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Application of Quality by Design Principles to Support Development of a Control Strategy for the Control of Genotoxic Impurities in the Manufacturing Process of a Drug Substance

Zadeo Cimarosti,*,† Fernando Bravo,† Paul Stonestreet,‡ Francesco Tinazzi,† Orsola Vecchi,† and Giulio Camurri†

GlaxoSmithKline R&D, Chemical Development, Via Fleming, 4, Verona, Italy, and GlaxoSmithKline R&D, Chemical Development, Old Powder Mills, Near Leigh, Tonbridge, Kent TN11 9AN, U.K.

Abstract:

As part of the search for drugs with activity on the central nervous system (CNS) a fluoroaryl-amine was identified and developed by GlaxoSmithKline. The manufacturing process was developed and optimised by following a quality by design approach whereby a control strategy was developed, underpinned by process understanding and risk analysis, for enhanced level of quality assurance. A summary of the overall control strategy for this process includes different elements of control (Quality Process Parameters, control of the Quality Attributes of starting materials, intermediates, solvents, in-process controls). The drug substance Critical Quality Attributes (drug substance-CQAs) related to the genotoxin content, methyl methanesulfonate (methyl mesylate, MMS), ethyl methanesulfonate (ethyl mesylate, EMS) and isopropyl methanesulfonate (isopropyl mesylate, IMS) are identified and discussed in detail to show the process development studies carried out to ensure quality control for the final drug substance. The process understanding developed could allow for the elimination of testing of the genotoxic impurities in the final drug substance.

1. Introduction

The pharmaceutical industry is currently undergoing a fundamental change in the approach to process development, by which quality is built in rather than tested in the product. This approach is called "quality-by-design" and is described in a number of industry and regulatory guidelines.[1] For example, ICHQ8 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. ICHQ9 describes the risk management tools that can be used to successfully manage the risk, and ICHQ10 introduced the concept of a control strategy, defined as a set of controls, derived from current product and process understanding that assures process performance and product quality. The development of a control strategy supported by appropriate process understanding is therefore key to ensuring that the quality of the drug substance or drug product is appropriate and consistent.

A quality-by-design approach has recently been applied to the development of the drug substance manufacturing process for the fluoroaryl-amine, **1**, a potential drug active in the central nervous system (CNS). In this report, we describe our general control strategy approach for the drug-substance manufacturing process for the fluoroaryl-amine, **1**, and give the specific example of the control strategy approach used for the control of genotoxic impurities in the drug-substance manufacturing process.

For the reader's benefit, a Glossary with the definitions of the terms used within this text is provided at the end of the text.

2. Approach to Control Strategy Concept

Within GlaxoSmithKline, the development of a control strategy, according to principles of quality-by-design, is the key to delivering enhanced quality assurance as well as robust manufacturing processes. This paper describes the development of a control strategy approach to achieve good process control as well as to provide the option to remove end product testing of drug substance-CQA (critical quality attributes) by moving the process control points upstream.

For the control of genotoxic impurities this can be very advantageous because of the challenges inherent in developing and validating methods to measure trace levels of genotoxic impurities. This can be achieved by using a series and/or combination of individual elements of control at specific points corresponding to process steps or unit operations whereby the critical quality attributes (CQAs) of the product are controlled, which ensures that patient safety and efficacy criteria are met.

Each of the elements of control can be categorised into three control *modes*, as follows:

(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 quality critical process parameters (QCPPs) and quality process parameters (QPPs) which are linked to CQAs
(iii) procedural controls, which describe operations linked to CQAs such as facilities setup, equipment configuration, order of addition, reagent and solvent choice, sequence of events, etc.

For each CQA, these may be used alone or in different combinations as appropriate. The overall control strategy is what GlaxoSmithKline will propose for assuring product quality in our quality-by-design approach and is what is presented in our regulatory submissions.

* To whom correspondence should be addressed. E-mail: zadeo.a.cimarosti@gsk.com.
† Chemical Development Verona.
‡ Chemical Development Tonbridge.

(1) ICHQ8 Pharmaceutical Development, ICHQ9 Quality Risk Management, ICHQ10 Pharmaceutical Quality System.

