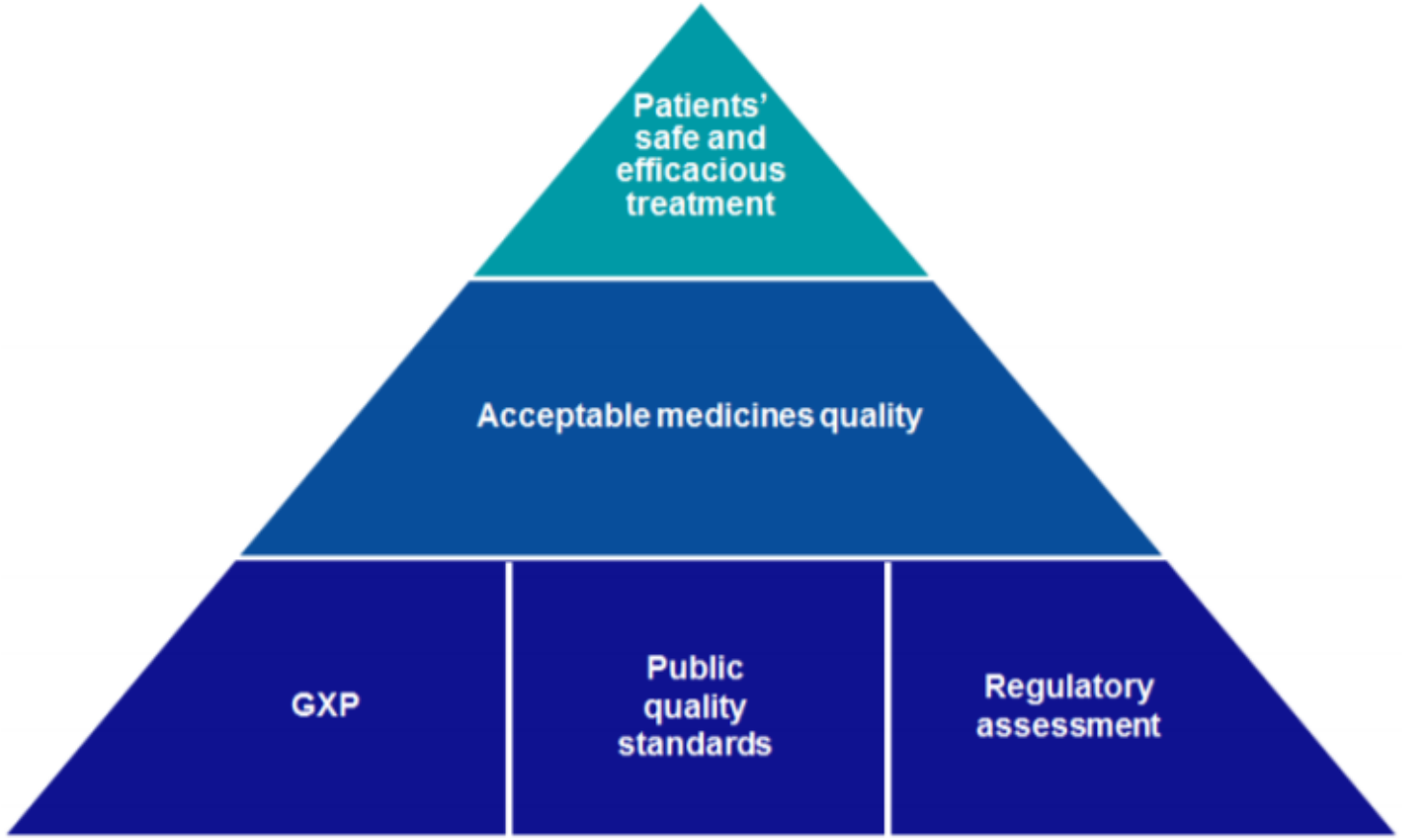
QbD for robust product

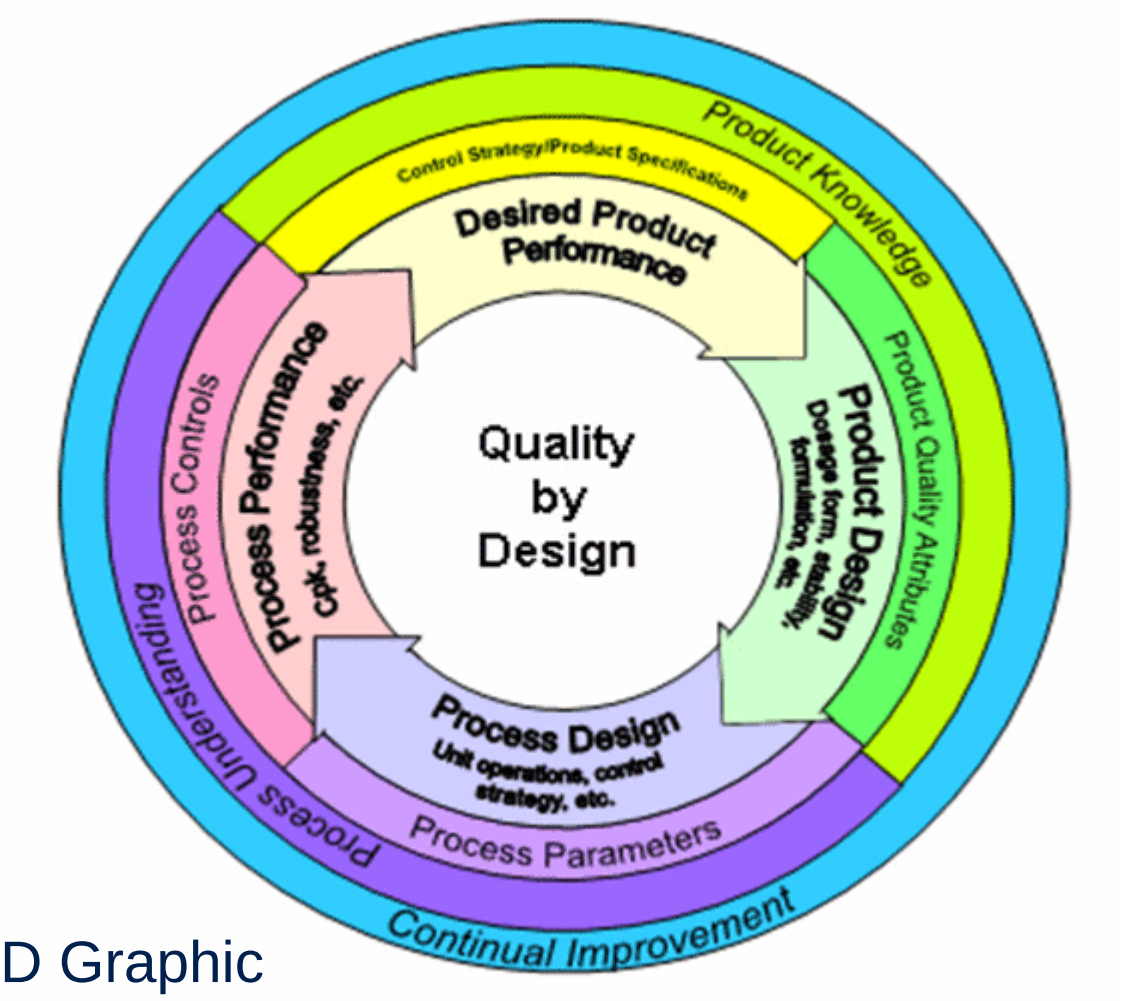
James Pound, IPA Mumbai 2020

Medicines & Healthcare products Regulatory Agency

Quality


Patients' safe and efficacious treatment
Acceptable medicines quality
GXP
Public quality standards
Regulatory assessment

Quality by Design (QbD)

