APPENDIX to Case Study: Facilitating Efficient Life-Cycle Management via ICH Q12

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Row	CTD Section	Condition	ICH Q12 Reporting Category (FDA reporting category)	Rationale/Comments
1	3.2.S.1.1	INN Name	NA	These ECs will not change.
2	3.2.S.1.2	Structure of the drug substance, including stereochemistry, molecular formula, molecular mass	NA	These ECs will not change.
3	3.2.S.2.1	Pfizer Ireland Pharmaceuticals facility name and location	Per FDA guidance [8]	This categorization is in line with FDA guidance [8].
4	3.2.S.2.2	Process description of an individual step	Changes to the process description using new materials PA (PAS)	A change to the route of synthesis of the drug substance using new materials would be reported as a PA, in line with FDA guidance [8].
			Changes to the process description using the same materials with the addition of a new impurity at a level >0.15% on the drug substance specification, regardless of the outcome of the mutagenicity assessment: PA (PAS)	Changes to the process description using the same materials (starting materials, solvents, and reagents) that impact the drug substance impurity profile or specifications will be reported as PA. (An impurity >0.15% may be added to drug substance specification.)
			Changes to the process description using the same materials and that do not impact the drug substance impurity profile or specifications (an impurity ≤0.15% may be added to drug substance specification): NM (CBE-30)	Because the product is used in the treatment of advanced cancer, QSAR findings for potential genotoxicity would not require low-level controls. Given this safety-based risk assessment, Pfizer proposes that an impurity in the range of 0.10% to 0.15% can be added to the specification via NM with appropriate validation data in line with the ECs.
5	3.2.S.2.2	Omission recrystallization step from the manufacturing process	NM (CBE-30)	The purification step is a recrystallization of the isolated intermediate. This step is not required to ensure drug substance quality but has still been included in the manufacturing process for further purge opportunity. Removal of this step from the manufacturing process would be formally assessed using the site change assessment process, managed within Pfizer's PQS and require revalidation.
6	3.2.S.2.2	8 critical process parameters (e.g., Step X stoichiometry, reaction temperature, water wash volume)	NM (CBE-30)	These CPPs can potentially impact CQAs. The process parameters control is not the only component of the overall control strategy for the associated CQAs. Other elements of the overall control strategy, such as the drug substance specification, still mitigate that risk. Although these parameters have an impact on a CQA, the material can be recovered through reprocessing, as allowed in ICH Q7 [12] because of the efficient purge of all impurities in the normal crystallization's unit operations.

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7	3.2.S.2.2	3 KPPs (stoichiometry, isolation temperature)	NL (AR)	These KPPs can potentially impact quality attributes that are not listed on the drug substance specification to a lesser degree than the CPPs. These quality attributes are well purged/controlled by the process. The process parameters control is not the only component of the overall control strategy for the associated quality attributes. The downstream elements of the overall control strategy, such as additional purifications and/ or the drug substance specification, still mitigate that risk.
8	3.2.S.2.2	42 noncritical process parameters (e.g., reaction temperatures, catalyst loading, stoichiometry, solvent volume)	NR	These noncritical process parameters do not impact CQAs (there is an absence of both a functional relationship with a CQA over a wide range and an identified edge of failure). All changes to any parameters are always reevaluated, confirmed, and verified to ensure drug substance quality (regardless of criticality or reporting category). These are managed in the PQS change management process.
9	3.2.S.2.3	Identity of starting material X, Y, Z	PA (PAS)	A change to the route of synthesis of the drug substance using new materials would be reported as a PA, in line with FDA guidance [8].
10	3.2.S.2.3	Starting material specifications for X, Y, Z	Changes to starting material specifications that impact the drug substance impurity profile or specifications (e.g. if impurity >0.15% is added to drug substance specification): PA (PAS)	If the change to the starting material specification impacts the drug substance impurity profile or specifications, the change will be reported as PA. New impurities will be qualified, and specifications updated in accordance with ICH S9 [14].
			Changes to starting material specifications that do not impact the drug substance impurity profile or specifications (an impurity ≤0.15% may be added to drug substance specification): NM (CBE-30)	Because the product is used in the treatment of advanced cancer, QSAR findings for potential genotoxicity would not require low-level controls. Given this safety-based risk assessment, Pfizer proposes that an impurity in the range of 0.10% to 0.15% can be added to the specification via NM with appropriate validation data, in line with the ECs.

