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PERSPECTIVE

Enhanced Approaches to the Identification, Evaluation, and Control of Impurities

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Abstract
A series of case histories from IQ consortium member companies will be presented to exemplify how the application of the ICH Q11 vision for enhanced or quality by design (QbD) development for the active pharmaceutical ingredient (API) can lead to differentiated outcomes for elements such as the API supply chain and control strategy, and how changes to such outcomes are managed over the lifecycle. A series of articles will address "flexibility" and look to provide recommendations for the further development of the ICH Q11 vision. The focus of this work will address flexibility associated with the "Enhanced Approaches to the Identification, Evaluation and Control of Impurities."

Keywords ICH · Q11 · Chemistry · Control strategy · Quality by design · QbD · Process · Methods · Models · CMC · Regulatory flexibility · PAT · ATP

Introduction

ICH Q11 emphasizes that a control strategy is a requirement for all active pharmaceutical ingredient (API) processes but also highlights the availability of both traditional and enhanced approaches to developing and implementing that control strategy. For APIs, the identification, evaluation, and control of impurities are of fundamental importance to the development of the control strategy and the manufacture of safe, efficacious, and optimal quality products for patients. In a traditional approach to API development, impurities are primarily controlled via the specifications of starting materials, intermediates, and the API. Moreover, those specifications are typically based on batch manufacturing experience, without consideration of the ability of the manufacturing process to purge such impurities, nor of the lack of knowledge of unknown impurities which have not yet been identified. For this reason, any substantial changes to the manufacturing process or supply chain can be seen as carrying significant risk. Under an enhanced ICHQ11 development approach, potential impurities are identified based on process understanding, including the impact of potential impurities in input materials and of manufacture anywhere within the defined process ranges. In this way, an enhanced approach ensures that actual and potential impurities, their origin, fate and purge, are more fully understood and that greater numbers of potential impurities are identified and assessed during development. However, this should not necessitate a commensurate increase in the complexity or number of analytical and parametric controls for such impurities. Understanding which impurities are efficiently purged, which are linked to CQAs (i.e., impact the drug substance impurity profile) and which of these need specific controls as part of a holistic control strategy is a fundamental output of enhanced development [1]. Where impurities (including by-products, solvents, metals, residual intermediates, or reagents) used in the manufacture of input materials or intermediates are efficiently purged, there is often little or no risk to quality of the final API. Such impurities need not be considered CQAs and their control strategy should reflect their low inherent risk. A deep understanding of potential impurities and their origin and fate allows controls to be designed into the manufacturing process. These can be any combination of inherent process controls (e.g., through changing the synthetic route or chemical reagents and solvents

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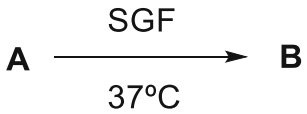
used to reduce or eliminate by-products, or the introduction of unit operations such as crystallisations, washes, or chemical quenches) or specific controls, such as defined operating ranges, analytical tests, or process analytical technologies (PAT). A fundamental consideration in developing each control is the role it plays in the overall control strategy. Controls, designed into the process, such as the destruction or purging of impurities under certain processing conditions, can often be coupled with additional controls in the raw materials and end products or intermediates. It is possible that any one of these controls alone provides a control strategy appropriate for the quality of the product and hence it may be argued on the basis of scientific understanding and risk that multiple points of control are not required. Overall, an enhanced development approach allows for different types of control strategy to be developed beyond simple testing of isolated intermediates and the API. The purpose of this work is to present case studies from IQ consortium member companies which illustrate an enhanced development approach to the identification, evaluation, and control of impurities has led to differentiated approaches to their control providing greater regulatory and operational flexibility over the product lifecycle [2].

Case Study 1: Use of In Vivo Chemical Fate Data to Support Drug Substance Control Strategy This case study illustrates the successful application of a control strategy using in vivo data for a potential mutagenic impurity during the process development of a clinical candidate. Impurity **A** is formed in-process just prior to the filtration unit operation and is observed in the isolated drug substance. After *in silico* assessment, impurity A was deemed a structural alert for potential mutagenicity, requiring control to ppm levels based on current ICH M7 guidance [3].

