Organic Process Research & Development **2010,** *14,* 832–839

Development of a Control Strategy for a Defluorinated Analogue in the Manufacturing Process of Casopitant Mesylate

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Abstract:

Casopitant mesylate was identified as part of the search for drugs with activity on the Central Nervous System (CNS) by GlaxoSmithKline. During late-phase development studies to develop the manufacturing process, a new impurity was found. This synthetic impurity, a defluorinated analogue of the drug substance, is discussed in detail to show the process development studies carried out to ensure quality control for the final drug substance following the principles of quality by design. The process understanding gained, in combination with risk analysis, allowed the development of a control strategy for enhanced level of quality assurance. This Control Strategy allows moving the control of this impurity to the point of origin instead of testing in the drug substance.

1. Introduction to Quality by Design and Process Background

Quality by design (QbD) is a new approach for process development to ensure the patients' needs and product performance by which quality is not just tested in the final drug substance or drug product, but it is built in within the process. The principles of QbD were initially introduced by the FDA in a seminal communication[1] and have been increasingly adopted by the pharmaceutical industry as a means to deepen the scientific understanding to ensure quality control and improve process and product robustness.[2] A number of regulatory guidelines to illustrate the QbD approach have followed the initial communication: for example, ICH Q8[3] describes an enhanced approach by the use of process understanding, whereby process performance over a range of material attributes, manufacturing process options, and process parameters is considered; ICH Q9[4] discusses quality risk management tools to perform a risk assessment and risk mitigation; ICH Q10[5] introduced the concept of control strategy, defined as a set of controls, derived from current product and process understanding, that assures process performance and product quality. The commercial process to synthesise casopitant mesylate (**1**) is a multistage convergent process, summarized in Scheme 1. The mesylate salt **1** is obtained after 8 stages, including two hydrogenation reactions (the first one using Rh/C as catalyst in stage 1, the second using Pd/C as catalyst in stage 2) and one reductive amination in stage 7.

In an advanced phase of the development of the compound, a new impurity, the defluorinated analogue **6** (see Scheme 2), was identified in isolated intermediate **2** at levels of ∼0.1% a/a.

Given the potential risk for the quality of the drug substance if this impurity is carried through to drug substance as is or after synthetic transformations, the development of a control strategy supported by appropriate process understanding was therefore considered key to ensure appropriate and consistent quality of the drug substance or drug product.

For the reader's benefit, a glossary section with the definitions of the terms used within this text is included in Appendix 1.

2. Discussion: The Control Strategy

The impact of the defluorinated impurity **6** on the quality of the drug substance was analysed by conducting a risk assessment, as indicated by ICH Q9,[4] which identified appropriate process understanding studies required for mitigation of the key risks. To assess the impact on the process, we examined the fate and origin of this new impurity. The impurity fate was determined by reacting pure impurity **6** through stages 4−7. With this approach, it was possible to conclude that the defluorinated analogue of the drug substance (**7** in Scheme 2) was formed. More importantly, this impurity had the same retention time of the drug substance **1** in the HPLC method used for its release.

An ad-hoc, nonroutine analytical method for the separation and quantification of this particular impurity **7** with respect to the drug substance **1** was developed, which employed a chiral, normal-phase HPLC coupled with an MS detector.[6] This new method allowed confirmation that impurity **7** was present in batches of drug substance at levels of ∼0.1% w/w, that is, this impurity is a drug substance-critical quality attribute (drug

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(1) Pharmaceutical cGMPs for the 21st century—A risk based approach (initiative launched in 2002).

(2) We have recently published an application of the QbD principles to the control of genotoxin impurities: Cimarosti, Z.; Bravo, F.; Stonestreet, P.; Tinazzi, F.; Vecchi, O.; Camurri, G. *Org. Proc. Res. Dev.* [Online early access]. DOI: 10.1021/op900242x. Published Online: Nov 6, 2009.

(3) ICH Q8 Pharmaceutical Development.

(4) ICH Q9 Quality Risk Management.

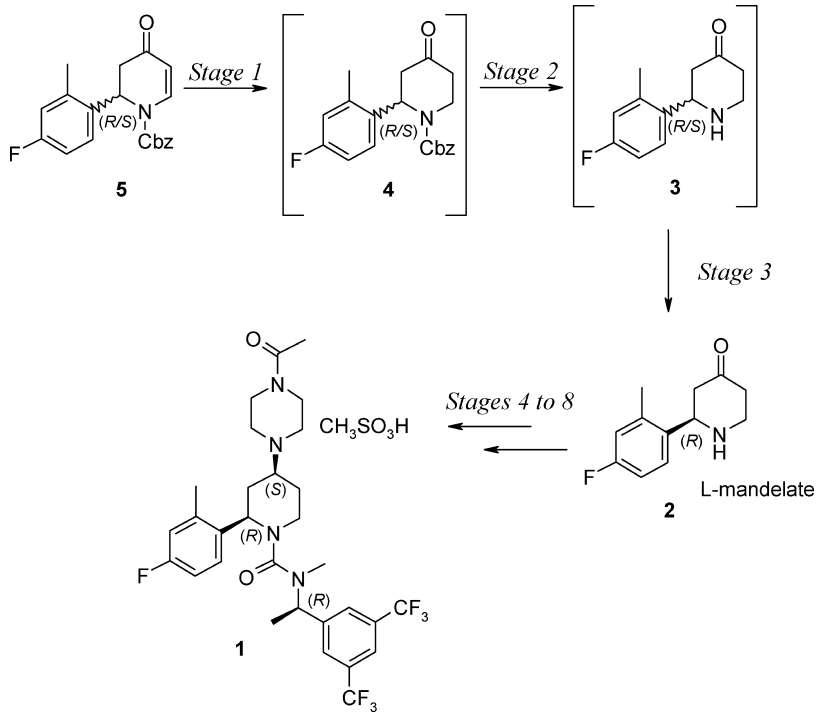
(5) ICH Q10 Pharmaceutical Quality System.