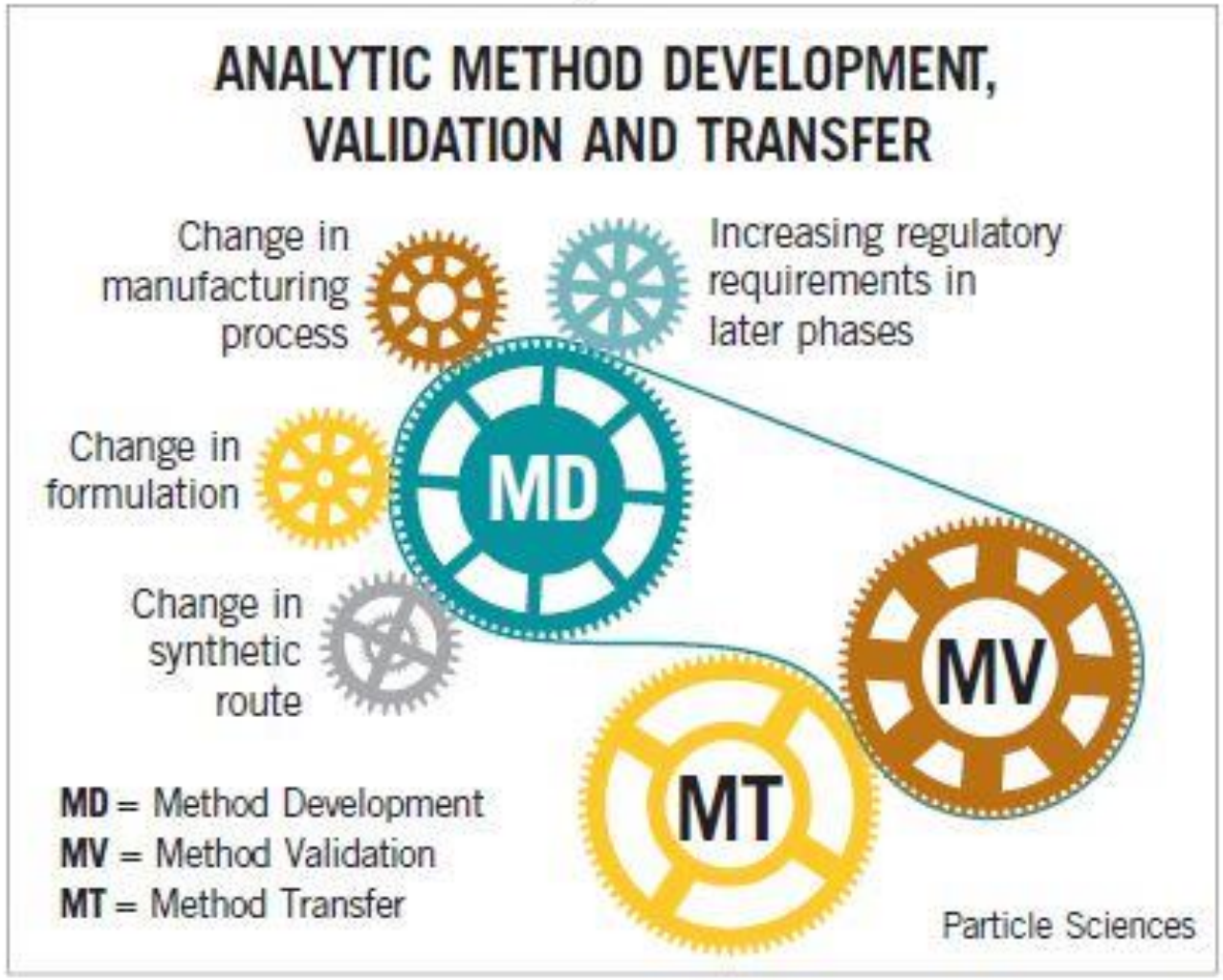


FDA QbD Graphic

- Systematic approach and predefined objectives
- Product and process understanding and control
- Based on science/data/evidence and risk management