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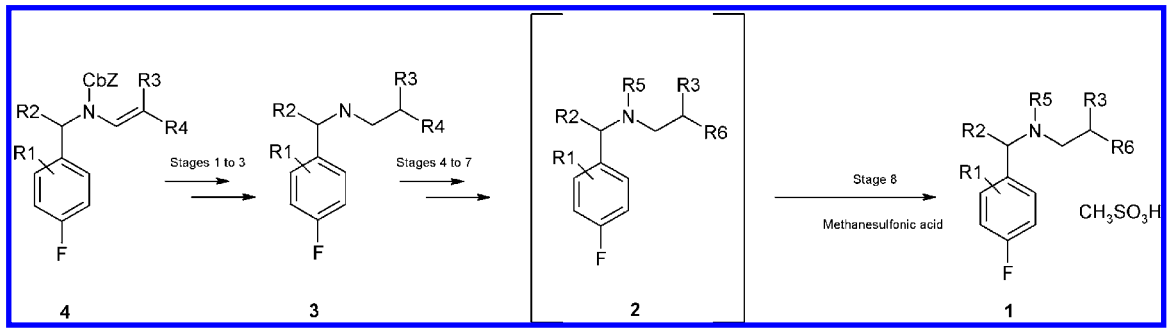
Scheme 1. **Some details of the commercial route for the fluoroaryl-amine mesylate 1**



This quality-by-design approach was adopted to develop a genotoxin control strategy for the fluoroaryl-amine **1** drug substance manufacturing process; an enhanced development approach was followed, by which the manufacturing process was assessed for possible control points and associated risks. This involved the investigation of the (multivariate) interrelationships of attributes and parameters in a systematic way using techniques such as statistical design of experiments and mechanistic modelling to gain a higher level of process understanding. For genotoxin control, GlaxoSmithKline follows a specific genotoxin risk management approach based on the principles of ICHQ9, and the control strategy is developed to allow for the removal of end-product testing where this approach is justified by the scientific understanding that has been collected about the manufacturing process. The control points are implemented at the most appropriate point in the process, i.e. upstream of the end product, based on the process understanding and risk mitigation.

The approach followed is consistent with the requirements to assess the synthetic process with respect to the risk of formation of mesylates and, where necessary, to validate the production method to demonstrate that alkyl mesylates are not detectable in the final product, as included in the atracurium besylate monograph, reported in the *European Pharmacopoeia;* 2008; Vol. 6.2, p 1230.

3. Synthetic Route

The commercial process to synthesise the fluoroaryl-amine, **1**, is a multistage convergent process and is summarized in Scheme 1. The key step of the process is Stage 8 where the fluoroaryl-amine **2** is effectively separated from the reaction mixture by selective seeded crystallisation of its mesylate salt **1**, using a solvent combination of ethyl acetate, acetone, and isooctane. A seeded process was selected to ensure the particle formation was predictable and consistent.

A risk assessment on this synthetic route was carried out by following the ICHQ9 guidelines, and three possible genotoxic impurities that could potentially contaminate the drug substance

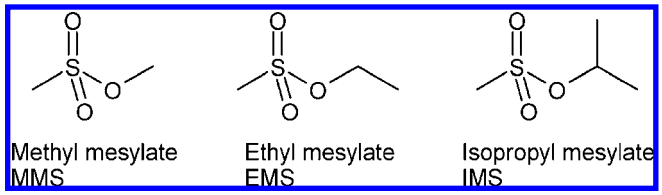
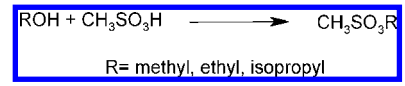


Figure 1. **Structures of methyl mesylate, ethyl mesylate, and isopropyl mesylate.**

Scheme 2. **Formation of mesylate esters**



were identified, namely, methyl mesylate (methyl methanesulfonate, MMS), ethyl mesylate (ethyl methanesulfonate, EMS), and isopropyl mesylate (isopropyl methanesulfonate, IMS). Accordingly, these genotoxins are classified as CQAs of the drug substance.

Considering the synthetic process and the different sources of alcohols (needed for the mesylate formation as shown in Scheme 2), the risk of drug substance contamination was considered low; this was also confirmed by the analysis of all the drug substance batches prepared in development where levels of mesylates (MMS, EMS, and IMS) were always less than 1 ppm (quantitation limit).

Applying on a threshold of toxicological concern (TTC) of <1.5 μg/day and a maximum drug dose of 150 mg/day, these CQAs need to be controlled to a ppm level in the drug substance.

It is worth noting that, when this study was carried out, the results of the in vivo study on the carcinogenic potency on EMS were not published, and the following discussion with the regulatory bodies, concerning the permitted daily exposure (PDE) of EMS at 2 mg/kg/day, had not yet been held.[2] Therefore, the limit of EMS was calculated using the TTC approach.

