Analytical Quality by Design: The What, Why, a Case Study, IQ Consortium Survey Summary, & Regulatory Status

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Analytical Quality by Design Journey!

- ★ Analytical guidelines from ICH and USP
- ★ What is Analytical Quality by Design (AQbD)?
- ★ AQbD case study
- ★ The current issues and IQ Consortium Work since 2012 through 2017
- ★ Regulatory status, ICH Q14 since ca. 2017 till current

“Analytical Guidelines” from FDA, ICH and USP: None on development

Source	Brief description	Comments
ICH	Q1A: Stability testing of new drug substances and drug products	Stress testing guidelines in here are often used in determining forced degradation (chemical, Q1) and photo degradation (Q1B) conditions in method development.
	Q1B: Photo-stability testing	
	Q8: Pharmaceutical development	QbD concepts for drug product development formed the basis of AQbD
	Q12: Pharmaceutical product LCM	• Annex IC on identification of established conditions for CZE analytical procedure for charged variants of active substance • Examples of NM (notification moderate, CBE 30): change in acceptance criteria • NL (Notification low, CBE 0): Reference standard concentration
FDA	Analytical Procedures and Methods Validation for Drugs and Biologics, July 2015	Section III, Analytical Methods’ Development recommends DoE approach “*Knowledge gained during these studies on the sources of method variation can help you assess the method performance*.” The document, however, does not provide regulatory relief in implementing any method changes post-approval.
USP	<621> chromatography	• Adjustments to a compendial procedure are permitted, e.g., pH, particle size, column temperature, etc., in order to meet system suitability requirements. • A planned change to expand on the allowable changes!

What is Analytical Quality by Design?

The basis of AQbD is the drug product QbD as described in ICH Q8

- ★ A systematic approach to development that begins with **predefined objectives** and
- ★ Emphasizes product and process **understanding and process control**,
- ★ Based on **sound science and quality risk management** as described in ICH Q9.
- ★ Together with product lifecycle management and continual improvement as described in ICHQ10 it should ensure that the **process is working** as anticipated and **delivers the product** with the appropriate quality.

What is Analytical Quality by Design?

Drug Product, ICHQ8	Analytical Procedure
Quality Target Product Profile	Analytical Target Profile
Risk Assessment	Risk Assessment
Critical Quality Attribute	Critical Method Attribute
Design Space	Method Operable Design Region
Control Strategy	Analytical Procedure Control Strategy
Ongoing Process Verification	Ongoing Method Verification

These QbD Product Development concepts are applied to Analytical QbD!

- Many Pharma and BioPharma companies have successfully employed AQbD concepts to resolve challenging issues with, mostly, chromatographic, but also non-chromatographic methods.
- Instead of using one-factor-at-a-time (OFAT) approach, the DoE based development employs multi-variant design to optimize the methods.

AQbD at Baxter Healthcare

- We purchased Fusion QbD software around 2010 at Baxter, and found an immediate need for a DoE based study to optimize an HPLC method for a drug, a preservative, and their impurities!

- We published this work in 2011:
  - S. Karmarkar, R. Garber, Y. Genchanok, S. George, X. Yang, and R. Hammond, Quality by Design (QbD) based development of a stability indicating HPLC method for drug and its impurities, J. Chroma Sci, 49 (2011): 439-446.