(6) Dams, R.; Bernabé, E.; Nicoletti, A.; Loda, C.; Martini, L.; Papini, D. Quantitation of Defluorinated Analogue of Casopitant Mesylate by Normal Phase Liquid Chromatography−Mass Spectrometry. Manuscript in preparation.

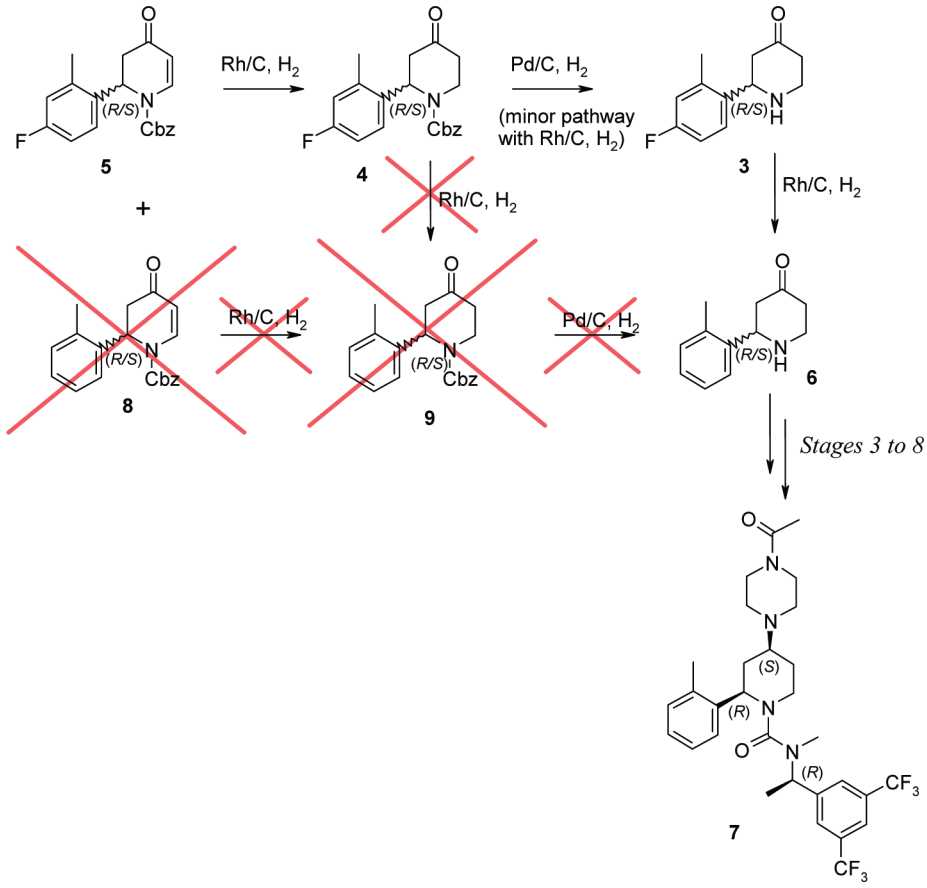
Published on Web 06/17/2010

10.1021/op1000836

Scheme 1. **Some details of the commercial route for the synthesis of casopitant mesylate (1)**



Scheme 2. **Reaction pathways in the formation of the defluorinated impurity 6**



substance-CQA, see glossary in Appendix 1). Moreover, this level constituted a high risk for the drug substance to fail the quality criteria, because at the point in time when this was discovered, it was not possible to obtain a toxicological qualification for this derivative **7**, which meant that this impurity would need to be controlled at levels below 0.15% w/w (according to ICH guidelines).[7] This risk impelled us into applying, once again, the concepts of QbD, specifically, to gain

(7) ICH Q6a Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances.

an understanding of the scientific basis for the formation of the defluorinated impurity **7** to be able to minimise it. In addition, the application of QbD would facilitate the moving of the attribute control upstream and controlling the impurity at its point of origin, instead of testing it in the drug substance. The rationale that supports bringing the control upstream is detailed in the next sections, and it contributes to the simplification of the problem because no modification of the registered method for drug substance specifications would be required.

A root cause analysis was used to identify the source of the formation of the impurity **6** in the isolated intermediate **2** and the impurity **7** in the final drug substance **1**. The details of this analysis are reported in the Supporting Information. This analysis brought us to the following possible explanations for the presence of the defluorinated by products **6** and **7**:

1. The source could be the starting materials used. The impurity **6** in isolated intermediate **2** could result from the presence of the corresponding defluorinated analogue of the starting material **5** (**8** in Scheme 2), which would be transformed into **6**, and then in turn into **7** through the process chemical transformations.
2. The defluorinated impurities **6** and/or **7** could be generated in the process, in particular as a result of a reduction reaction:
   a. Impurity **6** in isolated intermediate **2** could be formed during one or both the hydrogenations performed in stages 1 and 2.
   b. Additionally, we considered that a further source for impurity **7** could be the reductive amination occurring in stage 7.

The first and last hypothesis (i.e., 1 and 2b) were discarded on the basis of the following: the defluorinated impurity (hypothesis 1) could not come from the starting material because a marker of **8** was available, and it was confirmed that the starting material **5** was free of **8** as contaminant. The defluorination could not have occurred in the reductive amination (hypothesis 2b) because, when the reaction mixture was left for extended times, higher temperatures or higher equivalents of reducing agent that were added increased levels of impurity **7** compared to standard operating conditions did not occur.