In order to understand more fully the risk posed by impurity A, extensive studies were undertaken including (1) determining the mechanism of impurity A formation, (2) identification of potential process parameter control options, and (3) understanding the chemical fate under downstream conditions. Examination of the structure coupled with known reactivity of such structural motifs suggested a high probability of reactivity under acidic conditions. Through kinetic studies to evaluate chemical fate, impurity A was shown to rapidly convert to impurity B in simulated gastric fluid (SGF) (Scheme 1) at the first time point (10 min) of the study with < 1 ppm remaining of A.

Impurity B was shown to be non-mutagenic in an Ames study and with this data in hand, a proposal was put forth to regulatory authorities to control impurity A at the unspecified limit of NMT 0.10% *w/w*. The argument was made that although impurity A is a structural alert for potential mutagenicity, since it converts in vivo (aqueous acidic conditions of the gastric system) to the non-mutagenic impurity B in a timeframe that should avoid any concern over potential DNA reactivity, the inherent toxicity risk is therefore that of impurity B. The proposal was accepted, thus providing the needed flexibility in the impurity A specification required for the project. The flexibility gained significantly impacted the control strategy in a positive way, as without the allowance of changes, impurity A would have required specification at a ppm level. Instead, a specification of the MI could be set at NMT 0.10% *w/w*. This avoided the need for what otherwise would have been tight processing controls and extra operations leading to increased costs, development of process and methods, and overall risk on the supply chain.



Scheme 1 Chemical fate of impurity A in simulated gastric fluid

Chemical fate arguments for impurities, although standard in industry, do not typically consider what can happen in vivo. In case study 1, due to the high reactivity of the impurity under aqueous acidic conditions, the in vivo argument is logical. We believe this approach could be considered for other cases where an impurity is shown to be highly reactive rapid conversion into a benign impurity. The end result is greater flexibility while maintaining product quality.

Case Study 2: Impurity Risk Assessment via Purge Factor Predictions and Potential for Scope Expansion Establishing purge efficiency of mutagenic impurity (MI) or potentially mutagenic impurity (PMI) experimentally has been a common strategy taken in many companies during development. Predicted purge factors are calculated based on knowledge of the impurities physicochemical parameters (reactivity, solubility, volatility, ionizability, etc) and the processing conditions of the synthetic route. These predicted purge factors can be compared to a required purge factor (that which is needed to meet the TTC) with the resulting ratio representing a semi-quantitative risk determination of their potential impact on product critical quality attributes. However, with CMC activities more commonly on or near critical path during development, especially with programs receiving regulatory breakthrough designation, risk assessment of a mutagenic impurity (MI) or potentially mutagenic impurity (PMI) using the purge factor prediction approach is being used more widely in industry to support ICHQ11 control strategies [4–6].

In order to assess the use of purge factor predictions as a risk assessment tool supporting rapid development, this case study describes a retrospective analysis of three recent projects in which data derived from experimental purge work was compared to the purge factor predictions.

The experimental approach taken (Fig. 1) for assessing MIs or PMIs for three products started with a determination of whether an observed or potential impurity requires identification. Upon identification, each structure is tested for its