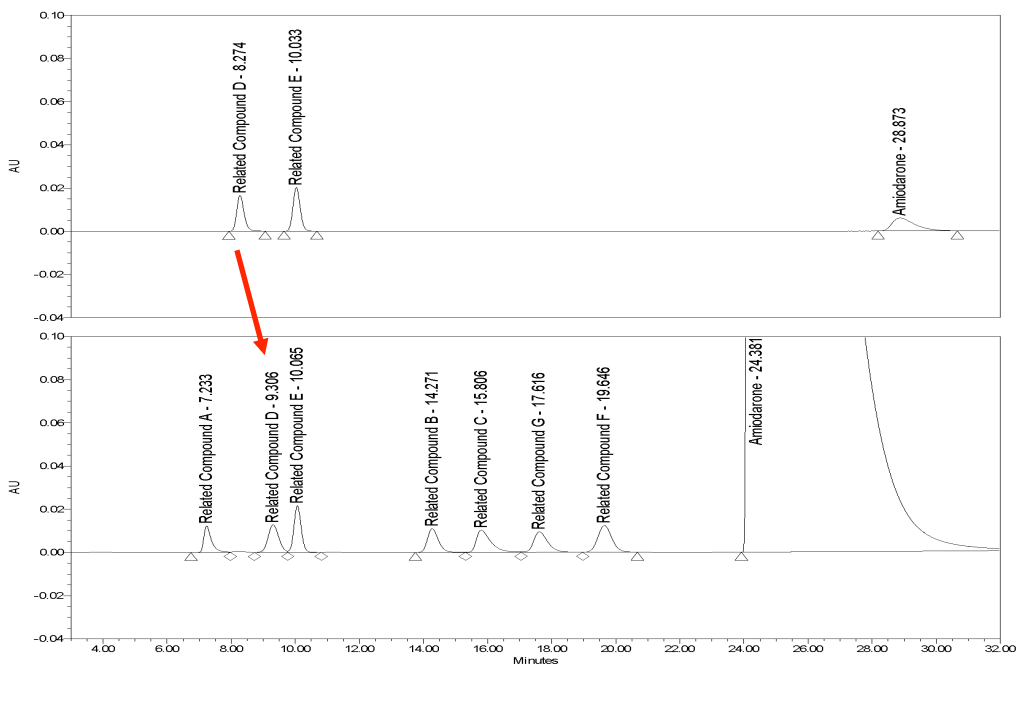
Success story: QbD based development and validation of an HPLC method for amiodarone and its impurities in the drug substance[1]

[1] S. Karmarkar, X. Yang, R. Garber, A. Szajkovics, and M. Koberda. Quality by Design (QbD) based development and validation of an HPLC method for amiodarone and its impurities, J. Pharm Biomed Anal, 100 (2014): 167-174.

Problem statement 1

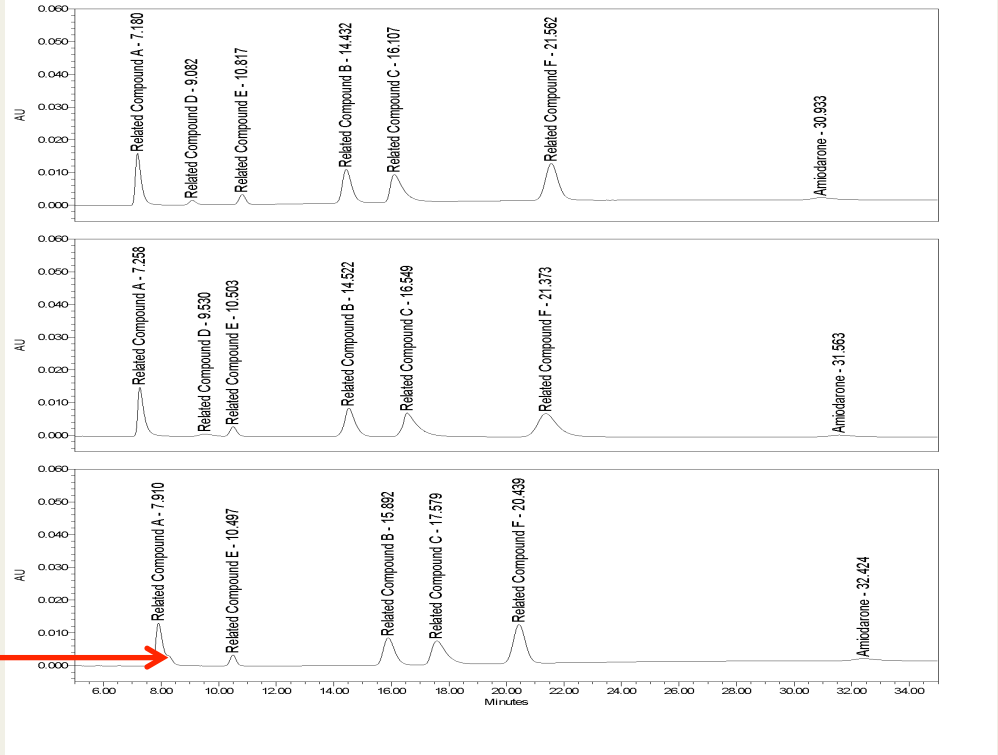
Standard: 0.01 mg/mL of amiodarone, and USP specified impurities D and E