Therefore, it was concluded that either the hydrogenation using Rh/C as catalyst in stage 1, the hydrogenolysis of the Cbz group using Pd/C as catalyst in stage 2, or both[8] contribute to the formation of the defluorinated analogue **6**, which is then converted into **7** when performing stages 4−8. It is worth mentioning that for procedural simplification, the hydrogenations were performed sequentially, this is, without filtration of the spent Rh/C catalyst once the formation of **4** was complete, followed by addition of Pd/C to the reaction mixture and in situ hydrogenolysis to form **5**.

Once the source of impurity **7** was identified (hypothesis 2a), a series of experiments to understand the formation of the impurity **6** (sections 2.2−2.5) and its relationship with impurity **7** (section 2.6) were undertaken. This would facilitate the identification of a series of mechanisms of control that would ensure the quality of the drug substance with respect to this particular drug substance-CQA.

2.1. Introduction to the Elements of Control of the Control Strategy. In general, each element of control can be categorised into one of three control *modes*. For the particular case of the drug substance-CQA **7**, examples of all three control modes were applied: (i) attribute controls, which include in-process controls (IPCs), and specifications for starting materials, intermediates, solvents, and drug substance, (ii) parametric controls, which involve operation within proven acceptable ranges (PARs) for parameters that have an impact on drug substance-CQAs (referred to as critical process parameters, CPPs, in ICH Q8[3]), and (iii) procedural controls, which describe operations linked to drug substance-CQAs, such as facilities setup, equipment configuration, order of addition, reagent and solvent choice, sequence of events, etc.

2.2. Initial Studies to Identify Potential Critical Process Parameters. Process research studies were undertaken to understand which parameters contribute to the formation of the impurity **6** during the hydrogenation of the double bond or the hydrogenolysis. Previous knowledge gained in the development was taken into account to identify these parameters, and, in particular, the information was derived from initial multivariate studies (design of experiments, DoE). When these multifactorial experiments were performed the impurity **6** had not been yet identified, and considering that impurity **6** results from an over-reduction reaction, it was decided to consider a similar over-reduction reaction as a model (reduction of the ketone group on the same substrate) and select those parameters that influenced this model reaction. The parameters of interest and their ranges are collected in Table 1. It is worth noting that

Table 1. **Parameters investigated in the initial DoE of stage 1**

parameter	levels studied (L/M/H)
5% w/w Rh/C loading (C in Figure *1*)	0.76/2.29/3.82% w/w (based on dry catalyst)
partial pressure of hydrogen (A in Figure *1*)	0.2/1.6/3.0 bar
volume of ethyl acetate (B in Figure *1*)	3/6.5/10 volume

(8) Activation of the strong C−F bond is a topic of growing interest, and different metals have been reported to perform this transformation. From a bibliographic search, it would seem more likely that Rh is the responsible due to a higher number of hits, although both Rh and Pd-based catalyst have been reported to conduct the defluorination reaction. Indeed, there is a relatively higher number of examples of defluorination of fluorobenzenes in the presence of Rh, in particular employing homogeneous Rh complexes; see for instance: (a) Aizenberg, M.; Milstein, D. *Science* **1994**, *265*, 359–361. (b) Aizenberg, M.; Milstein, D. *J. Am. Chem. Soc.* **1995**, *117*, 8674–8675. (c) Braun, T.; Noveski, D.; Ahijado, M.; Wehmeier, F. *Dalton Trans.* **2007**, 3820–3825. (d) Noveski, D.; Braun, T.; Stammler, A.; Stammler, H.-G. *Dalton Trans.* **2004**, 4106–4119. (e) Young, R. J.; Grushin, V. V. *Organometallics* **1999**, *18*, 294–296. Less common is the use of metallic Rh: ref 8e (Rh nanoparticles). (f) Freedman, L. D.; Doak, G. O.; Petit, E. L. *J. Am. Chem. Soc.* **1955**, *77*, 4262–4263 (Rh/Al_2O_3). (g) Stanger, K. J.; Angelici, R. J. *J. Mol. Catal. A: Chem.* **2004**, *207*, 59–68 (Rh supported on SiO_2 and Pd-SiO_2). In less extent, Pd-based catalyst have also been successfully employed. (h) Ukisu, Y.; Miyadera, T. *J. Mol. Catal. A: Chem.* **1997**, *125*, 135–142 (heterogeneous Pd/C). (i) Aramendía, M. A.; Borau, V.; García, I. M.; Jiménez, C.; Marinas, A.; Marinas, J. M.; Urbano, F. J. *C. R. Acad. Sci. Paris, Ser. IIC, Chim.* **2000**, *3*, 465–470. In contrast with the literature precedents, the information collected by catalyst suppliers suggests the use of Pd/C for defluorination, see: *Handbook of Pharmaceutical Catalysis*; Johnson Matthey Catalysts: Royston, U.K., 2009, p 37.

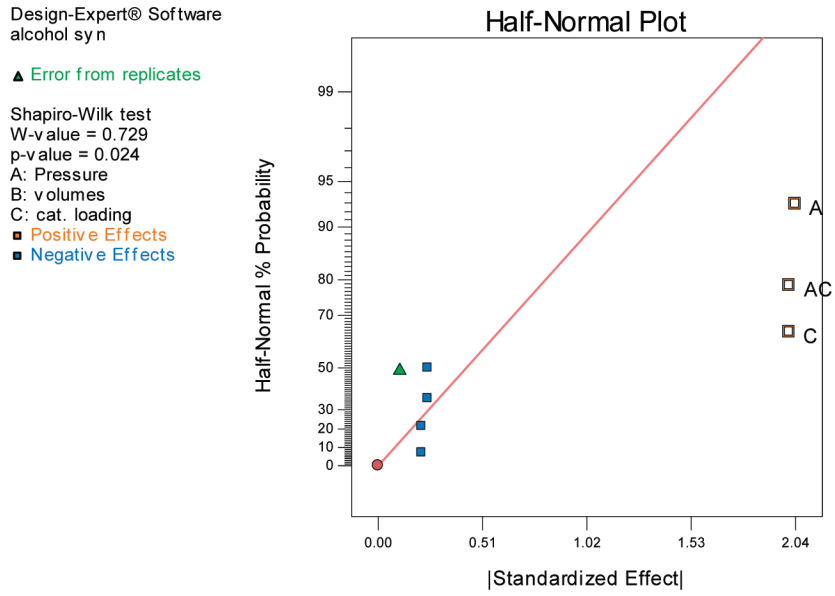


Figure 1. **Half-normal plot for the Rh/C hydrogenation: over-reduced by product.**

temperature is not included in this list because it was established that it did not influence the model reaction.