Focus on analytical methods – complexity

Figure 1

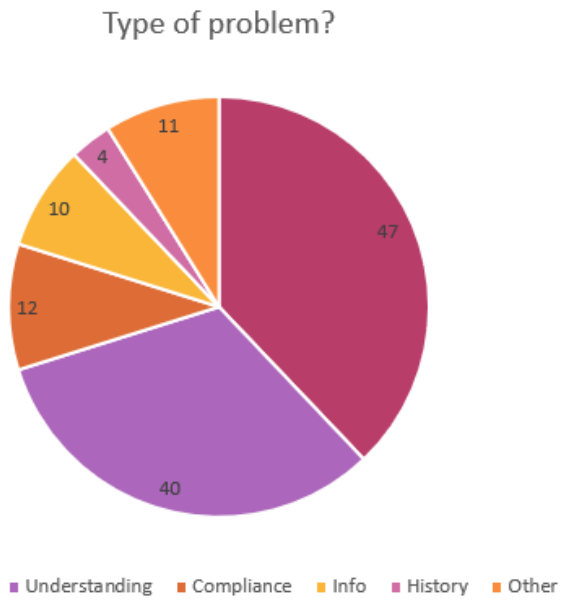


Credit: Particle Sciences Technical Brief 2009 Volume 5

Focus on analytical methods – evidence

Drugs

Cite Id	Reference Number	Short Description	Long Description	Frequency
1105	21 CFR 211.22(d)	Procedures not in writing, fully followed	The responsibilities and procedures applicable to the quality control unit are not [in writing] [fully followed]. Specifically, ***	185
3603	21 CFR 211.160(b)	Scientifically sound laboratory controls	Laboratory controls do not include the establishment of scientifically sound and appropriate [specifications] [standards] [sampling plans] [test procedures] designed to assure that [components] [drug product containers] [closures] [in-process materials] [labeling] [drug products] conform to appropriate standards of identity, strength, quality and purity. Specifically, ***	124



Credit: FDA FY 2017 Inspectional Observation Summaries

What is Analytical QbD?

- Analytical Quality by Design (AQbD) takes a structured approach to the development of analytical procedures to ensure they are fit for purpose and consistently deliver results that meet predefined objectives.

- It achieves this through a detailed understanding of all aspects of the analytical methods performance ensuring adequate control and an ability to react to changes which can affect the quality of results.

https://mhrainspectorate.blog.gov.uk/2019/08/21/analytical-quality-by-design-aqbd-questions-and-answers/

Global view


FDA
efpia
European Federation of Pharmaceutical Industries and Associations
MHRA
PhRMA
AMERICA'S BIOPHARMACEUTICAL COMPANIES
British Pharmacopoeia
ICH
harmonisation for better health
usp

MHRA/British Pharmacopoeia project

- Project to investigate the application of AQbD principles to compendial analytical methods.
- In order to fully explore the benefits and potential challenges of implementing AQbD, the development of a pharmacopoeial assay procedure for Atorvastatin tablets was selected as a case study.
- Collaborative - BP, Licensing Division, GMDP Inspectorate, Industry and Therapeutic Goods Administration (TGA) of Australia

MHRA/British Pharmacopoeia project

The project investigated:

- The application of risk based approaches and Design of Experiments (DoEs) to method development and verification, leading to an enhanced understanding of method performance and robustness

- Different approaches to (pre) define method performance requirements using the concept of an Analytical Target Profile (ATP), to better understand the use and value of this tool as well as to explore its relevance and applicability to compendial methods

Analytical Target Profile

An Analytical Target Profile (ATP) is designed to capture the quality attributes of a reportable value of a method through determining the level of acceptable variability of the method. A suitably designed and applied ATP can be a measure of assurance that an analytical method is fit for purpose throughout its lifecycle; from development, through to validation and into a commercial setting.