Sample: 5 mg/mL of amiodarone



Peak D in the sample preparation eluted much later than that in the standard solution

Problem statement 2



Compound D??

Lot-to-lot variability with ODS2 GL-Science column

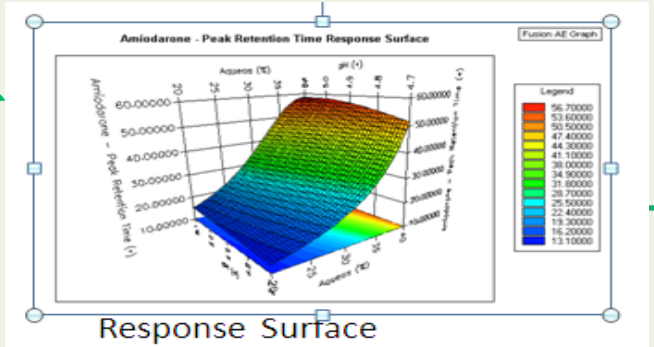
Multi-variate experiment & method optimization

Multi-variate QbD experiment

Fusion AE optimization using Experimental results

Optimization Goals
1. Highest resolution of neighboring peaks
2. Shortest runtime

Parameter	USP Method	Range studied
Mobile Phase pH	4.9	4.7-5.1
% Organic in the mobile phase	70 %	60-80 %
Column Temperature, ° C	30	25-40
Mobile Phase pH	4.9	4.7-5.1

