Validating an ASTM Method by USP <1225>

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Topic Overview

Where are you today?

Get to know USP

Key sections of method validation

Sample validation plan

Where are you today?

USP <621> Chromatography

USP <541> Titrimetry

USP <921> Water Determination

ASTM D7319

ASTM D7795

ASTM D7591

ASTM …

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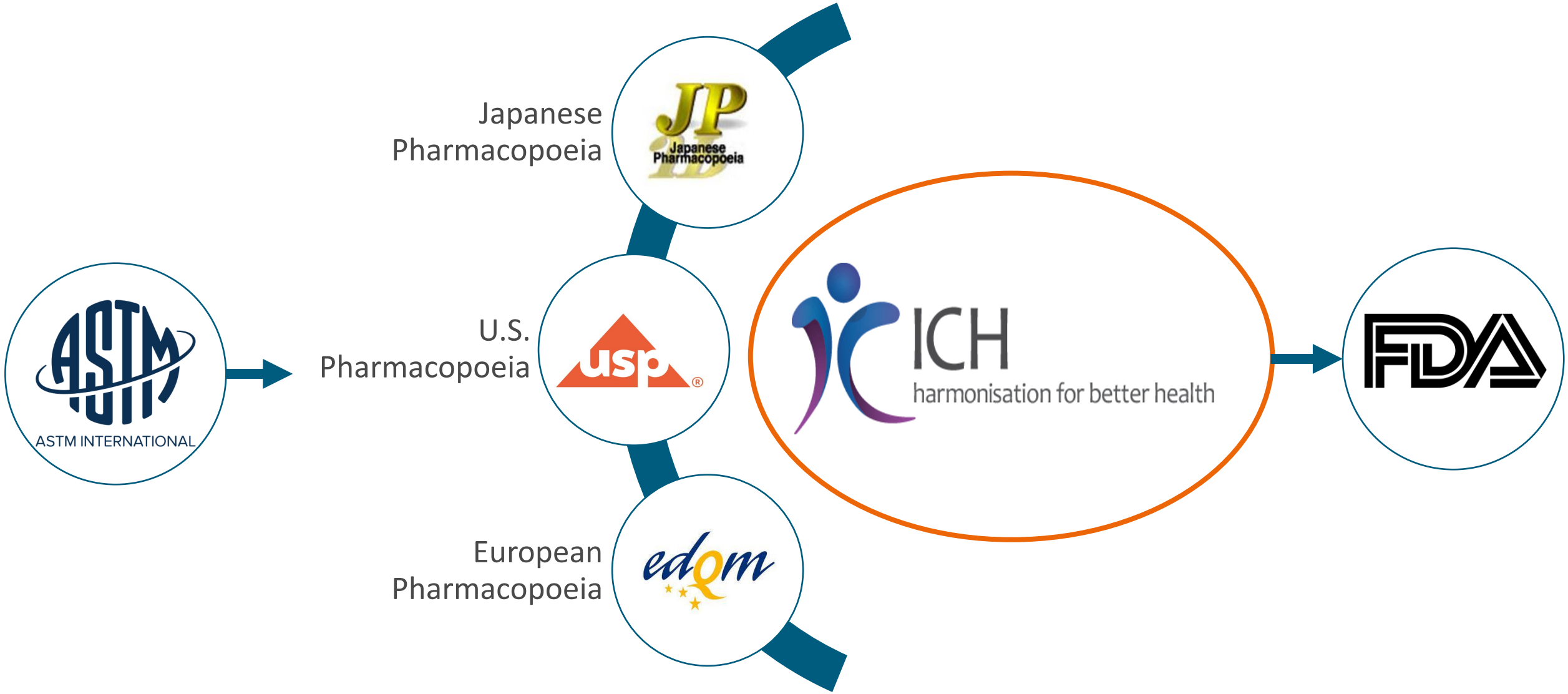
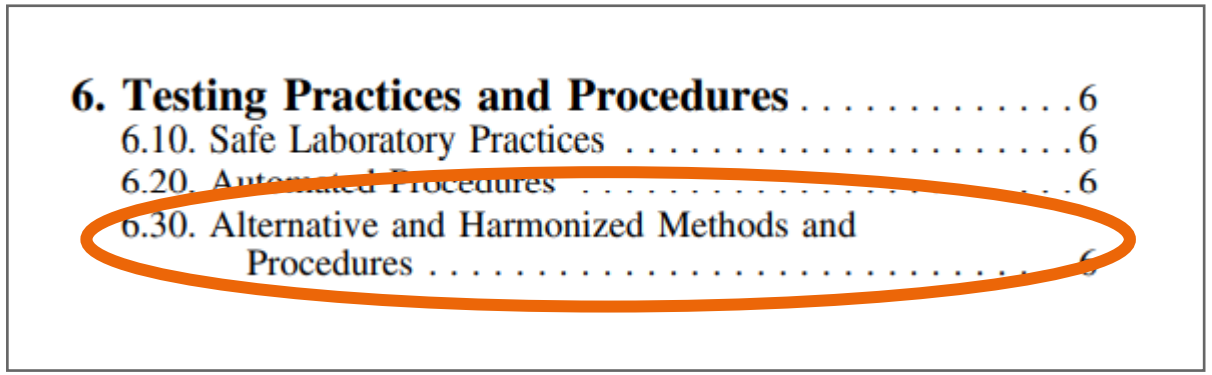
ASTM …