The experimental design chosen was 2-level (one high and one low value for each parameter of the study), full factorial experimental design comprising two centre points (10 experiments in total).

Figure 1 shows the analysis of the data obtained from these experiments and provides an assessment of the impact of the parameters on the over-reduction byproduct. The graphical representation is obtained from the commercially available software *Design Expert Version 7.0.3*, and it is called a *half-normal plot*. This half-normal plot is used to assess the significance of the individual parameters within the design. This can be seen as the parameters which have a higher effect also have a corresponding higher numerical *x*-axis value on the graph, and therefore, they appear further to the right-hand side of the half-normal plot.[9] From this figure, it is deduced that the most significant parameters impacting the over-reduction are pressure (A in Figure 1), catalyst loading (C in Figure 1), and their interaction (AC in Figure 1). Volume of ethyl acetate does not have significant effect on the response, at least in the ranges explored. The validity of this model is further addressed with the same software by an analysis of variance (ANOVA, more details are reported in the Supporting Information), which indicated that the parameters of pressure and catalyst loading have statistical significance on the response.

2.3. Forcing Experiments to Confirm Potential Critical Process Parameters. Our initial risk assessment suggested including partial pressure of hydrogen and catalyst loading as factors in a subsequent forcing experiment because they do have an impact on the formation of over-reduction by product. After further risk assessment, it was decided to include the temperature of the reaction in these forcing experiments because higher temperatures could accelerate the kinetics of formation of the defluorinated impurities. In a QbD context, these parameters (partial pressure of hydrogen, catalyst loading, and temperature) are all considered potential CPPs of the reaction. These forcing experiments were performed to understand if only one catalyst or the combination of both catalysts contributed to the formation of impurity **6**. In most cases, the spent Rh/C catalyst was filtered after completion of stage 1 to differentiate both catalysts and their impact. Table 2 collects the information gained with these experiments.

The experiments collected in Table 2 allowed the following conclusions:

1. In all the experiments, the amount of impurity **9** (see Scheme 2), the defluorinated analogue of non isolated intermediate **4**, is negligible or very small.
2. The Rh/C catalyst also promotes the formation of minor amounts (∼5% a/a) of compound **3** (i.e., a minor amount of the product of stage 2 is formed after completion of stage 1). The levels of **3** after stage 1 increased to ∼20% a/a in the case of the stressed conditions of entry 4.
3. Entry 1 represents the standard operating conditions, without intermediate filtration of the spent Rh/C catalyst once stage 1 is completed. Quite surprisingly, these conditions gave the highest levels of impurity **6** of the experiments performed.
4. Under the same conditions of entry 1, the inclusion of an intermediate filtration of Rh/C (entry 2) gave only small levels of the defluorinated impurity **6**.
5. Stressed hydrogenation conditions in stage 2 (Pd/C hydrogenolysis, entry 3) did not contribute to an increased formation of the impurity **6** compared to entry 2.
6. Stressed hydrogenation conditions in stage 1 (Rh/C hydrogenation, entry 4) resulted in the formation of impurity **6** at much higher levels compared to entry 2.

From the comparison of entries 2 and 3, it could be deduced that Pd/C does not contribute to the formation of impurity **6**, only Rh/C is responsible for its formation. Furthermore, it is also apparent that Rh/C performs the defluorination on the substrate **3** (the product of stage 2) and not on substrates **4** or **5**. To further confirm this hypothesis, a couple of experiments with compound **3** were performed, as collected in Table 3.

(9) The *y*-axis of the graph is defined as "cumulative probability, a measure of the % of individuals expected to fall below a given level". The *x*-axis is defined as "a measure of the magnitude of the effect".

Table 2. **Stressed experiments on stage 1 and stage 2**

entry	conditions for stage 1	filtration of spent Rh/C at end of stage 1	conditions for stage 2	level of **6** in non isolated intermediate **3**
1	TV[a]	no	TV[a]	0.26% a/a
2	TV[a]	yes	TV[a]	0.03% a/a
3	TV[a]	yes	stressed[b]	0.02% a/a
4	stressed[b]	yes	TV[a]	0.21% a/a

[a] TV refers to target value conditions: partial pressure of hydrogen = 2.5 bar; T = 25 °C; loading of 5% Rh on Charcoal = 0.0229 wt; loading of 5% Pd on charcoal = 0.0302 wt (based on dry catalyst). [b] Stressed conditions are as follows: partial pressure of hydrogen = 4.0 bar; T = 40 °C; loading of 5% Rh on Charcoal = 0.0358 wt; loading of 5% Pd on Charcoal = 0.0469 wt (based on dry catalyst).

Table 3. **Stressed experiments performed on 3 as substrate for Rh/C and Pd/C hydrogenations**

entry	conditions	level of **6** in non isolated intermediate **3**
1	none (initial value)	0.02% a/a
2	stressed[a] Rh/C hydrogenation conditions	0.59% a/a
3	stressed[a] Pd/C hydrogenation conditions	0.02% a/a

[a] Stressed conditions are as follows: partial pressure of hydrogen = 4.0 bar; T = 40 °C; loading of 5% Rh on charcoal = 0.0382 wt; loading of 5% Pd on charcoal = 0.0464 wt.