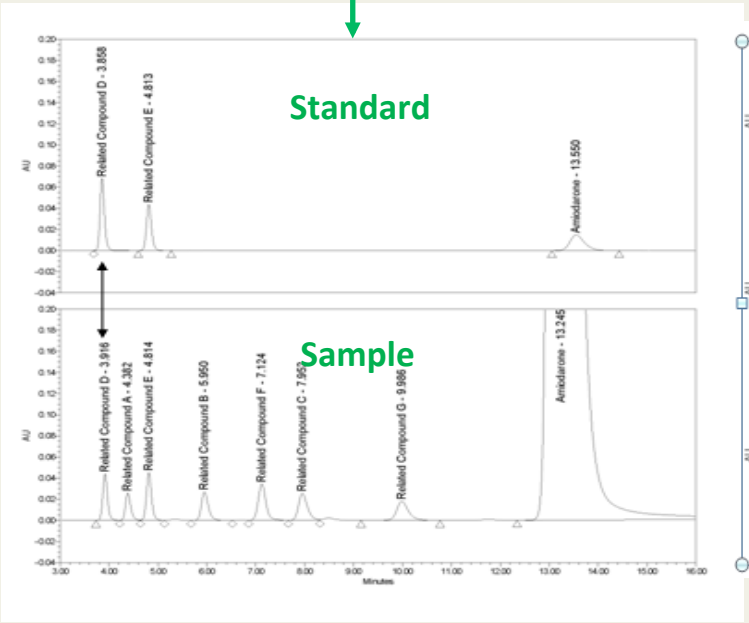


Response Surface

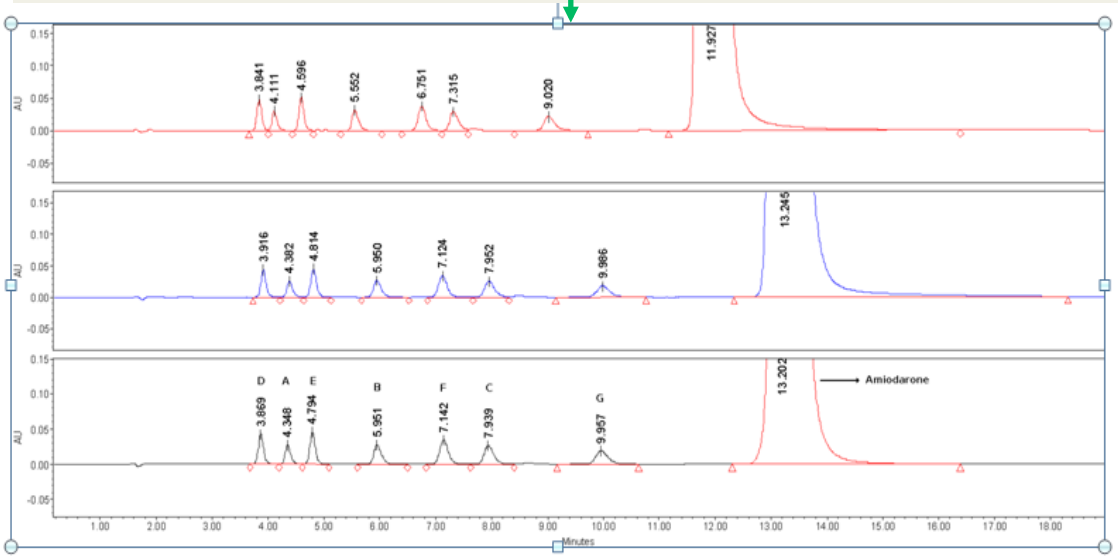
Optimized method!!

Optimized HPLC method: Both problems solved!

Constant peak D retention time!



Column lot-to-lot variability minimized!



Summary of AQbD based Optimization of HPLC method for amiodarone & its seven impurities

1. In the optimized method using Waters' Atlantis T3 column, lot-to-lot variability was negligible.
2. Peak D retention time remained constant from standard to sample.
3. The method was successfully validated in terms of accuracy, precision, linearity, range, and specificity. The mobile phase, standard, sensitivity solution, resolution solution, and sample preparation were found to be stable for about 7 days.
4. The elution order for impurities was different than that in the USP method. In order to ascertain system suitability for separation of closely eluting peaks, requirements on resolution between peaks D and A and that between A and E were implemented.
5. The method provides results for impurities that are equivalent to the results obtained per the USP method.
6. The method is robust with respect to % buffer (18-20%) and column temperature (40 $\pm$ 2 °C). The buffer pH has to be controlled exactly at pH 4.70.
7. The method was successfully transferred to the manufacturing plant.

Analytical Quality by Design Implementation Challenges

The Why sounds obvious:

- ☑ Develop AQbD based procedures, instead of the OFAT approach, resulting in rugged and robust methods, and
- ☑ Also seek regulatory relief in post-approval changes to the procedure.

Applicants feel there is a no regulatory relief when the analytical methods are developed using AQbD approach

- ⊙ Oliver Grosche, director of business operations and strategy in quality at Switzerland's Seagen International GmBH recently presented at the CMC strategy forum.
- ⊙ His lab wanted to implement a method change for a chiral column used to separate optical isomers to increase its performance, as the pressure in the column was too high.
- ⊙ The cost of securing the regulatory approval to change the method worldwide was prohibitive: $250,000! Therefore, instead of changing the method, the company decided to frequently change the columns.

Source: CMC Strategy Forum sponsored by the California Separation Science Society (2021)

Findings from an IQ Consortium survey: How far have we progressed in Analytical Quality by Design (AQbD)?