4. Genotoxin Control Strategy Definition

4.1. Process Assessment. The structures of the three alkyl-methane sulfonate genotoxins are shown in Figure 1.

These genotoxins are esters of methanesulfonic acid. A process risk assessment using prior process knowledge identified Stage 8 as the stage where they can be formed or introduced in the process. In stage 8 the sources for these mesylate esters are:

- MMS and EMS can be present in the methanesulfonic acid used in the final salt formation and crystallisation (Stage 2d).
- MMS, EMS, and IMS can theoretically be formed in Stage 8 by esterification of methanesulfonic acid in the presence of methanol, ethanol, and 2-propanol as shown in Scheme 2.

Correspondingly, the sources of methanol, ethanol, and 2-propanol in the current process were assessed to be the following:

Table 1. **Process parameters for the formation of mesylate esters in Stage 8**

process parameter	rationale for selection	forcing conditions	standard conditions
amount of methanesulfonic acid	kinetic effect: higher amount of methanesulfonic acid and MeOH, EtOH, and *i*PrOH could increase the rate of formation of MMS, EMS, and IMS	0.8 mol equiv	0.6 mol equiv
amount of alcohols (MeOH, EtOH, *i*PrOH)		0.2% w/w each	*about* 0.01% w/w each
ageing time before seed addition	kinetic effect: longer time could increase the amount of MMS, EMS, and IMS formed	1 h	0.5 h
ageing time before isooctane addition		2.5 h	1 h
ageing time before filtration		12 h	3 h

- Methanol (MeOH) could be present in the input material to Stage 8 as a result of the reduction of one reagent in the preceding Stage 7. Methanol could also be present in the reagents used in Stages 6 and 7, and in one of the starting materials, depending on the supplier route of synthesis.
- Ethanol (EtOH) could be present in the Stage 8 reaction mixture because it is present in the ethyl acetate used as solvent. Also, it could be present in the input material to Stage 8 as a result of the reduction of one reagent in the preceding Stage 7. In addition it may be formed by hydrolysis of ethyl acetate in the basic conditions of the workup of Stage 7.
- 2-Propanol (isopropanol, *i*PrOH) could be present in the Stage 8 reaction mixture because it is contained in the isolated intermediate **3**, and it could also be present in acetone used as solvent in Stage 8.

The mechanism of mesylate ester formation was recently studied in detail,[3] and it was confirmed for the reaction of formation of methyl mesylate that its formation proceeds by initial protonation of methanol and nucleophilic attack of sulfonate anion on the protonated alcohol to give sulfonate ester and water. Additional key information from the above-mentioned study was the demonstration that the presence of water significantly decreases the extent of mesylate ester formation and the presence of base in excess inhibits their formation.

Both factors would have been important as additional elements of control for the control strategy proposed, but they could not be considered for the following reasons:

- The amount of water had to be controlled carefully in Stage 8 (accepted level not greater than 0.4% w/w) as it could have impacted the product physical properties and the yield.
- The amount of methanesulfonic acid selected in Stage 8 was higher than 1 mol equiv compared to the amount of base to maximize the yield.

Stage 8 comprises three sequential steps as follows:

- crystallisation
- isolation and washings
- drying

(2) Questions and answers to the follow-up to the contamination of Viracept (nelfinavir) with ethyl mesylate. EMEA/CHMP/375807/2008. London: European Medicines Agency, 2008. http://www.emea.europa.eu/humandocs/PDFs/EPAR/Viracept/Q&A_Viracept_37580708en.pdf (accessed 10 October 2009).

(3) Teasdale, A.; Eyley, S. C.; Delaney, E.; Jacq, K.; Taylor-Worth, K.; Lipczynski, A.; Reif, V.; Elder, D. P.; Facchine, K. L.; Golec, S.; Schulte Oestrich, R.; Sandra, P.; David, F. *Org. Process Res. Dev.* **2009**, *13*, 429–433.

Table 2. **Process parameters impacting the crystallization output for the precipitation of mesylate esters in Stage 8**

process parameter	rationale for selection	range of interest[a]	
seeding temperature[b]	parameters impacting the crystallization output	34 °C	44 °C
volume of ethyl acetate		3.0 vol	5.0 vol
volume of acetone		4.2 vol	4.8 vol
volume of isooctane		2.5 vol	3.5 vol
volume of isooctane		0.5 h	1.5 h

[a] Target value for the crystallization process is in the middle of the reported range. [b] Temperature kept for all the crystallization; details are provided in the Experimental Section.