These experiments confirm that Pd/C does not contribute to the formation of the defluorinated impurity **6** because levels in entry 3 (stressed Pd/C hydrogenation conditions) are equivalent to the initial value. It is worth noting that, when the starting material **5** is reacted with Pd/C, no defluorination is observed, only debenzylation occurs, the resulting deprotected dihydropyridone is purged in the crystallization and does not contaminate the intermediate **2.**

The experiment in entry 2 confirms the role of the Rh/C catalyst in the defluorination on the substrate **3**.

All the previous information allowed generating a mechanistic scheme for the formation of defluorinated impurities, which is summarised graphically in Scheme 2.

One logical conclusion that can be reached by observing the pathway for the formation of the defluorinated impurity **6** is to include a filtration for the spent Rh/C catalyst after completion of stage 1. This unit operation, although introducing a minor complexity in the procedure, would have a considerable impact in the quality of isolated intermediate **2** because the conversion of **3** into **6** would be minimised, and hence improve the quality of the final drug substance **1**. The filtration constitutes the first element of control (procedural control) of the control strategy.

2.4. Risk Assessment and Definition of Proven Acceptable Ranges. The previous information also confirms that, when Rh/C catalyst is used, the parameters of the reaction (i.e., partial pressure of hydrogen, Rh/C catalyst loading and temperature) do have an impact on the level of defluorinated impurity **6** that is formed and are, therefore, confirmed as CPPs. Furthermore, a thorough risk assessment (see below) identified low volumes of reaction as one potential CPP; the rationale is that substrate **5** has low solubility in the ethyl acetate used as reaction solvent, and a slow reaction leading to long contact time between the substrate/products and the catalyst/hydrogen system can take place under these conditions, which would in turn favor over-reduction pathways. For such parameters, which show a demonstrated impact on the quality of the drug substance, or a potential impact identified with the use of strict risk assessments tools, suitable ranges of operation (PARs) are needed. Our approach to define and verify the PARs for these parameters was to perform verification experiments, run at 1 L scale. This scale was considered adequate to account for any scale dependency, on the basis that agitation conditions at equivalent power-per-unit volume (P/V) ratio were used in vessel with the same geometric configuration as the commercial vessel. The verification experiments were based on a statistical methodology whereby two sets of conditions are run, namely, *forcing* and *mild* conditions and where all parameters are modified at once in the forcing and mild conditions. The aim is to maximise or minimise the effect of the formation of the impurities, which takes into account inherently the interaction among parameters. The results of these experiments are presented in Table 4. These tests were performed without the intermediate filtration of the spent Rh/C catalyst after completion of stage 1 to have a worst case scenario.

Table 4. **Verification experiments to set PARs for parameters in Rh/C hydrogenation**

entry	conditions	defluorinated impurity **6** in isolated intermediate **2**
1. (verification forcing)	$P = 2.5^a + 0.3$ bar of H_2 $T = 25^a + 12$ °C cat loading = $0.0229^a + 0.0027$ wt $V = 2.0^a - 0.6$ vol	0.05% a/a
2. (verification mild)	$P = 2.5^a - 0.3$ bar of H_2 $T = 25^a - 12$ °C cat loading = $0.0229^a - 0.0027$ wt $V = 2.0^a + 0.6$ vol	0.03% a/a

[a] These are the target value conditions.

Because the derived intermediate **2** contained the impurity **6** at levels lower than 0.15% a/a (this level of impurity **6** in intermediate **2** is considered appropriate as explained in section 2.6), the ranges obtained for these parameters are considered valid and therefore constitute their PARs. Working inside the PARs for these parameters collected in Table 5 represents a second element of control (parametric control).

2.5. Final Risk Assessment: Definition of Quality Critical Process Parameters and Quality Process Parameters. GlaxoSmithKline has its own internal QbD methodology, whereby a risk assessment process and a risk quantification tool (failure mode and effects analysis, FMEA, see ICH Q9)[4] are used to discern between two types of CPPs. On the basis of the following criteria, these parameters are classified:

1. Quality critical process parameter (QCPP) is a parameter that influences a drug substance-CQA and has a

Table 5. **PARs for parameters in Rh/C hydrogenation**

parameter	lower PAR	upper PAR
partial pressure of hydrogen	2.2 bar	2.8 bar
temperature of the Rh/C hydrogenation	13 °C	37 °C
Rh/C catalyst loading	0.0202 wt	0.0256 wt
volume of solvent for the Rh/C hydrogenation	1.4 vol	none[a]

[a] On the basis of experiments, the volume of solvent impacts only because of limited solubility of **5** that gives slower reaction and favors over-reduction pathways, and therefore, only a lower PAR limit is required.

high risk to fall outside the design space (i.e., the PAR). QCPPs typically require tight controls.

2. Quality process parameter (QPP) is a parameter that influences a drug substance-CQA and has a low risk to fall outside the design space (i.e., the PAR).

The FMEA gives a numeric assessment of the risk derived from a multidisciplinary assessment, where functional experts from organic chemistry, engineering, analytical sciences, and plant operations are present to evaluate the risk on the basis of existing scientific understanding and process knowledge. In this case, the risk that the drug substance would fail to comply with the quality requirements for the drug substance-CQA **7** was considered low for all parameters, and therefore, no QCPPs are found; only QPPs remain.