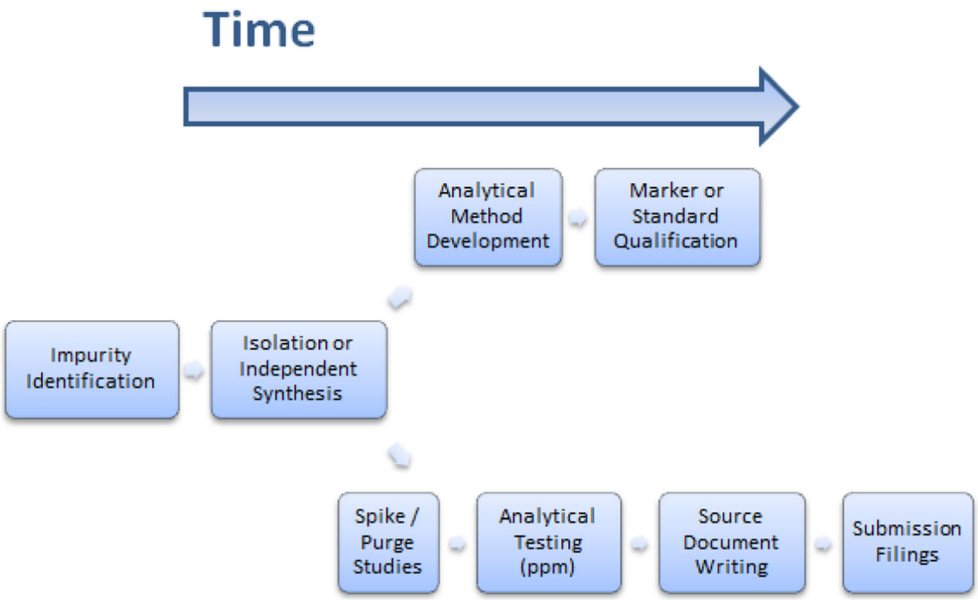


Fig. 1 Experimental assessment approach of mutagenic or potentially mutagenic impurities, and the associated time and costs

potential to have DNA reactivity *in silico*, as required by M7, and to determine if additional testing and action is required. Typically, each alerting impurity is synthesized or isolated for characterization. A spiking and testing plan is developed requiring low-level, quantitative, analytical method development, spike/purge studies and testing of resulting batches of intermediates or API with the goal of setting specifications. While this experimental approach is effective in ensuring product quality, it creates a significant resource and time burden which can impact access to new medicines or the introduction of new, more sustainable chemistry.

In considering for MIs and PMIs, there are four control options described in ICH M7 Section 8:

- Option 1: Testing as a specification in the drug substance at the threshold of toxicological concern (TTC).
- Option 2: Testing as a specification in the raw material or intermediate at the TTC.
- Option 3: Testing as a specification at the raw material, intermediate or IPC stage with a higher limit than the TTC along with downstream purge understanding.
- Option 4: Such low risk that no testing is required.

In order to gain the flexibility of utilizing an option 4 strategy, this challenge can be addressed via a risk assessment approach utilizing predicted purge factors. Where risk is judged medium or low, the experimental approach is not required to justify an option 4 control strategy.

Table 1 summarizes the findings of a retrospective analysis of three recent projects in a company within the IQ consortia. Over the three projects, a total of 45 MIs and PMIs were identified as potential or observed impurities. Using the historical experimental path taken, the majority (42) are controlled using an option 3 strategy where spike or purge data was used to justify a starting material, intermediate or IPC specification that ensures the TTC is met in the drug substance. In no case did we utilize option 4 [3]. Predicted purge factors were calculated with Lhasa Mirabilis software and required purge factors were determined based on the starting level of the MI or PMI taking into account the TTC of the impurity in the drug substance [7]. Using a conservative purge factor threshold ratio of 100–1,000× (predicted/required), option 4 could have been utilized for 27 impurities [8]. For project C in particular, 86% of the impurities could have been controlled using option 4, leading to a savings of 3–4 months of development time and significant associated costs in compound preparation and characterization. In all cases where the purge factor risk assessment led to ICH M7 option 4 control, the experimental data previously gathered supports this assessment, therefore supporting the use of a predicted purge factor approach. The purge factor risk assessment approach for MIs or PMIs spearheaded by Teasdale et al. is being used by many in industry to support project development and regulatory filings.

While conducting our retrospective analysis of projects, additional discussions spurred ideas for the potential use of purge factors outside the scope of MI and PMI risk assessment as described in ICH M7, but instead with standard impurities as well. For example, could the approach of purge factors be applied in supplementing the justification of starting material, intermediate or IPC specifications? Using the same physicochemical parameter groupings, the predicted purge factor of an observed upstream material impurity via downstream processing could be additional information used along with batch history and other data to set a specification for that observed impurity. Where this could be of most help would be in cases

Table 1 Summary of retrospective risk assessment

Project	No. of MIs/ PMIs	Option 1, 2, 3, or 4		% of impurities moved to option 4
		Original approach	Purge factor approach	
A	18	1–1 2–none 3–17 4–none	1–1 2–none 3–11 4–6	33%
B	6	1–none 2–1 3–5 4–none	1–none 2–none 3–3 4–3	50%
C	21	1–none 2–1 3–20 4–none	1–none 2–none 3–3 4–18	86%

where an observed impurity is purged to <LOD (limit of detection) in the drug substance, but there is a desire for more flexibility with the impurity's acceptance criterion than might be possible strictly based on other factors.

Figure 2 outlines a scenario where use of a purge factor approach could provide for a significantly higher acceptance criterion. Important in this risk assessment approach, as is for MI/PMI risk assessment, would be the need to hold to a conservative threshold ratio between predicted and required purge factors, ensuring product quality.