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11	3.2.S.2.3	Reagent, solvent, and auxiliary material specifications	Changes to toluene specification for benzene content <0.22%: NM (CBE-30)	If there is no impact on drug substance quality or safety, a reporting category of NM is proposed, whereas a change that impacts drug substance quality or safety would be reported as a PA. New impurities will be qualified, and specifications updated in accordance with ICH S9 [14]. The only change to raw material specifications that is expected to impact drug substance safety is an increase in benzene content >0.22%; this would be reported as a PA in line with FDA guidance [8].
			Changes to raw material specifications that impact the drug substance impurity profile or specifications (e.g., if impurity ≥0.15% is added to drug substance specification): PA (PAS)	
			Changes to raw material specifications that do not impact the drug substance impurity profile or specifications (an impurity ≤0.15% may be added to drug substance specification): NM (CBE-30)	
12	3.2.S.2.4	Reaction completion specification A, B and C	NM (CBE-30)	This control can potentially impact a CQA listed on the drug substance specification. This analytical control is not the only analytical control of this CQA. Other elements of the overall control strategy, such as the drug substance specification, still mitigate that risk. The reporting category of NM is in line with FDA guidance [8].
		End of milling IPC		
		End of distillation water content	NL (AR)	These factors do not impact CQAs listed on the drug substance specification. The analytical control is not the only component of the overall control strategy for the associated CQAs.
		Intermediate C specification		
13	3.2.S.3.1	Monohydrate form A	PA (PAS)	The process results exclusively and consistently in the production of monohydrate form A due to the presence of water in the solvent system for the recrystallization in the final step.
14	3.2.S.4.1	Relaxing acceptance criteria for appearance, identification, assay, water, residual solvents, residue on ignition, particle size	PA (PAS)	These categorizations are in line with FDA guidance [8].
		Relaxing acceptance criteria or deleting test to comply with official compendia changes for appearance, identification, assay, water, residual solvents, residue on ignition, particle size	NM (CBE-30)	
		Tightening acceptance criteria for appearance, identification, assay, water, residual solvents, residue on ignition, particle size	NL (AR)	

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15	3.2.S.4.1	Addition of specification for new impurity that requires toxicological qualification	PA (PAS)	If a new impurity is added to the drug substance specification with an acceptance criterion >0.15%, PA is proposed. New impurities will be qualified, and specifications updated in accordance with ICH S9 [14].
16	3.2.S.4.1	Addition of a new impurity with a limit >0.10%, but <0.15%.	NM (CBE-30)	Because the product is used in the treatment of advanced cancer, QSAR findings for potential genotoxicity would not require low-level controls. Given this safety-based risk assessment, Pfizer proposes that an impurity in the range of 0.10% to 0.15% can be added to the specification via NM with appropriate validation data in line with the ECs.
17	3.2.S.4.2	Identity, assay, and purity determination of drug substance method principle: reversed phase column chromatography	PA (PAS)	Changes to the method principle will be reported as PA.
18	3.2.S.4.2	Performance criteria as per ICH Q2(R1) [12]: 14 items (e.g., specificity, linearity, accuracy)	PA (PAS)	If a change to the performance criteria is necessary, it will be reported as PA.
19	3.2.S.4.2	High-level parameters: 5 items (e.g., a column change, method of detection, organic modifier) System suitability: 7 items	NM (CBE-30)	The potential risk associated with these changes, taking into consideration the control strategy, is deemed moderate. In addition, the revised method must meet the validation criteria defined above as ECs.
20	3.2.S.4.2	Slightly more detailed parameters: 3 items (e.g., wavelength and relative response factors)	NL (AR)	The potential risk associated with these changes, taking into consideration the control strategy, is deemed low. Validation results reported to the performance criteria set as ECs should demonstrate that the revised method is equivalent to or better than the original method.
21	3.2.S.4.2	Operational details: 8 items (e.g., column temperature, gradient profile)	NR	These are non-ECs. The potential risk associated with these changes, taking into consideration the control strategy is deemed low. All changes to any parameters are always reevaluated, confirmed, and verified to ensure quality (regardless of reporting category). These are managed in the PQS change management process.
22	3.2.S.6	Packaging components and specifications	Per FDA guidance [8]	Categorization is in line with FDA guidance [8].
23	3.2.S.7.1	Retest period	NL (AR)	Categorization is in line with FDA guidance [8].
24	3.2.P.1	Qualitative and quantitative formulation	Per FDA guidance [9]	Categorization is in line with FDA guidance [9].