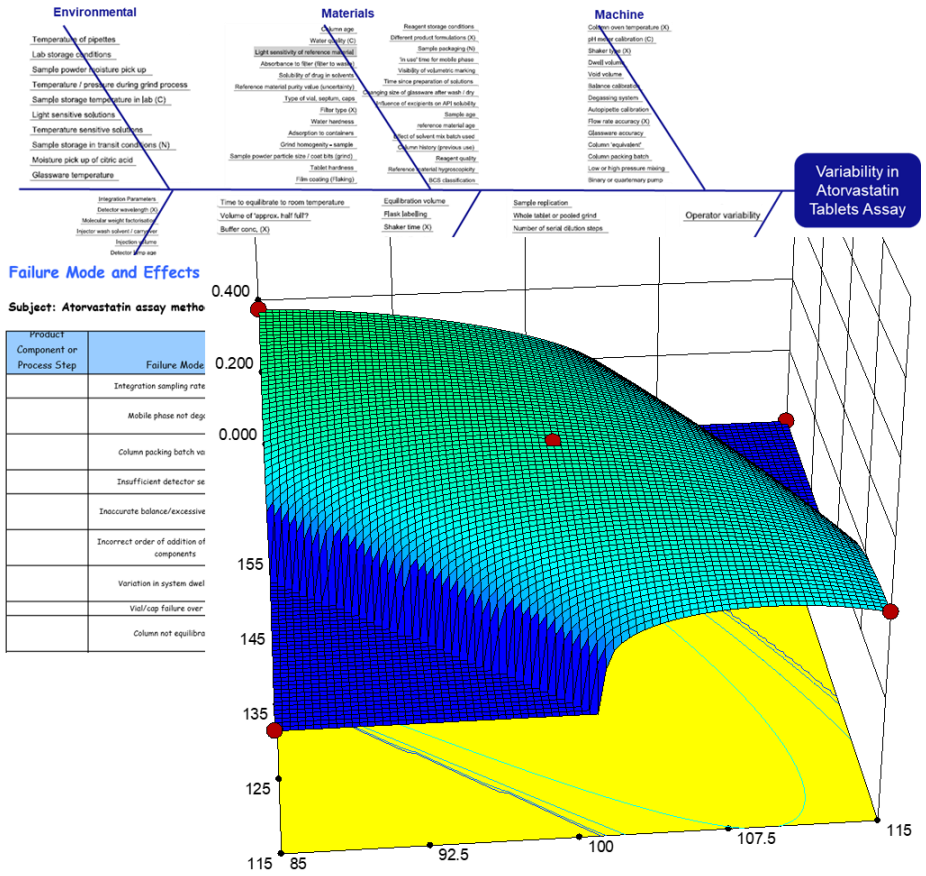
(amalgam of thinking from USP, EFPIA and others)

EXAMPLE:

The analytical method is capable of quantifying [ACTIVE] in [ACTIVE] Tablets from 70 to 130% of the true value with accuracy and precision of not more than 3.0%, with 95% probability.

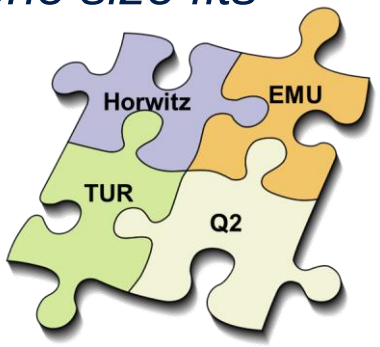
Systematic approach

- **Critical Method Parameters**
  - E.g. Fishbone / Failure Mode Effects Analysis
- **Representative Sample Selection**
  - E.g. Identification of 5 samples to represent the 100+ marketed Atorvastatin Tablet products
- **Design of Experiments**
  - Ability to assess all factors using a statistical approach reducing 162 runs to just 24
- **Method operable design region (MODR)/analytical design space**

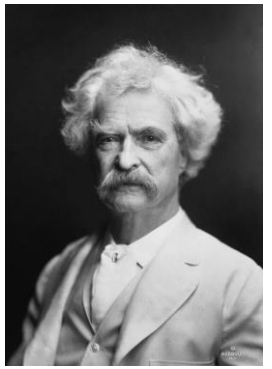


Lessons learned

- ATP
  - Confidence in the method – *ensure it is fit for purpose*
  - Variety of approaches/models for ATPs – *no one size fits all*



  - Rationale and justification for statistical analysis - *"Lies, damned lies, and statistics"*

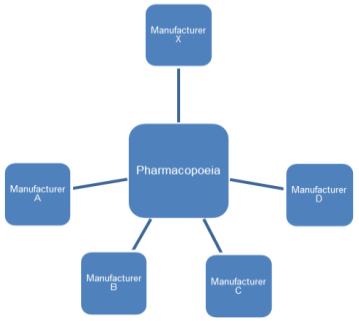


  - Demonstration of equivalence – *framework for the use of alternate methods*

Lessons learned

- Enhanced approaches

– Knowledge transfer - *becomes even more important*



– Structured risk assessment - *focus resource on risk*

– Multiple formulations - *additional complexity*

e.g. In the UK for Metformin Tablets 20,658,987 prescription items/year, 94 products across 33 MAHs

– Design of Experiments – *understand where method can fail, streamline resource*

Conclusions

- Enhanced risk-based approach to method development and evaluation
  - Improved method understanding
  - Confidence a method will be fit for its intended purpose
  - Focussing resource on risk