Case study 2 shows how knowledge of the physicochemical properties of MIs and PMIs, and therefore the calculation of predicted purge factors, can be used to build efficiency and flexibility into the impurity control strategy of a drug substance by justifying an ICH M7 option 4 strategy. In addition, there is potential scope expansion for using purge factors in other aspects of process development such as setting material impurity specifications that could provide further value through increased flexibility.

Case Study 3: QbD-Based Control for a Family of Potentially Mutagenic Impurities The synthetic process to prepare a good manufacturing practice (GMP) intermediate proceeds through formation of an allylic bromide which subsequently reacts further to afford the desired product. During the development of this process, ten allylic bromide impurities were identified as being potentially mutagenic due to their common reactive functional group. A traditional control strategy for these impurities might involve synthesis of each impurity, determination of which impurities are mutagenic by Ames testing, and development of analytical controls for each of the mutagenic impurities at the TTC defined limit of NMT 67 ppm in this case. Such an approach would lead to a heavy burden on analytical method development and testing of the intermediates. To decrease the analytical burden while still ensuring clearance of these allylic bromide impurities, an alternative approach, based on QbD principles, was identified. This approach would take advantage of the high reactivity of the allylic bromide functional group by transforming this family of potentially mutagenic impurities to a family of non-mutagenic impurities. To this end, a quench of the reactive allylic bromide impurities was developed wherein 2-mercaptoethylamine hydrochloride is used to convert the

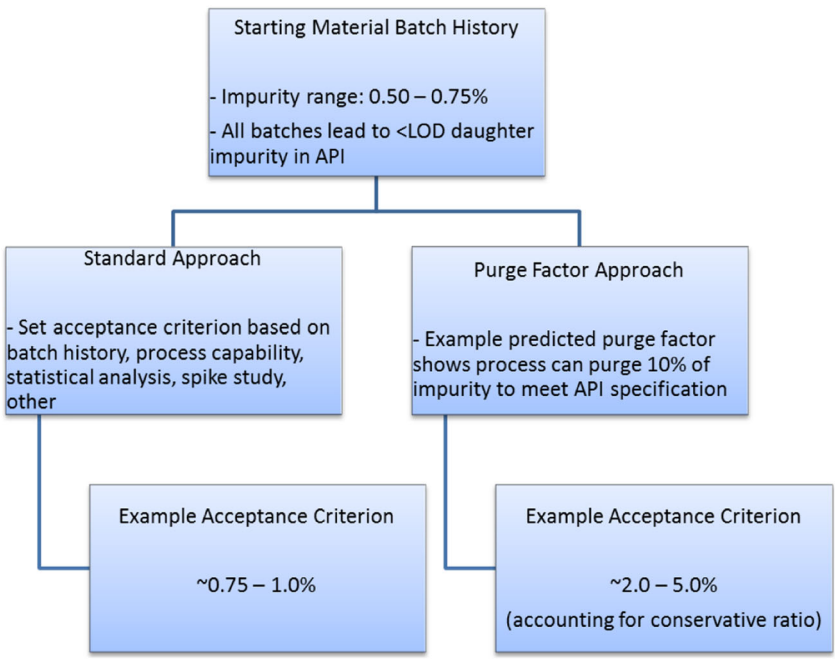


Fig. 2 Purge factors used in setting material impurity specifications

allylic bromide functional group of the process impurities to non-mutagenic thioethers (Scheme 2).

To ensure that the reactive quench would consume the entire family of allylic bromide impurities, a determination was made, based on a risk assessment, that studying the reactivity of two family members would be representative of the entire family. The first allylic bromide, 1, is the reaction intermediate and was determined to be the family member at the highest level in the process. The second allylic bromide, 2, was expected to be the least reactive allylic bromide based on additional steric bulk in the vicinity of the allylic bromide functional group. In addition, it was determined that the total amount of the entire family of allylic bromide impurities would not exceed 5 mol% in the process. The two allylic bromides, 1 and 2, were prepared and subjected independently to the reactive quench.