USP <1225> Validation of Compendial Procedures


Japanese Pharmacopoeia
JP
Japanese Pharmacopoeia
U.S. Pharmacopoeia
usp
European Pharmacopoeia
edqm
ASTM
ASTM INTERNATIONAL
ICH
harmonisation for better health
FDA

Get Confident with USP and ICH Guidelines

- USP does not enforce its standards, rather that is the responsibility of FDA and states that have adopted/adapted USP standards
- **USP General Notices** are definitions and assumptions that apply to all articles of the USP and to meet regulatory requirement



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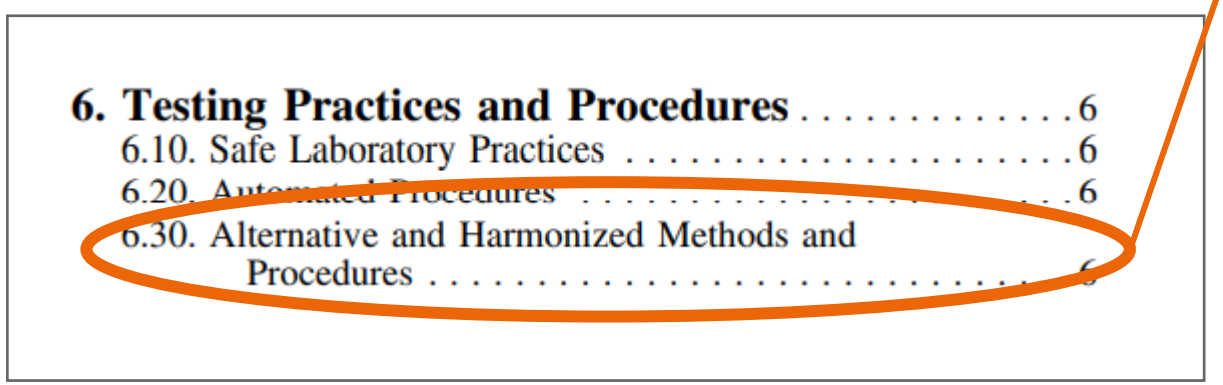


6. Testing Practices and Procedures 6
6.10. Safe Laboratory Practices 6
6.20. Automated Procedures 6
6.30. Alternative and Harmonized Methods and Procedures 6

6.30. Alternative and Harmonized Methods and Procedures

Alternative methods and/or procedures may be used if they provide advantages in terms of accuracy, sensitivity, precision, selectivity, or adaptability to automation or computerized data reduction, or in other special circumstances. Such alternative procedures and methods shall be validated as described in the general chapter *Validation of Compendial Procedures* ⟨1225⟩ and must be shown to give equivalent or better results. Only those results obtained by the methods and procedures given in the compendium are conclusive.