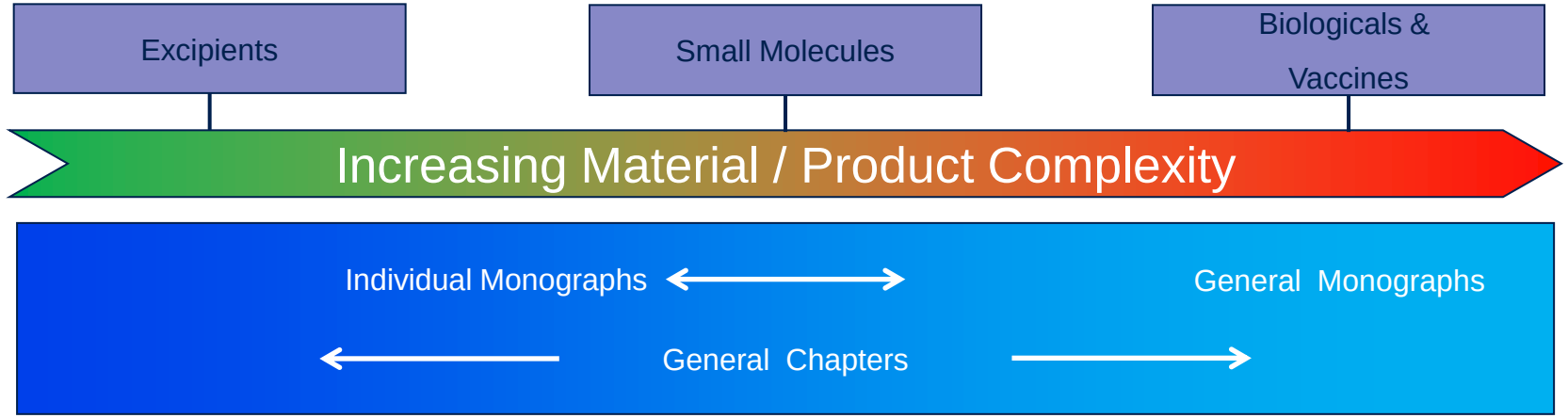
- ATP
  - Pre-defined requirements for method – ensure fit for purpose
  - Value for assessing suitability of an alternate method

Taken together, the enhanced risk-based approaches and the ATP concept provide a potential platform for ensuring that the analytical method can continue to evolve throughout its lifecycle

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/807416/AQbD_Technical_Document_-_Final_04_June_2019.pdf

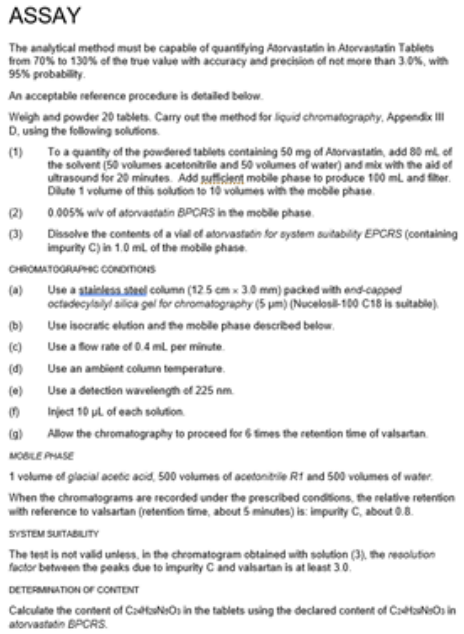
Compendial standards

- Where can the pharmacopoeias add value – specific monographs, general guidance or something else?
- Application – where can we derive most benefit – small molecules, biologics?



Acknowledgement: Adapted from Mark Wiggins, MSD/Merck

Compendial standards



ASSAY

The analytical method must be capable of quantifying Atorvastatin in Atorvastatin Tablets from 70% to 130% of the true value with accuracy and precision of not more than 3.0%, with 95% probability.

An acceptable reference procedure is detailed below.

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To a quantity of the powdered tablets containing 50 mg of Atorvastatin, add 80 mL of the solvent (50 volumes acetonitrile and 50 volumes of water) and mix with the aid of ultrasound for 20 minutes. Add sufficient mobile phase to produce 100 mL and filter. Dilute 1 volume of this solution to 10 volumes with the mobile phase.

(2) 0.005% w/v of *atorvastatin BPCRS* in the mobile phase.