2.6. Correlation of Impurity 6 with Drug Substance-Critical Quality Attribute 7. Spiking experiments demonstrated that the relationship of the impurity **7** in the drug substance with respect to impurity **6** in intermediate **2** is approximately 1:1 (see Table 6). These data are derived from batches produced at scale (100 kg scale for entries 2−6). This result constitutes another element of the control strategy: to obtain drug substance **1** with levels of **7** of no more than (NMT) 0.15% w/w, it is possible to move the control upstream by placing a specification for impurity **6** in isolated intermediate **2** of NMT 0.15% a/a (attribute control).

Table 6. **Levels of impurity 7 in the final drug substance 1 as a function of level of impurity 6 in intermediate 2**

entry	impurity **6** present in intermediate **2**	impurity **7** present in drug substance **1**
1	0.18% a/a	0.12% w/w
2	0.10% a/a	0.06% w/w
3	0.06% a/a	0.06% w/w
4	0.04% a/a	0.03% w/w
5	0.05% a/a	0.04% w/w
6	0.10% a/a	0.08% w/w

2.7. Summary of the Control Strategy for Defluorinated Drug Substance-CQA 7. From all the above information, an overall control strategy for the control of the defluorinated drug substance-CQA **7** is derived, which comprises the following elements of control:

1. Attribute control, whereby a specification limit of NMT 0.15% w/w of impurity **7** in drug substance **1** is replaced with a specification limit of NMT 0.15% a/a of impurity **6** in isolated intermediate **2**.
2. A parameter control point, whereby the process is run within the PARs determined for the QPPs, as follows:
   a. Partial pressure of hydrogen: TV ± 12%.
   b. Temperature of the Rh/C hydrogenation: TV ± 48%.
   c. Rh/C catalyst loading: TV ± 10.5%.
   d. Volume of solvent for the Rh/C hydrogenation: ≥TV − 30%.
3. A procedural control, whereby filtration of the spent Rh/C catalyst, once stage 1 is complete, is performed. This control certainly helps in reducing the levels of impurity **6** in intermediate **2**, but because the previous PARs had been determined without intermediate filtration of the spent catalyst, it is not strictly necessary to obtain drug substance of adequate quality, and we could keep the flexibility of removing the filtration to simplify the process if required for operational reasons at a later stage. Indeed, this demonstrated an advantageous outcome of the QbD paradigm, which allows the introduction of regulatory flexibility, once a sound scientific rationale has been found.
4. A further level of attribute control was introduced in our control strategy on the basis of risk assessment, which is to avoid that the levels of **6** in intermediate **2** could be higher by unexpected contamination of the starting material **5** with its defluorinated analogue **8**. Although all batches of the starting material **5** analysed to date were free of impurity **8**, we set a restrictive specification limit for this impurity of 0.05% a/a.

The control strategy is summarised graphically in Figure 2.

3. Conclusion

By following the principles of QbD, we have derived a control strategy based on the above-mentioned four elements of control. The application of the QbD principles has allowed us understanding the basic science behind the formation of the impurity, introducing a degree of regulatory flexibility (e.g., working inside the conditions of the PARs for QPPs; desirable, but optional filtration of the spent Rh/C catalyst), and moving the control upstream, which constitutes a simplification of the analytical procedure.

4. Experimental Section

General Procedure for the Hydrogenation and Hydrogenolysis: Synthesis of 2-(4-Fluoro-2-methylphenyl)-4-piperidinone (3). In a clean and N_2/vacuum-purged hydrogenation reactor, phenylmethyl 2-(*R*/*S*)-(4-fluoro-2-methylphenyl)-4-oxo-3,4-dihydro-1(2*H*)-pyridinecarboxylate (**5**) (50 g, 1 wt) is introduced. A catalytic amount of 5% Rh on Charcoal (1.145 g, 0.0229 wt based on the dry catalyst) is added into the reactor, and then the reactor is purged with three cycles of N_2/venting. Ethyl acetate (100 mL, 2 vol) is added, the reactor is purged once more with 3 cycles of N_2/vacuum, followed by 5 cycles of H_2/vacuum, and then it is pressurized to 2.5 bar of H_2. The reaction is stirred for *ca.* 1 h at 25 °C until complete conversion of the starting material into non isolated intermediate **4**. The catalyst is filtered and the spent catalyst is washed with ethyl acetate (2 × 15 mL, 2 × 0.3 vol). The filtered catalyst waste is disposed appropriately. The reactor is purged with 3 cycles of N_2/vacuum, and 5% Pd on charcoal (1.51 g, 0.0302 wt based on the dry catalyst) is added over the reaction mixture. The