Alternative procedures should be submitted to USP for evaluation as a potential replacement or addition to the standard (see section 4.10, *Monographs*).

Validate existing methods by USP <1225> instead of attempting to convert legacy USP methods to the ethanol industry.

Important Definitions in USP <1225>

Analytical Characteristics Used in Method Validation


Accuracy


Precision


Specificity


Detection limit


Quantitation limit


Linearity and range


Robustness


System suitability

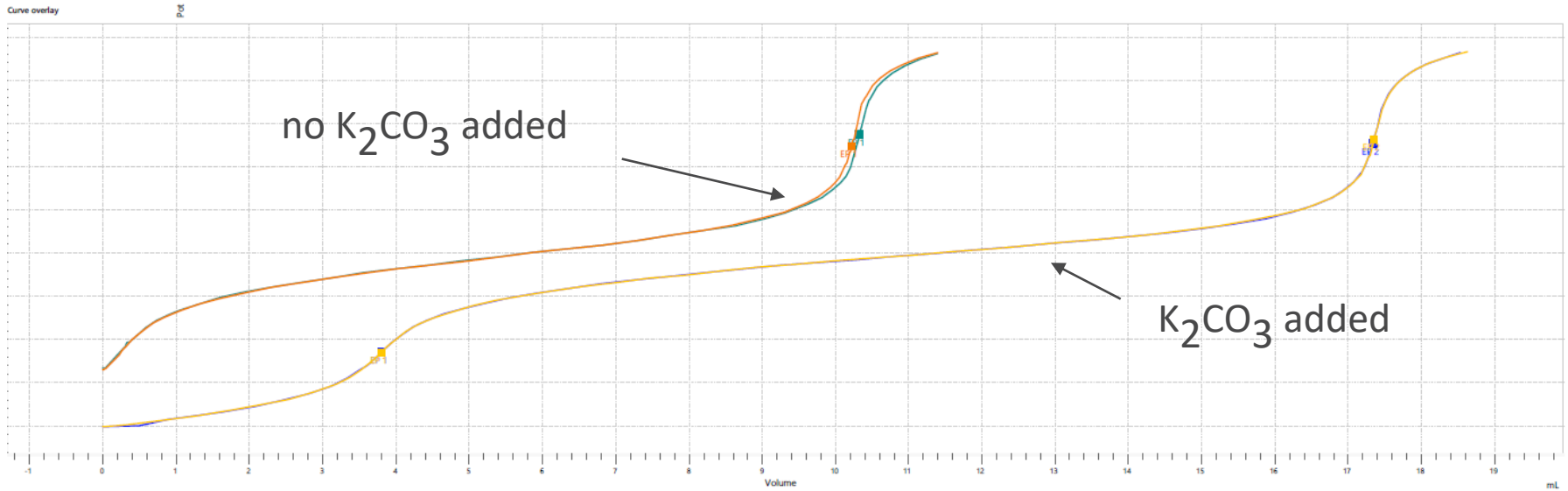
As you review, notice references to the *ICH guideline Validation of Analytical Procedures*

- ICH has guidelines for how to execute, what results to expect and recommended data