These steps have been considered separately in the following paragraphs.

4.1.1. Crystallisation. A risk assessment was carried out to identify the parameters in Stage 8 that could contribute to the formation and precipitation of MMS, EMS, and IMS (mesylates esters). Table 1 and Table 2 report all the parameters obtained from the risk assessment and their effects. The reaction parameters were divided in two groups, process parameters for the formation of mesylate esters in Stage 8 (Table 1) and process parameters impacting the crystallization output for the precipitation of mesylate esters in Stage 8 (Table 2).

- Parameters that could specifically affect the kinetics of formation of these genotoxic impurities (Table 1): in this case it could be predicted from prior knowledge how the parameters would affect the formation of the genotoxic impurities, thus they were set at forcing conditions to maximize genotoxin formation.
- Parameters that were likely to impact the crystallisation (Table 2) but where it was not known *a priori* how they would affect the formation/precipitation of the genotoxins. The ranges investigated for these parameters were selected by considering the results of studies carried out previously.

It is worth noting that the amount of methanesulfonic acid reported in Table 1 is calculated on the amount of Intermediate 3 for consistency with the other details of the experimental section. This amount, if calculated with respect to Intermediate 2 (see Scheme 1, Stage 8), is 1.6 and 1.2 mol equiv of methanesulfonic acid, for the forcing and standard conditions respectively, confirming that in the conditions of the multivariate study the amount of base present in the system was always substoichometric with respect to the amount of methanesulfonic acid. This amount of methanesulfonic acid was selected to maximize the potential of formation of genotoxins.

Accordingly, an experimental design (DoE) was performed to investigate ranges for the second group parameters (Table

Table 3. **Reaction conditions used in the experimental design**

run	block	EtOAc (vol)	acetone (vol)	isooctane (vol)	temp (°C)	isooctane addition time (h)
1	1	2.5	4.2	3.5	34	0.5
2	1	1.5	4.5	3	39	1
3	1	0.5	4.8	2.5	34	0.5
4	1	0.5	4.2	3.5	44	1.5
5	1	2.5	4.8	2.5	44	1.5
6	2	1.5	4.5	3	39	1
7	2	0.5	4.2	2.5	44	0.5
8	2	0.5	4.8	3.5	34	1.5
9	2	2.5	4.8	3.5	44	0.5
10	2	2.5	4.2	2.5	34	1.5

2), where the first group parameters were held constant at the forcing conditions shown in Table 1.

A 2^{5-2}_{III} quarter fractional factorial design in two blocks with two center points (one for each block) was performed in a 10-reaction study. The conditions used in the DoE are reported in Table 3.

In each experiment, the levels of MMS, EMS, and IMS were determined in the suspension before filtration and in the isolated fluoroaryl-amine mesylate. In all the experiments, the levels of MMS, EMS, and IMS were below 1 ppm in the suspension before filtration, and the isolated fluoroaryl-amine mesylate contained less than 1 ppm (quantitation limit) of MMS, EMS, and IMS.

This study successfully demonstrated that the process does not produce MMS, EMS, and IMS when operated inside the ranges of the proposed parameters; therefore, there are neither quality process parameters (QPPs) nor quality critical process parameters (QCPPs) linked to the control of MMS, EMS, and IMS in Stage 8 crystallisation.

4.1.2. Isolation and Washings. After the removal of mother liquors by filtration, the drug substance filter cake was washed with 12 volumes of ethyl acetate. Two studies were performed to understand and assess the possibility of forming MMS, EMS, and IMS during filtration and washes.

In the first study, the fluoroaryl-amine **1** was crystallised under standard reaction conditions (target values for the process parameters as for Table 1 and 2), the mother liquors were removed, and then the wet cake was suspended in 4 volumes of ethyl acetate containing 0.2% w/w (typical process levels are less than 0.01% w/w) of each alcohol (MeOH, EtOH, and *i*PrOH) and methanesulfonic acid (0.1 equiv with respect to the isolated intermediate **3**) to ensure an excess of the acid in the system and maximise genotoxins formation. The resulting suspension was stirred for 2 h at 30 °C, to simulate a first wash under kinetically forcing conditions. The solid was filtered, the mother liquors were fully deliquored and dried without any further washes. Levels of MMS, EMS, and IMS were measured in the suspension before filtration and in the solid after drying. The levels of MMS, EMS, and IMS in both the suspension and dried solid were below 1 ppm, demonstrating that the washes do not generate these mesylate esters, even under these kinetically forcing conditions.