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25	3.2.P.3.1	Drug product manufacture, testing, batch release, packaging and final product release site	Per FDA guidance [8]	Categorization is in line with FDA guidance [8].
26	3.2.P.3.2	Batch size	Per FDA guidance [9]	Categorization is in line with FDA guidance [9]. Validation will be completed at scale prior to commercialization.
		Batch formula		
27	3.2.P.3.3	Screening mill, diffusion mixers, tablet press, pan coater	For changes within same design and operating principles: NR	Changes that have no significant impact on quality for equipment within the same design and operating principles will be managed by the PQS change management process.
			For changes to equipment with different operating principles: PA (PAS)	Categorization is in line with FDA guidance [8].
		Screen aperture	NL (AR)	Screen is for de-lumping only, and screening does not impact particle size. Different screen sizes were used in development with no impact on tablet quality attributes. There is an absence of a functional relationship with a CQA over the range studied.
28	3.2.P.3.4	Blend: Blend (revs)	For changes outside application ranges: NM (CBE-30)	Categorization is in line with FDA guidance [8]. Significant experience with this product over a wide range of blending revolutions has demonstrated excellent content uniformity and no trends.
		Blend: Lubrication blend (revs)		
		Compression IPC: Tablet hardness	For changes outside application ranges: NL (AR)	Categorization is in line with FDA guidance [8]. No edge of failure was identified.
		Compression IPC: Tablet weight	For changes outside application ranges: NL (AR)	Tablet weight was monitored throughout development and demonstrated low relative standard deviations in tablet weight. Tablet weight is monitored throughout compression to allow adjustment if it is required to maintain tablet weight.
		Film-Coating IPC, weight gain (average film-coated tablet weight)	For changes outside application ranges: NL (AR)	Film coat is nonfunctional. There is extensive prior knowledge of the equipment and coating system at the commercial site.
29	3.2.P.4.1	Specifications for noncompendial film-coating mixture	NL (AR)	NL is in line with FDA guidance for addition of a new test [10].
30	3.2.P.4.2	Analytical procedure for noncompendial film-coating mixture		
31	3.2.P.5.1	Release testing: Drug product specification according to 3.2.P.5.1 specification(s)	Per FDA guidance [8]	Categorization is in line with FDA guidance [8].

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32	3.2.P.7.1	Packaging: 30 tablet bottle count	Per FDA guidance [8]	Categorization is in line with FDA guidance [8].
		Packaging components: components and suppliers		
33	3.2.P.7.2	Packaging specifications		
34	3.2.P.8.1	Shelf life: 60 months packaged in high-density polyethylene bottles with 1 g desiccant	Per FDA guidance [8]	Categorization is in line with FDA guidance [8].

[a] *Additional methods for both drug substance and drug product are included in the full PLCM. This table includes one representative method for illustration of the ECs and reporting categories selected for analytical performance.*