Example: Specificity

Assay of Potassium Bicarbonate by Titration with Hydrochloric Acid

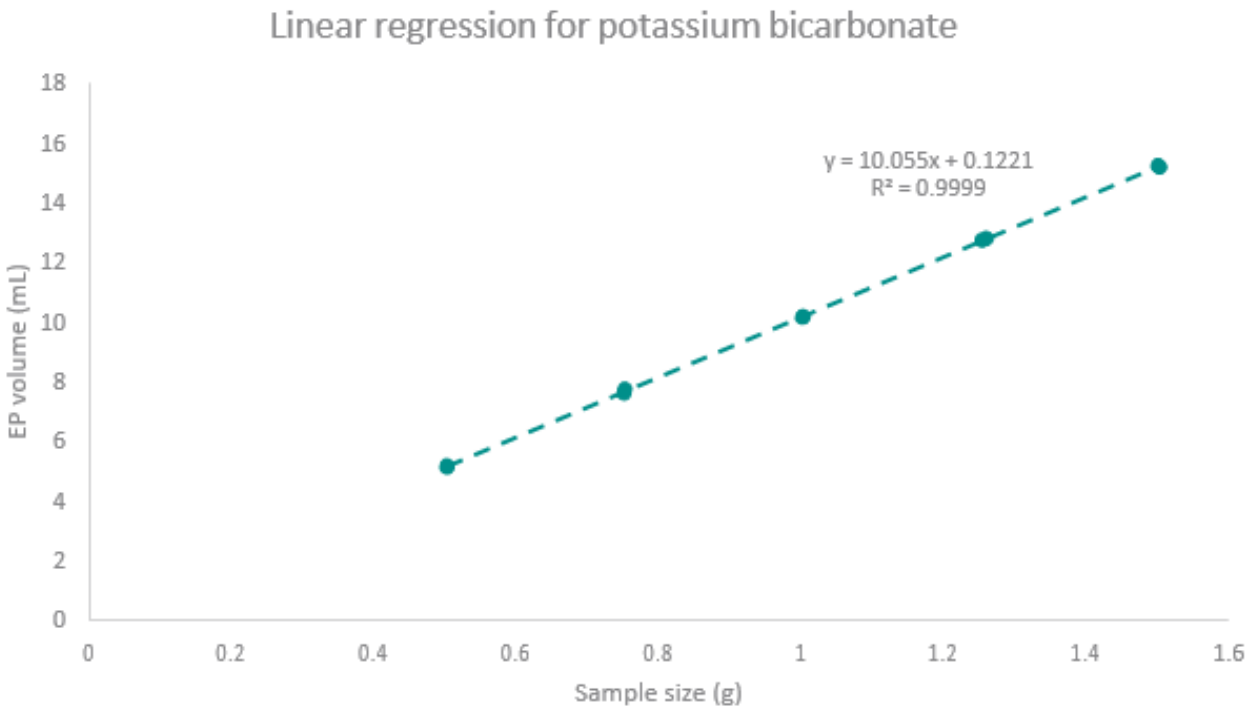
Curve overlay of the specificity test using 1 g $KHCO_3$ with and without 0.5 g K_2CO_3



Example: Linearity and Range

Data for titration of potassium bicarbonate

Sample weight (%) for linearity	Sample Weight (g)	Equivalence Point Volume (mL)	Assay (%)
50	0.5022	5.1897	102.21
50	0.5023	5.1482	101.37
75	0.7520	7.7571	102.03
75	0.7506	7.6197	100.41
100	1.0012	10.1627	100.40
100	1.0026	10.1881	100.51
125	1.2599	12.8030	100.51
125	1.2534	12.7439	100.57
150	1.5030	15.1888	99.95
150	1.5007	15.2459	100.48



Data Elements Required for Validation

Category I: Procedures for quantitation of major components of bulk drug substances or active ingredients (including preservatives) in finished pharmaceutical products.

Category II: Procedures for determination of impurities in bulk drug substances or degradation compounds in finished pharmaceutical products. These procedures include quantitative assays and test limits

Validation Parameter <USP 1225>	Category I (Assays)	Category II (Impurities)	
		Quantitative	Limit Tests
Accuracy	Yes	Yes	*
Precision	Yes	Yes	No
Specificity	Yes	Yes	Yes
Detection Limit	No	No	Yes
Quantitation Limit	No	Yes	No
Linearity	Yes	Yes	No
Range	Yes	Yes	*
Robustness	Development Study	Development Study	Development Study