The second study was an extreme spiking study carried out by adding the genotoxin impurities directly into the process stage to study the ability to purge MMS, EMS, and IMS at artificially elevated levels of these mesylate esters in the Stage 8 isolation step. The fluoroaryl-amine mesylate was crystallised at the target value conditions using methanesulfonic acid containing 2500 ppm of MMS and 2600 ppm of EMS (corresponding to approx. 5× the limit of specification for MMS and EMS in methanesulfonic acid) and 1200 ppm of IMS. Additional quantities of MMS, EMS, and IMS were further introduced just before the filtration (1600, 2200, and 2900 ppm, respectively). At the end of the crystallisation, the solids were filtered, and different washing regimes were applied, i.e., no wash, 4 volumes, 8 volumes, and 12 volumes of ethyl acetate. The solids of these experiments were fully deliquored and dried under vacuum at 40 °C with no agitation. The levels of MMS, EMS, and IMS in the solids were tested, and the results are shown in Table 4.

Table 4. **Levels of MMS, EMS, and IMS in the isolated fluoroaryl-amine**

volumes of ethyl acetate used in the wash	level of MMS, EMS, and IMS in the cake after wash (ppm)		
	MMS	EMS	IMS
deliquoring (0)	1	1.6	1.8
4	<1	<1	<1
8	<1	<1	<1
12	<1	<1	<1

These analyses confirm that the levels of MMS, EMS and IMS in the isolated drug substance are close to the quantitation limit of the method after the cake was fully deliquored, i.e., even before any wash was performed. The successive washings further decreased the risk of producing drug substance containing MMS, EMS, or IMS, providing a wide margin of safety.

4.1.3. Drying. The possibility of formation of MMS, EMS, and IMS during the drying of the fluoroaryl-amine **1** was also studied. In this experiment the fluoroaryl-amine wet cake coming from Stage 8 crystallisation and isolation run at the target value process conditions, was suspended in one volume of ethyl acetate containing 0.2% w/w of each MeOH, EtOH, and *i*PrOH (highest levels found in the process were not greater than 0.01% w/w each), and the suspension was heated at 60 °C for 13 h under atmospheric conditions, well above the target drying conditions of 40 °C, under vacuum. The solvent was then removed by filtration, and the solid was dried. Levels of MMS, EMS, and IMS were measured in the suspension before filtration and in the solid after drying. The levels of MMS, EMS, and IMS in both the suspension and dried solid were found to be below 1 ppm, demonstrating that the drying does not generate these mesylate esters, even under these forced conditions.

4.2. Final Control Strategy. In summary, the studies on the Stage 8 process have demonstrated the following:

- The presence of excessive amounts of methanol, ethanol, and 2-propanol (up to 0.2% w/w each) in the salt formation and crystallisation does not result in the formation of MMS, EMS, and IMS.
- The presence of methanol, ethanol, and 2-propanol in the filtration and washing operations does not result in the formation of MMS, EMS, and IMS.
- The isolation is very effective for the removal of MMS, EMS, and IMS.

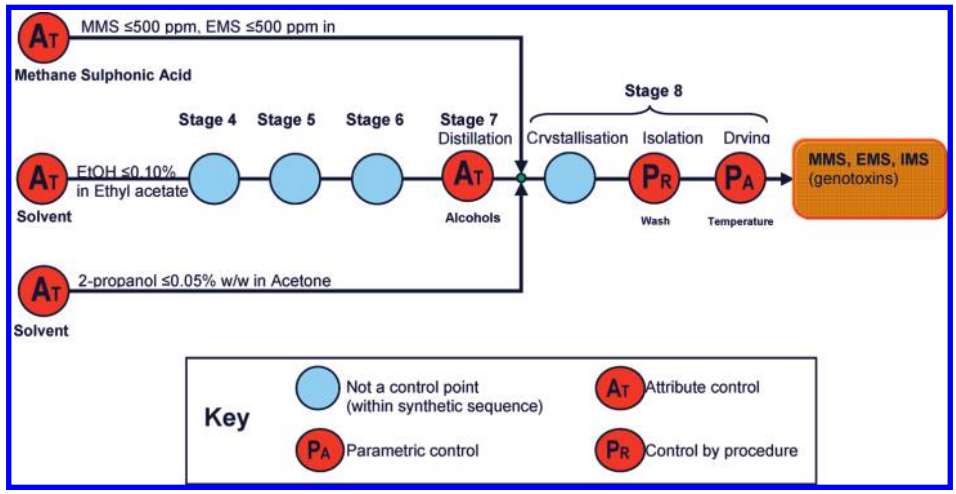


Figure 2. **Control strategy for genotoxins in the fluoroaryl-amine.**

- The drying operation does not generate MMS, EMS, and IMS even in the presence of elevated levels of methanol, ethanol, and 2-propanol at temperatures up to 60 °C. Because no data were available above this temperature, it was decided to set this as the upper limit for drying.