The reaction conditions of the quench correspond to the process conditions at the time of the quench:

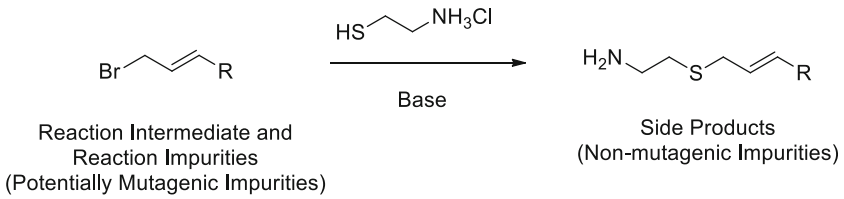
- Reaction concentration corresponding to the impurity present at 5 mol%.
- Two molar equivalents of 2-mercaptoethylamine HCl relative to compound 1 or 2.
- Similar solvent composition and base amount as the process conditions.
- A reaction temperature of 19 °C, which is below the nominal process quench temperature.

The conversion of allylic bromides 1 and 2 to the corresponding allylic thioether was monitored by HPLC analysis (Fig. 3) and demonstrated consumption of 1 and 2 which could be described by first order kinetic analysis (Fig. 4). The data also confirmed the expectation, based on the risk assessment, that allylic bromide 2 would be less reactive than that of allylic bromide 1. From the first order kinetic analysis, the k_{obs} and half-lives of 1 and 2 could be determined under these reaction conditions (Table 2). With an understanding of the reaction rate for the quench, it can be determined if the reactive quench can control the impurities to appropriate levels. Based on the kinetic data, a stir time of 30 min for the quench represents 25 half-lives of conversion for the slowest reacting allylic bromide impurity.

This would result in the conversion of the entire family of allylic bromide impurities from a maximum of 50,000 ppm (or 5.0%) to 0.0015 ppm post-quench, a level 45,000 times below the limit of 67 ppm as determined by the TTC. As a further confirmation, the effectiveness of the quench, ten multi-kg batches were analyzed for the residual allylic bromide 1. In each isolated intermediate, < 20 ppm of 1 was quantified (the practical quantification limit of the analytical method is 20 ppm of 1). Several of the quench parameters were determined to be critical to ensure the quench continues to be effective. These parameters are the lower temperature limit (NLT 20 °C), the lower stir time (NLT 30 min), the charge amount of 2-mercaptoethylamine HCl (NLT 0.10 equiv.). Additionally, a critical reaction completion IPC was put in place for the reaction (NMT 1.0% allylic bromide 1 remaining), in order to limit the amount of allylic bromide impurities heading into the quench operation.

In conclusion, the development and understanding of the reactive quench allows for the control of an entire family of impurities without the need to test each impurity individually. The study allowed for the identification of specific critical controls which will ensure the long-term effectiveness of the reactive quench. This QbD approach to control strategy development provides flexibility during development of the process by decreasing the synthetic and analytical burden to prepare and develop methods for each impurity of this family and also provides flexibility over the lifecycle by limiting the need to transfer and maintain analytical methods, while ensuring the effective removal of an entire family of potentially mutagenic impurities.

Case Study 4: Example: Attaining Analytical Procedure Flexibility Through Using Technique Specific System Suitability Criteria or a Technique Independent Analytical Target Profile The analytical target profile (ATP) is analogous to the quality target product profile (QTPP) and has most recently been defined by the USP as "the objective of the test and quality measurements, including the expected level of confidence, for the reportable result that allows the correct conclusion to be drawn regarding the attributes of the material that is being measured" [9–13]. The ATP serves as a reference point for assessing the fitness of an analytical procedure during all changes within the analytical lifecycle and is not linked to a specific analytical method. The EMA and FDA [14] have highlighted that there is currently no international consensus on the definition of the ATP but acknowledge that it can be used as a qualifier of the expected performance of an analytical method. The agencies currently do not consider analytical methods that have different principles (e.g., LC and NIR) equivalent solely on the basis of conformance with the ATP