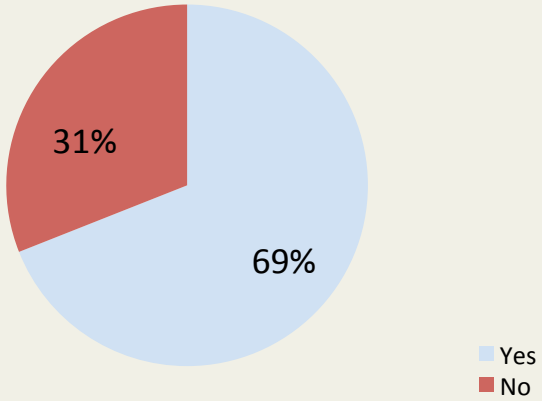
IQ Consortium

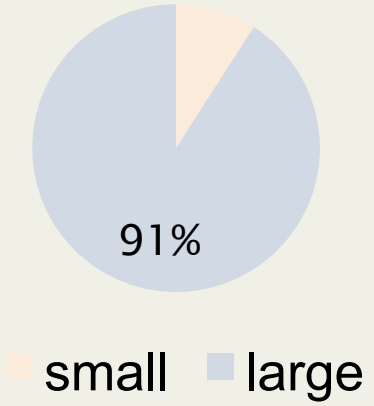
- IQ (Innovation & Quality) is a not-for-profit organization of about 40 pharmaceutical and biotechnology companies
- Mission: Advance science and technology to augment the capability of member companies to develop transformational solutions that benefit patients, regulators, and the broader R&D community.
- Working group on AQbD/LCM consisted of 22 representatives from 17 companies
  - Goal: Advocate scientifically based strategies and solutions that enable robust and appropriate analytical methodologies and controls throughout an analytical method lifecycle.
- AQbD Working Group within the IQ Consortium's Analytical Leadership Group conducted a survey of small and large molecule pharmaceutical companies in 2015 on implementation of AQbD concepts.

Evaluating Progress in Analytical Quality by Design, Pharmaceutical Technology-04-02-2017, Volume 41, Issue 4, pages 52-29

Implementation of AQbD

Of the 16 companies surveyed: 4 were small size and 12 were large size companies



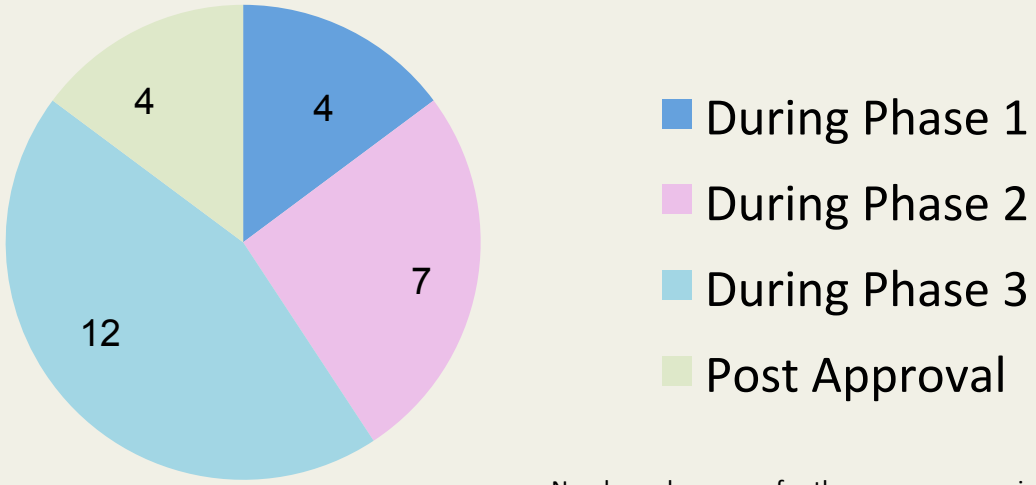


Breakdown of all responding companies that have implemented AQbD (11 out of 16).

Breakdown of companies (by size) that have implemented AQbD

Among the companies that have not implemented AQbD, 60% are small size companies (3 out of 5), and 40% are large size companies.