(3) Dissolve the contents of a vial of *atorvastatin for system suitability EPCRS* (containing impurity C) in 1.0 mL of the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 3.0 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil-100 C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.4 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 225 nm.

(f) Inject 10 µL of each solution.

(g) Allow the chromatography to proceed for 6 times the retention time of valsartan.

MOBILE PHASE

1 volume of *glacial acetic acid*, 500 volumes of *acetonitrile R1* and 500 volumes of *water*.

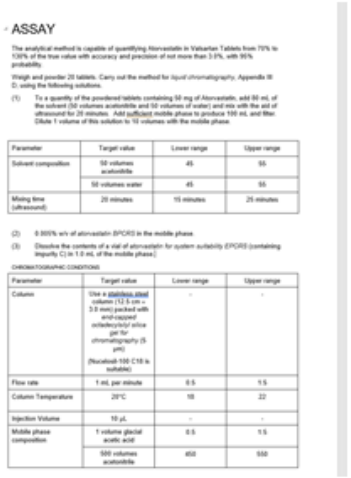
When the chromatograms are recorded under the prescribed conditions, the relative retention with reference to valsartan (retention time, about 5 minutes) is: impurity C, about 0.8.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the peaks due to impurity C and valsartan is at least 3.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{24}H_{28}NiO_5$ in the tablets using the declared content of $C_{24}H_{28}NiO_5$ in *atorvastatin BPCRS*.



ASSAY

The analytical method is capable of quantifying Atorvastatin in Valsartan Tablets from 70% to 130% of the true value with accuracy and precision of not more than 3.0%, with 95% probability.

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) To a quantity of the powdered tablets containing 50 mg of Atorvastatin, add 80 mL of the solvent (50 volumes acetonitrile and 50 volumes of water) and mix with the aid of ultrasound for 20 minutes. Add sufficient mobile phase to produce 100 mL and filter. Dilute 1 volume of this solution to 10 volumes with the mobile phase.

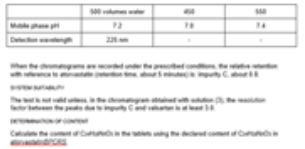
Parameter	Target value	Lower range	Upper range
Solvent composition	50 volumes acetonitrile	45	55
	50 volumes water	45	55
Mixing time (ultrasound)	20 minutes	15 minutes	25 minutes

(2) 0.005% w/v of *atorvastatin BPCRS* in the mobile phase.

(3) Dissolve the contents of a vial of *atorvastatin for system suitability EPCRS* (containing impurity C) in 1.0 mL of the mobile phase.

CHROMATOGRAPHIC CONDITIONS

Parameter	Target value	Lower range	Upper range
Column	Use a stainless steel column (12.5 cm × 3.0 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil-100 C18 is suitable)	-	-
Flow rate	1 mL per minute	0.5	1.5
Column Temperature	20°C	18	22
Injection Volume	10 µL	-	-
Mobile phase composition	1 volume glacial acetic acid	0.5	1.5
	500 volumes acetonitrile	450	550



	500 volumes water	450	550
Mobile phase pH	7.2	7.0	7.4
Detection wavelength	225 nm	-	-

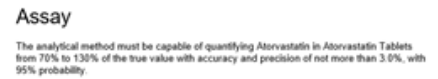
When the chromatograms are recorded under the prescribed conditions, the relative retention with reference to atorvastatin (retention time, about 5 minutes) is: impurity C, about 0.8

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the resolution factor between the peaks due to impurity C and valsartan is at least 3.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{24}H_{28}NiO_5$ in the tablets using the declared content of $C_{24}H_{28}NiO_5$ in *atorvastatin BPCRS*.



Assay

The analytical method must be capable of quantifying Atorvastatin in Atorvastatin Tablets from 70% to 130% of the true value with accuracy and precision of not more than 3.0%, with 95% probability.

Status quo **MODR/ADS** **ATP**

Method understanding/flexibility/added value

The future

- MHRA open consultation 2019 - https://www.gov.uk/government/consultations/consultation-on-the-application-of-analytical-quality-by-design-aqbd-principles-to-pharmacopoeial-standards-for-medicines

- Consultation response due to be published in early 2020

- Other developments

Thank you

Questions?

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