Scheme 2 Allylic bromide impurities convert to non-mutagenic

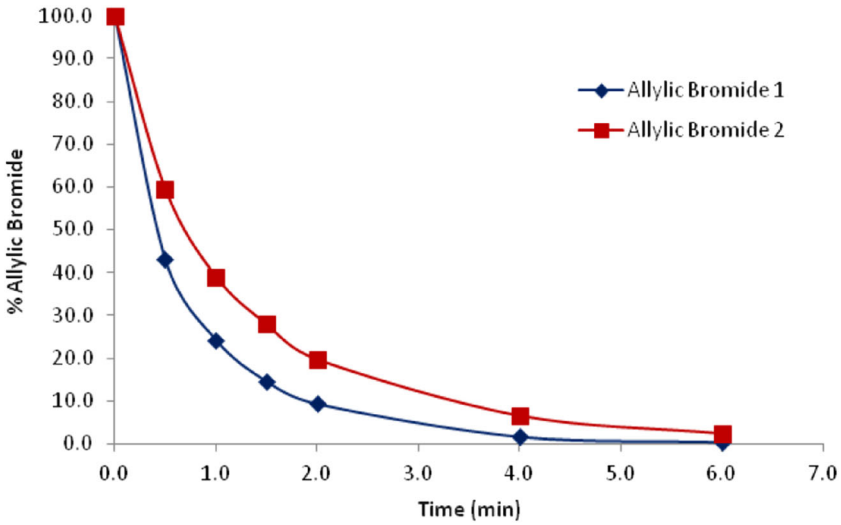


Fig. 3 Reactivity of allylic bromides 1 and 2

[14]. Use of the ATP to attain greater operational flexibility for analytical methods using the same technique (e.g., HPLC to UPLC which are both LC methods) will be evaluated by the EMA and FDA on a case-by-case basis. The development of a drug substance impurities method for the analysis of Examplain.HCl API using QbD principles has previously been described in the literature [10] (Fig. 5).

The control strategy requires impurities A, B, and C to be measured in the drug substance. The specification limit for impurities A, B, and C are 0.2% *w/w*, 0.3% *w/w*, and 0.5% respectively and the reporting limit is 0.05%. The ATP for this control method can therefore be written as "The method should be able to quantify impurities A, B, and C in the presence of Examplain.HCl API, over a range of 0.05–0.5% relative to the API. The combined accuracy and precision of the method must be such that the 95% of the reportable results fall within ± 15% of the true value for impurity levels from 0.05 to 0.15% and ± 10% for impurity levels > 0.15%. Two analytical methods were developed for the analysis of impurities A, B, and C using HPLC and UPLC as it was envisioned that the manufacturing site would replace their old HPLC systems with new UPLC systems in the next 5 years. The conditions in Table 3 were developed for the HPLC and UPLC methods respectively. Method validation was performed for both the HPLC and UPLC methods. Both methods met the criteria in the analytical target profile (see Table 4 for comparison of some of the key method validation results (note: the results from the robustness [15] and ruggedness [16] testing are not shown here)). The sensitivity of the UPLC method was over 60% more sensitive than the HPLC method so switching to

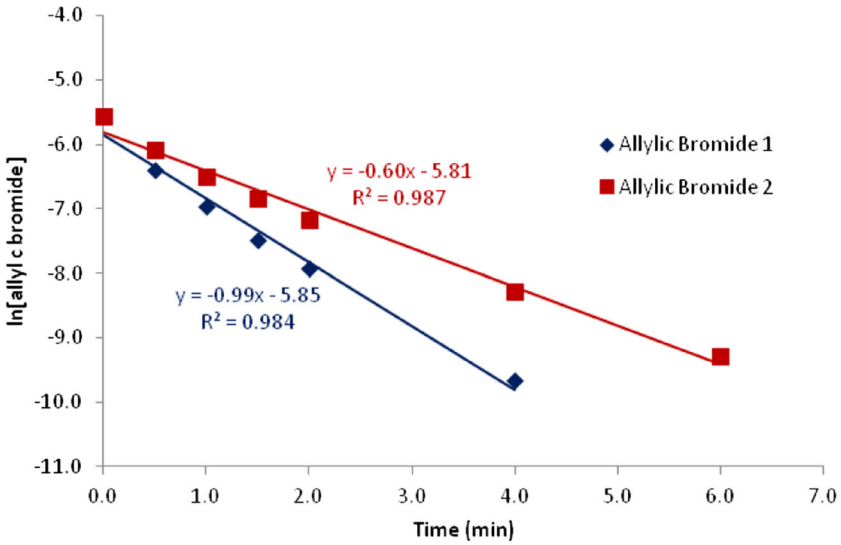


Fig. 4 First-order kinetic analysis

Table 2 First-order kinetic parameters for allylic bromides 1 and 2

Allylic bromide	k_{obs} at 19 °C	Half-life at 19 °C
1	0.99 min^{-1}	0.7 min
2	0.60 min^{-1}	1.2 min