Timing for AQbD implementation



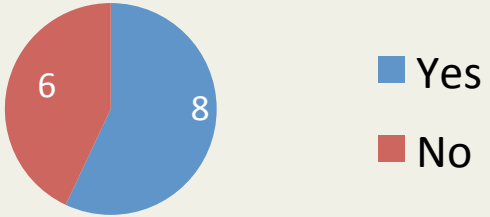
Numbers shown are for the responses received, i.e., a respondent may have a response in more than one section.

AQbD implementation predominantly takes place in later stages of development and post-approval. A few pertinent comments in the survey:

- Most effort > 80% spent during Phase 3.
- More systematically in Phase 3 but a subset of tools (modeling) are routinely used in early stage.

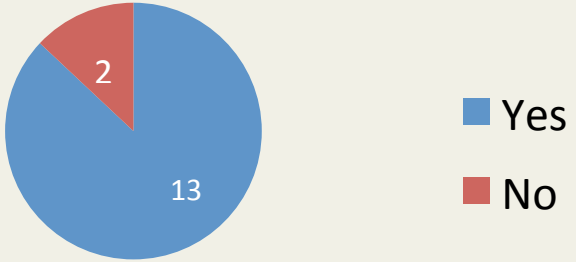
Implementation of AQbD

Time saving compared with OFAT



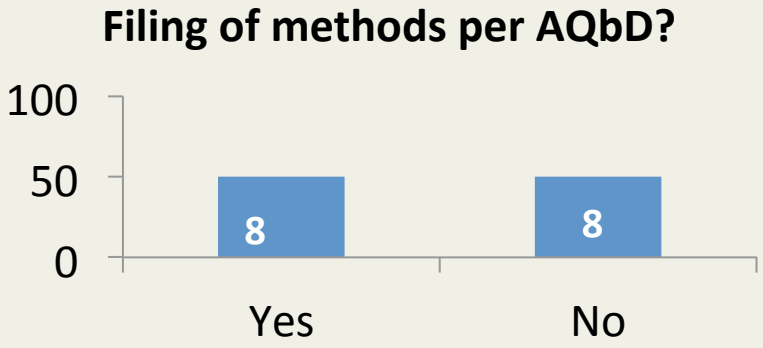
Respondents have applied statistics (92%) and experimental design (100%) in AQbD implementation. Modeling was used by 64% of the respondents

Software/modeling tools



- Fusion AE
- DryLab
- Design Expert DOE Software
- Both DryLab and LC Simulator as well as method development screening system developed in-house
- Chromsword
- Autochrom
- Multivariate software more important than a chromatography tool

Findings on regulatory aspects



Filing details

- Used to provide Analytical Target Profile (ATP) details over 5 years ago, but have moved away since there are no benefits. File includes general approach to analytical method risk assessments, and detail the statistical studies for the highest risk methods in S4.3 and P5.3
- Same level of details as provided historically: No filing of ATPs, risk assessments, stats beyond those already used for method validation and robustness.
- Method outline plus appendix to define criteria to allow method adjustments outside of MODR or validated operating range.
- Only results are presented
- Only robustness validation
- None, just final method

Regulatory filing

Have you had a successful regulatory review when implementing AQbD?

- 4 out of 9 respondents stated Yes
  - Positive feedback on AQbD approach with exception of using ATP for claiming greater operational flexibility
- 2 stated “no”, and one stated “not sure”
- 1 stated “N/A”, and 1 stated “not filed yet”

Comments received

- Regulators prefer MODR instead of Analytical Design Space (ADS) term.
- Yes, mainly concerning use of ATP for claiming operational flexibility
- Standard regulatory questions challenging specifications based on process capability – not AQbD specific
- Yes, mainly clarification questions
- Filed in US, EU, and Japan. AQbD principles were well received, but received pushback from the regulators on use of ATP as vehicle for gaining greater operational flexibility.

Sharing AQbD example

Departmental SOP

A slight majority of respondents, 59%, said they had no formal SOP on the application of analytical quality by design.