*May be required depending on nature of specific test

Sample Validation Plan for Analytical Work

Analytical Performance Characteristics	Sample and Procedure	Acceptance Criteria
Specificity	Diluent, Resolution solution, Standard solution, and Sample solution	(i) No interference or co-elution with the XX peak (ii) Resolution of the nearest peak from XX should be NLT 3.0 & Tailing NMT 2.0. (iii) Critical pair: Resolution between XX and adjacent impurity peak should be NLT 1.5
System Suitability	6 replicate injections of standard solution	The 6 replicate injections' area RSD should be NMT 0.5%
Solution Stability	Standard & Sample solutions	Analyze the solutions every 4 hours for 24 hours and monitor the change in peak area. The change in peak area is NMT 2.0% from the initial time point.
Linearity	Five Linearity Solutions covering from 50%–150% of X (10.0, 15.0, 20.0, 25.0, & 30.0 mg/L)	Correlation Coefficient (R) NLT 0.999 Y- intercept bias: ± 2.0% of 100% linearity level response

Sample Validation Plan for Analytical Work (cont.)

Analytical Performance Characteristics	Sample and Procedure	Acceptance Criteria
Repeatability	*Repeatability solutions* analyzed against *Standard solution* (six replicate injections)	(i) The average Assay result should be NLT 40.0% and NMT 43.5% of XX (ii) The RSD of the six Assay results should be NMT 1.0%.
Accuracy	*Accuracy solutions (Sample solutions* are spiked with standard solution at 10%, 20%, 30% of nominal concentration (*i.e.* 110%, 120%, and 130%). Prepare in triplicate at each level and analyze against average response of six replicate injections of *Standard solution*	The average recovery result at each spiked level should be within 100 ± 3%.

Sample Validation Plan for Analytical Work (cont.)

Analytical Performance Characteristics	Sample and Procedure	Acceptance Criteria
Intermediate Precision	*Repeatability solutions* analyze against *Standard solution* (six replicate injections) by a different analyst on a different day and using a different batch of analytical column	(i) The average result should be NLT 40.0% and NMT 43.5% of XX (ii) The RSD of the six Assay results should be NMT 1.0%. (iii) The two average results for first and second analyst do not differ by more than 2.0%. (iv) The RSD of the 12 Assay results
Sample Assay Test	*Sample solutions* in duplicate using the drug product not used in the validation experiments and analyze against *Standard solution* (six replicate injections)	Report Assay value Compare with the monograph specification, NLT 40.0% and NMT 43.5% of XX
ID Validation	Compare the RT of XX peak in *Sample* and *Standard solutions*	XX peak retention time in *Sample solutions* should be within ± 1% of *Standard solution*.

How to get started

1. Get confident with your options → Review USP General Notices and Requirements
2. Create a validation plan → Review USP <1225> and ICH Guideline
3. Execute your validation study → Document everything
4. Protect your data and method → Get an NDA with USP
5. Send your validation packet to USP → Recieve acceptance and/or feedback

Conclusions

- Current ASTM methods are proven approach for quality testing of ethanol and ethanol products
- USP (therefore FDA) allows for alternative methods to be used
- Alternative methods need to be validated following USP <1225> and submitted to the USP for review
- Get started by mapping out a validation plan
- Report your results and document everything along the way (e.g., reference material ID, instrument configuration and parameters, reagent and standard CoA)
- Most importantly: Maintain your records

References and Recommended Reading

ICH Guidance Q2(R1) – Validation of Analytical Procedures: Text and Methodology, ICH, 2005. www.ich.org

Kerri-Ann Blake and Margareth Marques, “Importance of Titrations in Pharmaceutical Analysis,”

Lucier Meier, “How to Transfer Manual Titration to Autotitration,” Mar 25 2020, Analysis, Fundamentals, Metrohm Blog.

Margareth R. C. Marques, Horacio Pappa, Michael Chang, Lori Spafford, Michael Klein, Lucia Meier, “Recommendations for converting a manual titration procedure into an automated titration procedure,” usp.org/resources/compendial-tools (last accessed 8/25/2021).

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USP, Replacing Indicators with electrodes, usp.org/resources/compendial-tools (last accessed 8/25/2021).

USP. Potassium Bicarbonate. In: USP 43 – NF 38, First Supplement. Rockville, MD: USP; 2020.

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