Table 3 HPLC and UPLC method conditions

HPLC Parameter	Value		
Column	150 × 4.6 mm 3.5 um Zorbax Bonus-RP		
Column temp	40 °C		
Mobile phase A	Water + 0.05% *v/v* TFA		
Mobile phase B	MeCN + 0.05% *v/v* TFA		
Gradient	Time (min)	%A	%B
	0	75	25
	30	5	95
	31	75	25
	36	75	25
Flow rate	1.0 mL/min		
Detection	UV at 245 nm		
Injection volume	10 uL		
UPLC Parameter	Value		
Column	100 × 2.1 mm 1.7 um Zorbax Bonus-RP		
Column temp	40 °C		
Mobile phase A	Water + 0.05% *v/v* TFA		
Mobile phase B	MeCN + 0.05% *v/v* TFA		
Gradient	Time (min)	%A	%B
	0	75	25
	10.29	5	95
	10.63	75	25
	12.40	75	25
Flow rate	0.41 mL/min		
Detection	UV at 245 nm		
Injection volume	1.4 uL		

the new UPLC method in the future would actually result in enhancing the analytical control strategy (see Fig. 6 for typical chromatograms (of a typical test mixture) for both analytical methods). Both methods were registered in the analytical procedures section (S4.2) of the common technical document (CTD) which provided the manufacturer flexibility to move between a fixed HPLC method and a fixed UPLC method (see Table 3). The use of the term/concept "established conditions" (ECs) is currently being developed and refined as part of the review of the evolving ICHQ12 guideline [17]. For methods such as the above where an enhanced (QbD) approach has been used to develop the method (using risk based DoE [15] and ruggedness studies [16]), sufficient method understanding will have been established to implement ECs based on method performance criteria. This would enable any developed method within a given technique (LC in this example) to be used as long as method performance criteria are met [18]. In the case study presented, this could take the form of system suitability criteria. In the example presented, this could include a RRT check of all the named peaks, resolution of > 1.5 between the critical peak pairs, a discrimination factor [19] of not less than 0.9 for any low-level impurities (less than 0.05%) eluting right after the main peak, a 0.05%*w/w* LOQ check and a combined accuracy/precision check (using a retained well characterized batch of drug substance) of not more than ± 15% for each of the 3 impurities.

This would mean that changes to all method parameters within the demonstrated operable range (otherwise known as an MODR—"method operable design region") for a given technique would not be considered as established conditions. In this case, a switch between different stationary phases (columns) or mode of chromatography (e.g., HPLC to UPLC) would not be reportable (falling into the category of

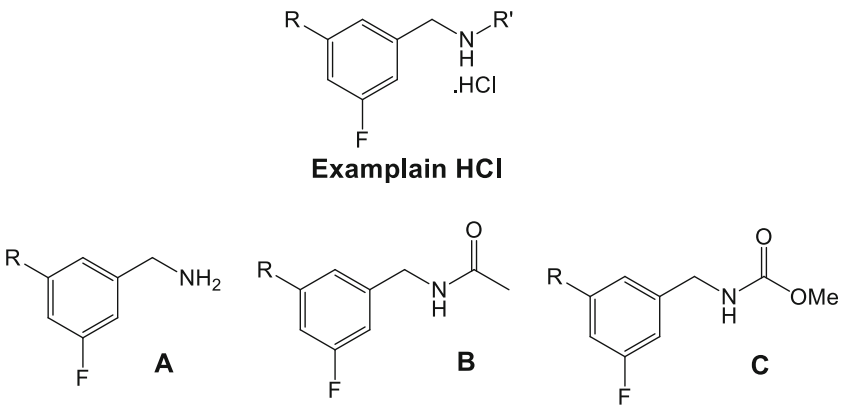


Fig. 5 Examplain.HCl API (note this is not the real name of the drug substance)