- A couple of respondents stated that they follow guideline. One respondent stated that they have an existing white paper, and are working towards developing a more extensive guideline.
- The comments on this question suggested that some groups felt specific guidance on QbD was not necessary and some that QbD aspects of analytical work was documented alongside those work-packages (e.g. method development or validation) rather than as a separate entity in its own right.

Noted business drivers for implementing AQbD

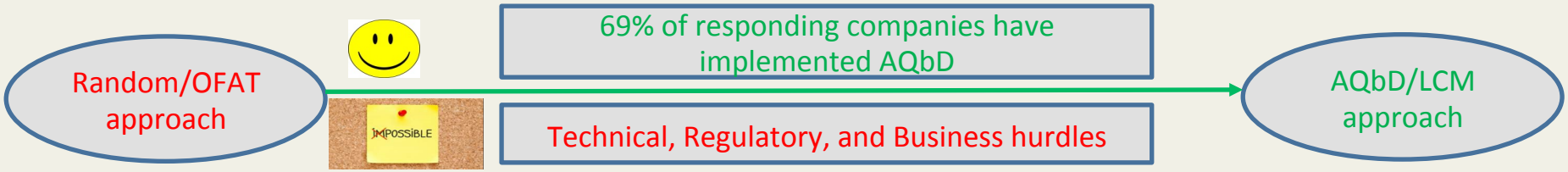
Business Driver	# Responding*		% Responding*	
	Yes	No	Most Important	Greatest return on Investment
Improved Performance of Analytical Methods and Robustness	15/15	0/15	67	43
Improved Knowledge about Analytical Methods	14/15	1/15	20	7
Regulatory Relief with Operational Flexibility	9/14	5/14	7	8
Development of Consistent Business Processes for Method Management	10/13	3/13	0	0
Other-Facilitate Lab to Lab Transfer	1/1	0	0	0

* Note: Total are not the same across all business drivers as some respondents omitted an answer.

Greatest benefits were seen in developing robust methods, better validation packages and method knowledge, and flexibility in method operation/regulatory flexibility

Conclusions: How far have we progressed?

- IQ survey on AQbD implementation with 34 questions on technical, regulatory, and business aspects
- Findings from 18 respondents representing 16 IQ member companies
- 69% of the responding companies have implemented AQbD
  - The respondents were equally split between implementation started just now and those who have been practicing AQbD concepts for a while.
  - AQbD has been implemented mostly during Phase 3 and post commercial
- Improved method performance, robust methods, and improved knowledge about analytical methods are the key drivers and benefits of AQbD implementation.
- The implementation hurdles include
  - Technical aspects, e.g., aligning practices across sites, statistical and DOE expertise, and developing ATP concepts
  - Regulatory aspects: No regulatory relief from the additional Quality by Design (QbD) information they provided. The flexibility hoped to be gained from the analytical target profile approach to method registration is not yet agreed
  - Business aspects: extra resource burden and return on investment



On the AQbD and ICHQ14

- No ICH guideline on analytical procedure development: applicants often report analytical validation results alone and rarely present performance evaluation with analytical development outcomes. This makes regulatory communication unproductive when non-conventional (e.g., multivariate models for process control) analytical procedures are employed.
- Additionally, the lack of guideline impedes opportunities for the applicant to present a scientific basis for flexible regulatory approaches (e.g., Quality by Design concept) to post-approval Analytical Procedure changes.
- ICH Q2(R1) is not directly applicable to analytical procedures such as Near Infrared (NIR) Spectroscopy. The lack of clear guidelines can lead to submissions with inadequate validation data for these analytical procedures, resulting in recursive information requests and responses, which can delay application approval.
- ICH Q14 goal is to provide an opportunity to present the knowledge obtained through applying enhanced approaches to validation of analytical procedures, to provide the guidance on how to apply and to indicate a policy for more flexible regulatory approaches. Applying the enhanced approach for analytical procedures (i.e., Quality by Design) will contribute to the resource-efficient drug development and streamline post-approval CMC changes.
- Expecting the draft ICH Q14 in the near future.


Thank
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