C	25°C
SE-HPLC	% Main peak		XX	XX	XX	XX
	% HMW		XX	XX	XX	XX
	% LMW		XX	XX	XX	XX
CEX-HPLC	% Acidic peak		XX	XX	XX	XX
	% Main peak		XX	XX	XX	XX
	% Basic peak		XX	XX	XX	XX
rCE-SDS	% (Pre-LC + LC+HC)		XX	XX	XX	XX
HIAC[a]	Average counts / container	≥ 2 μm	XX ± XX	XX ± XX	XX ± XX	XX ± XX
		≥ 5 μm	XX ± XX	XX ± XX	XX ± XX	XX ± XX
		≥ 10 μm	XX ± XX	XX ± XX	XX ± XX	XX ± XX
		≥ 25 μm	X ± X	X ± X	X ± X	X ± X
MFI[a]	% Spherical		XX	XX	XX	XX
	% Non-spherical[b]		XX	XX	XX	XX

[a] Average of 3 results
[b] Non-spherical is defined as having an aspect ratio of less than XX

2. Patient Compatibility

The components of the AI/pen subassemblies do not come into contact with the drug product; the only contact is with the user. The parts of the prefilled AI/pen that come into contact with human skin are made from common engineering thermoplastic acrylonitrile butadiene styrene (ABS) and polycarbonate. A biological risk assessment of the AI/pen was performed to test all skin contacting components of the AI/Pen for biocompatibility (Device Design Verification [Device]). Tests were performed for cytotoxicity, skin sensitization, and skin irritation. All tests passed, indicating the skin contacting components of the AI/Pen are biocompatible.

3. Conclusion

The prefilled AI/pen containing the glass PFS product delivery conditions did not result in particle formation, aggregation, or multimerisation of <<INN>>, nor is a change in charge or mass profiles detected. The compatibility of the autoinjector/pen with the PFS containing the drug product also is supported by the on-going stability program (3.2.P.8.1, Stability Summary and Conclusions [Device]). Therefore, these data in combination with the stability program, indicate that the quality of <<INN>> drug product is not impacted by the primary container closure system (syringe) or the delivery device (AI/pen) and that compatibility of active product with the prefilled AI/pen system has been demonstrated.