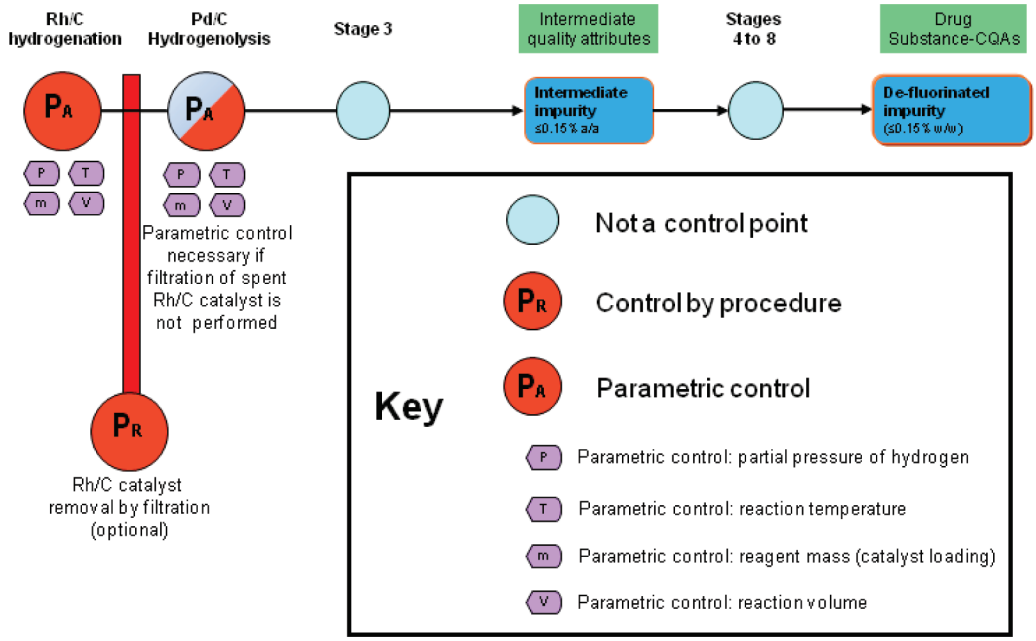


Figure 2. **Overall control strategy for defluorinated impurity 7 (drug substance-CQA).**

reactor is sealed, purged with 3 cycles of N_2/vacuum, followed by 5 cycles of H_2/vacuum, and finally pressurized at 2.5 bar of H_2. The stirring is kept at 25 °C, and the headspace is vented with cycles of H_2/vacuum and repressurized with H_2 regularly throughout the reaction in order to remove the CO_2 until complete conversion into **3** (ca. 1 h) The mixture is filtered and the solution of **3** in EtOAc is collected. The reactor and the spent catalyst are washed with ethyl acetate (1 × 50 mL - 1 × 1 vol -; then 2 × 25 - 2 × 0.5 vol). Finally, the filtered catalyst waste is disposed appropriately.

Compound **3** can be precipitated as the (*rac*)-camphorsulfonate salt as follows: 2-propanol (100 mL, 2 vol) is added and the solution is concentrated to 175 mL (2.5 vol). The resulting solution is diluted with more 2-propanol (225 mL, 4.5 vol), and then racemic camphorsulfonic acid (34.0 g, 0.68wt) dissolved in 2-propanol (100 mL, 2 vol) is added at room temperature in 5 min, and the resulting solution is stirred for 10 min. The solution is concentrated to 175 mL (3.5 vol), toluene (550 mL, 11 vol) was added and the mixture concentrated to 175 mL (3.5 vol); the racemic camphorsulfonate salt of **3** precipitates from the medium. More toluene is added (325 mL, 6.5 vol), and the slurry was stirred overnight (*ca.* 14 h) at room temperature. The solid was isolated by filtration, and washed three times with toluene (3 × 50 mL, 3 × 1 vol), dried in a vacuum oven at 40 °C for 15 h to give the racemic camphorsulfonate salt of **3** (40.51 g, 74% th).

^{1}H NMR (600 MHz, DMSO-d_6): δ ppm 9.51 (br.s., 1H), 9.32 (br.s., 1H), 7.70 (dd, 1H), 7.19 (m, 1H), 7.16 (dd, 1H), 4.98 (d, 1H), 3.62 (m, 2H), 2.95 (dd, 1H), 2.90 (m, 1H), 2.89 (d, 1H), 2.63 (m, 1H), 2.55 (m, 1H), 2.53 (m, 1H), 2.40 (d, 1H), 2.37 (s, 3H), 2.24 (m, 1H), 1.94 (t, 1H), 1.85 (m, 1H), 1.80 (d, 1H), 1.28 (m, 2H), 1.03 (s, 3H), 0.74 (s, 3H). MS: *m/z* 208 $[M + H]^+$, as free base.

Synthesis of the Defluorinated Impurity 2-(2-Methylphenyl)-4-piperidinone (6). To a suspension of Mg (6.2 g, 0.31 wt) and iodine (120 mg, 0.006 wt) in dry THF (140 mL, 7 vol) at 60 °C, a portion of 2-bromotoluene (1.0 mL, 0.05 vol) was added. Once the reaction started (the yellow-brown colour of the solution disappeared and the solvent started refluxing), the remaining 2-bromotoluene (27.4 mL, 1.37 vol) was added dropwise (within 20 min) keeping a gentle reflux. The reaction mixture was stirred at reflux for 30 min then cooled to room temperature, giving the Grignard solution. Contemporaneously and in a separate flask, benzyl chloroformate (33.2 mL, 1.66 vol) was added dropwise (within 15 min) to a solution of 4-methoxypyridine (20 g, 1 wt) in dry THF (200 mL, 10 vol) at 0 °C. After the addition was completed, the white suspension obtained was stirred at 0 °C for 30 min. The Grignard solution was added dropwise (within 20 min) over the suspension at 0 °C and the reaction mixture was stirred at 0 °C for 1 h. Then a 20% w/w solution of NH_4Cl (80 mL, 4 vol) was added at 0 °C and the mixture was stirred at 20 °C for 5 min. More water (50 mL) was added to enhance the separation of the phases. The two layers were separated and the organic layer was treated with a 95:5 mixture of 20% w/w solution of NH_4Cl/20% solution of HCl (80 mL, 4 vol). The aqueous phase was discarded, and the organic layer was concentrated, and 2-propanol was added (this operation was repeated twice). The solid formed was collected and washed with 2-propanol. The solid was dried under vacuum in the oven at 50 °C overnight, giving **8** (47.48 g, 80.6% th).

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 8.22 (dd, 1H), 7.07−7.35 (m, 9H), 5.82 (d, 1H), 5.37 (d, 1H), 5.13−5.23 (m, 2H), 3.29 (dd, 1H), 2.32−2.39 (m, 1H), 2.27 (s, 3H). HRMS (ES+) Calcd. for $C_{20}H_{19}NO_3$ $[M + H]^+$: 322.1443; found 322.1449.