On the basis of these results, and since all the batches manufactured to date have been tested for the CQAs of these drug substances (MMS, EMS, IMS) and they have not been present above the quantitation limit of the analytical method (1 ppm), a sound scientific rationale can be made to remove end-product testing of the drug substance for these genotoxic impurities and to control the impurities upstream in the manufacturing process by four attribute controls, one parametric control, and one procedural control, as follows:

- attribute control by placing a specification of NGT 500 ppm for MMS and EMS in methanesulfonic acid
- attribute control by placing a limit on ethanol of NGT 0.1% (w/w) in ethyl acetate
- attribute control by placing a limit of on 2-propanol of NGT 0.05% (w/w) in acetone
- attribute control by placing a limit on the levels of methanol, ethanol, and 2-propanol before the final crystallisation at the end of the Stage 7 to NGT 0.10% w/w each
- parameter control by placing an upper limit of NGT 60 °C (proven acceptable range) on the drying temperature, which is a QPP (quality process parameter) of the process. This process parameter was defined as a QPP after rigorous risk assessment as it can influence a drug substance-CQA (genotoxins content), but the risk for the process operated at target value conditions (40 °C) to fall outside the proven acceptable range (not greater than 60 °C) is considered low (see also the definitions in the Glossary).
- procedural control by washing the filter cake after filtration

This control strategy is summarised diagrammatically in Figure 2.

5. Conclusions

The Quality-by-Design principles outlined in ICH and other guidance provide a structured approach to gaining process knowledge and developing robust manufacturing control strategies. This has been applied successfully to developing a control strategy for the fluoroaryl-amine mesylate, **1**, drug substance manufacturing process, in particular for the control of potential genotoxic impurities.

These control points described here will limit MMS, EMS, and IMS formation to negligible levels, thus providing a robust control strategy.

On the basis of the process understanding provided, it has been demonstrated that the control of genotoxic impurities can be robustly achieved by the elements of control described above, allowing testing the final drug substance to be omitted.

6. Experimental Section

Procedure for Crystallization Experiments. A solution of the fluoroaryl-amine free base **2** (0.86 wt)[4] in EtOAc was spiked with the required amount of methanol, ethanol, and 2-propanol (0.2% w/w each). The obtained solution was then diluted with EtOAc (overall ethyl acetate from 3 to 5 vol) and acetone (from 4.2 to 4.8 vol), and heated to the required temperature (from 34 to 44 °C). Then neat methanesulfonic acid (0.8 mol equiv) was added, the mixture stirred for 1 h, a slurry of seed (0.005 wt) in EtOAc (0.05 vol) was added, and the obtained suspension stirred for 2.5 h. Then isooctane (from 2.5 to 3.5 vol) was added in the required time (from 0.5 to 1.5 h), and the obtained suspension was cooled to 20 °C in 2 h and stirred overnight (~12 h).

The suspension was sampled and filtered, and the solid was washed with EtOAc (3 × 4 vol). The white solid was dried overnight under vacuum at 40 °C to give the desired fluoroaryl-amine **1**.

Procedure for Isolation Experiment. The fluoroaryl-amine mesylate **1** was crystallised under standard conditions (target values for the process parameters). The details followed in the isolation experiment including the levels of alcohols and mesylates added are reported in section 4.1.2.

Procedure for Drying Experiments. The fluoroaryl-amine mesylate **1** was crystallised under standard conditions (target values for the process parameters). The details followed in the

(4) Amount of intermediate coming from 1 wt of the isolated intermediate **3**.

drying experiments including the levels of alcohols added are reported in section 4.1.3.

Analytical Characterisation. All the fluoroaryl-amine mesylate **1** obtained in these experiments has been analysed by genotox content as reported above; in addition, NMR and HPLC data were collected, confirming consistency with all the other samples obtained during development.

Acknowledgment

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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 in the unit operation or stage inputs, stage outputs, device, etc.	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.
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 ranges.
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	a (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: words in parentheses are felt unnecessary.)
Proven Acceptable Range (PAR)	upper and/or 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. 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).

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