Table 4 Method validation results for HPLC and UPLC methods

Parameter	HPLC			uHPLC		
Linearity of API	y-intercept = 0.7%			y-intercept = 1.4%		
	$R = 0.9999$			$R = 0.9997$		
Linearity of impurities	y-intercept (range) = − 2.0% to 0.7%			y-intercept (range) = 0.4 to 3.2%		
	R (range) = 0.999 to 1.000			$R = 0.999$ (for all 3 impurities)		
Repeatability of API	%RSD = 0.2			%RSD = 0.1		
Repeatability of impurities	%RSD = 0.5 (for all impurities)			%RSD (range) = 1.6 to 2.2		
Accuracy	Impurity A	89%		Impurity A	108%	
	Impurity B	105%		Impurity B	98%	
	Impurity C	87%		Impurity C	101%	
Sensitivity		QL	DL		QL	DL
	Impurity A	0.013	0.004	Impurity A	0.003	0.001
	Impurity B	0.009	0.003	Impurity B	0.003	0.001
	Impurity C	0.012	0.003	Impurity C	0.007	0.002

"do and tell") for a post approval change as long as system suitability criteria were met. Note: Diana et al. [20] classifies a change from HPLC to UPLC as a medium change and suggests the requirement of completed method validation prior to implementation of comparability study(ies). Åsberg et al. provide a similar example to the outlined above where they propose the use of a system suitability test to support switching between HPLC and UPLC methods for the analysis of the drug Nexium [21]. An even more ambitious approach would entail defining the ATP as the established conditions which would enable methods across different techniques to be managed by the PQS (Pharmaceutical Quality System).

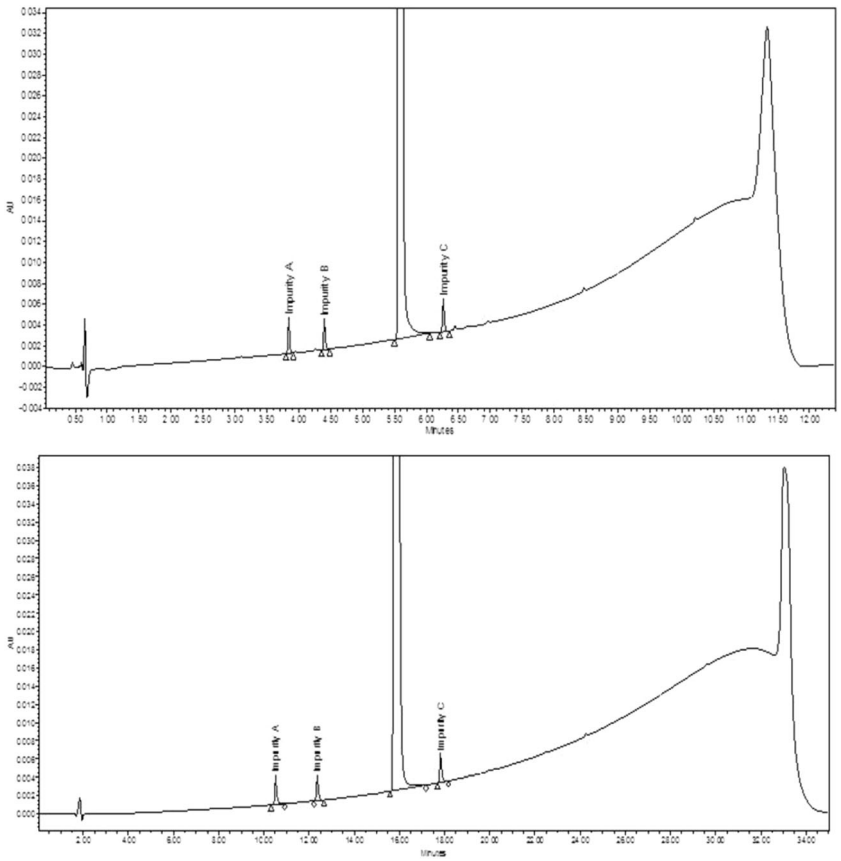


Fig. 6 Example chromatograms from UPLC (top) and HPLC (bottom) methods

Conclusions

Enhanced QbD development will improve process and product understanding and should ultimately result in improved robustness and quality of medicines and their supply chains. In addition, these case histories illustrate that enhanced development can also provide "flexibility" for API manufacturers, by allowing for different development and control strategies based on a scientific understanding of the risk associated with an impurity, rather than by a prescriptive, one-size-fit-all traditional approach.

It is important that industry and regulators look to the science and process understanding that result from an enhanced development approach in order to allow the introduction of innovative control strategies for impurities. It is recommended by IQ that further collaboration between industry and regulators occurs, with the aim of accelerating the adoption of science-and risk based approaches to the control of impurities in API in order to help deliver the holistic ICH Q8-Q11 vision.

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