8 (256.2 g, 1 wt) was charged in an hydrogenation reactor and reacted with hydrogen as described in the general procedure for hydrogenation and hydrogenolysis; after removal of the solvent, crude **6** was obtained (150 g). Compound **6** can be precipitated as the (*rac*)-camphorsulfonate salt as follows: To 50 g of the crude obtained after the hydrogenation/hydrogenolysis, 2-propanol was added (120 mL) and then concentrated under vacuum. This operation was repeated. Then more

2-propanol (425 mL, 8.5 vol) was added followed by (*rac*)-camphorsulfonic acid (49.2 g, 0.8 equiv). The mixture was stirred for 2 h, and then 180 mL of 2-propanol were added. The solid was collected by filtration and washed with 2-propanol (2 × 85 mL), cyclohexane/2-propanol 1/1 (170 mL) and cyclohexane/2-propanol 3/1 (255 mL). The solid was dried under high vacuum at room temperature, obtaining of the racemic camphorsulfonate salt of **6** (52.47 g, 46.8% th).

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 9.42 (br.s, 2H), 7.66 (dd, 1H), 7.31−7.37 (m, 2H), 7.28 (dt, 1H), 4.99 (dd, 1H), 3.54−3.68 (m, 2H), 2.90−2.99 (m, 2H), 2.90 (d, 1H), 2.59−2.69 (m, 1H), 2.50−2.59 (m, 2H), 2.41 (d, 1H), 2.36 (s, 3H), 2.20−2.28 (m, 1H), 1.94 (t, 1H), 1.80−1.91 (m, 1H), 1.80 (d, 1H), 1.23−1.34 (m, 2H), 1.03 (s, 3H), 0.74 (s, 3H). HRMS (ES+) Calcd for $C_{12}H_{15}NO$ $[M + H]^+$: 190.1232; found 190.1235.

Synthesis of the Defluorinated Impurity (2*R*,4*S*)-4-(4-Acetyl-1-piperazinyl)-*N*-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-*N*-methyl-2-(2-methylphenyl)-1-piperidinecarboxamide (7). Prepared as described in the published literature.[10]

Compound **7** can be precipitated as the methanesulfonate salt as described in the published literature.[10a]

^{1}H NMR (600 MHz, DMSO-d_6): δ ppm 9.65 (br.s., 1H), 8.01 (s, 1H), 7.70−7.76 (m, 2H), 7.20 (d, 1H), 7.10 (d, 1H), 7.07 (t, 1H), 7.03 (t, 1H), 5.36 (q, 1H), 4.40−4.49 (m, 1H), 4.24 (dd, 1H), 3.94−4.04 (m, 1H), 3.53−3.62 (m, 1H), 3.43−3.52 (m, 3H), 3.39 (t, 1H), 3.10−3.22 (m, 1H), 2.93−3.03 (m, 1H), 2.84−2.94 (m, 1H), 2.80 (t, 1H), 2.75 (s, 3H), 2.36 (s, 3H), 2.33 (s, 3H), 2.13−2.19 (m, 1H), 2.07−2.13 (m, 1H), 2.02 (s, 3H), 1.85−1.96 (m, 1H), 1.64−1.74 (m, 1H), 1.46 (d, 3H). HRMS (ES+) Calcd for $C_{30}H_{36}N_4O_2F_6$ $[M + H]^+$: 599.2821; found 599.2805.

Acknowledgment

We are grateful to Orsola Vecchi, Simon Bryant, Riet Dams, Giulio Camurri, Stefano Provera, Lucilla Turco, Ornella Curcuruto, Jill Trewartha, Paola Russo, Anna Nicoletti, Luca Martini, Matteo Gonzi, Vern De Biasi, Vance Novack, Damiano Papini, and Luca Mantilli for helpful discussions and to Matt Kersey for critical reading of the manuscript.

Appendix 1: Glossary

Drug Product Critical Quality Attributes or Drug Substance Critical Quality Attributes measurable properties of drug product or API that are critical to ensuring patient safety and efficacy. The property must be within a predetermined range to ensure product quality. A property which is measured outside the range indicates a batch failure.

Critical Quality Attributes measurable properties of inputs and outputs that (as determined by risk assessment) present a **high risk** to the process falling outside the design space or proven acceptable ranges in the unit operation or stage inputs, stage outputs, device etc.

Quality Attribute in the Unit Operation or Stage Inputs, Stage Outputs, Device etc measurable property of inputs and outputs that (as determined by Risk Assessment) present a low risk to the process falling outside the design space or proven acceptable range.

Critical Process Parameter (CPP) process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality [ICH Q8].

Design Space multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality; working within the design space is not considered as a change, and movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. Design Space is proposed by the applicant and is subject to regulatory assessment and approval [ICH Q8].

Quality Critical Process Parameter process parameter that influences a critical quality attribute and (as determined by risk assessment) presents a high risk to the process falling outside the design space or proven acceptable ranges.

Quality Process Parameter process parameter that influences a critical quality attribute but (following a risk assessment) presents a low risk of the process falling outside the design space or proven acceptable ranges.

Control Strategy (planned) set of controls, derived from (current) product and process understanding that assures process performance and product quality; the controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control. (ICH Q10 definition).

Proven Acceptable Range (PAR) upper and lower limits for process parameter or attribute values between which the parameter or attribute is known to produce a process output (e.g., intermediate, API or DP) that meets the CQAs; the PAR may or may not represent the point of failure, and the PAR for a given process parameter or attribute may be dependent upon the PAR values for one or more other process parameters or attributes (e.g., multivariate).

Supporting Information Available

Detailed description of the root cause analysis mentioned in paragraph 2 by using the Ishikawa diagram and the ANOVA analysis of the DOE reported in paragraph 2.2. This material is available free of charge via the Internet at http://pubs.acs.org.

Received for review March 26, 2010.

OP1000836

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