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U.S. Pharmacopeial Convention

The USP Excipients Stakeholder Forum
Meeting #1
June 7, 2013

Excipients in the Medicines Compendium: Progress and Perspectives

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2013. 6

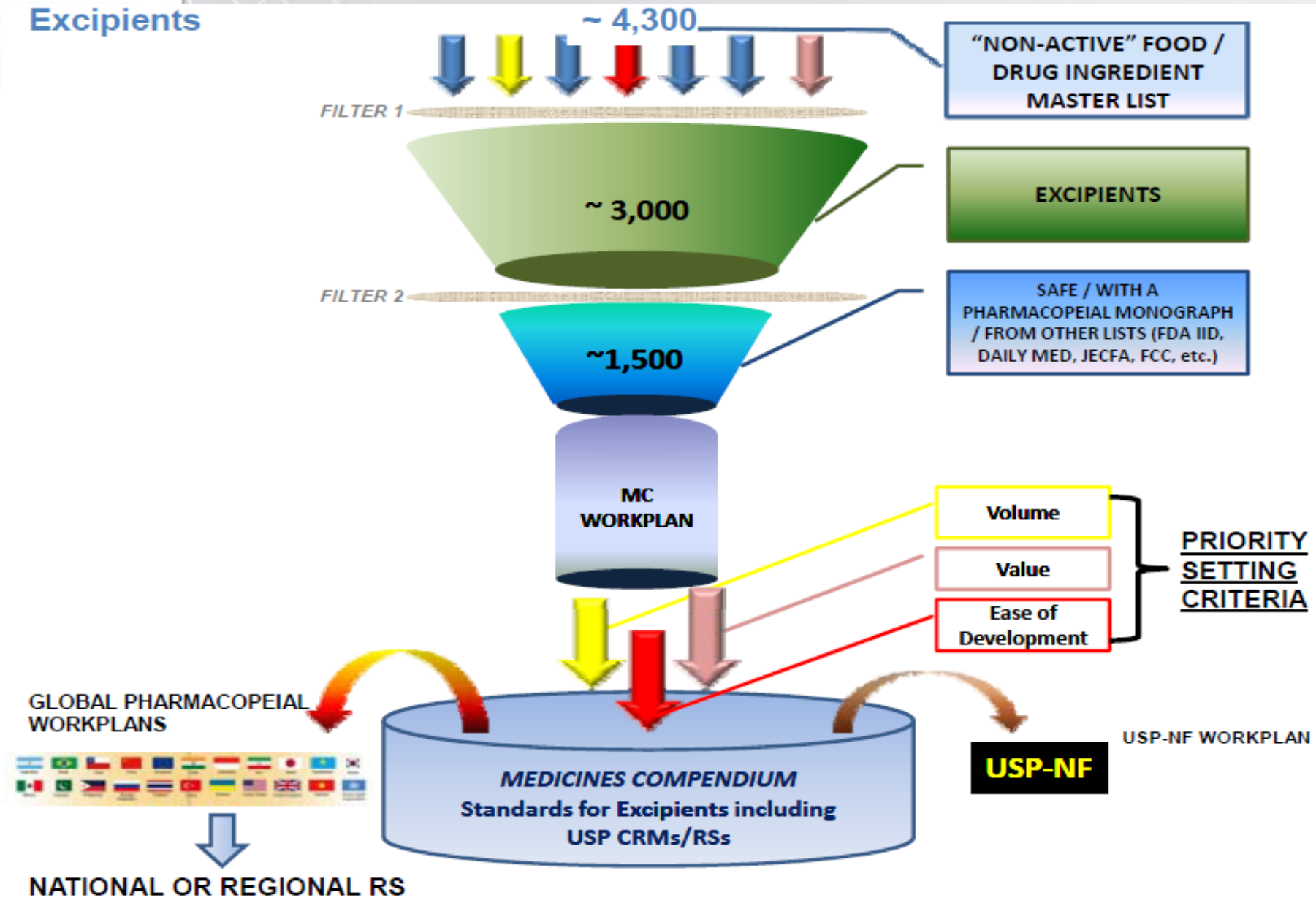
Agenda

- Pharmaceutical Excipients in MC: funnel model
- Performance-based monographs of Excipients
- Introduction for the Committee
- Updated progresses
- Perspectives

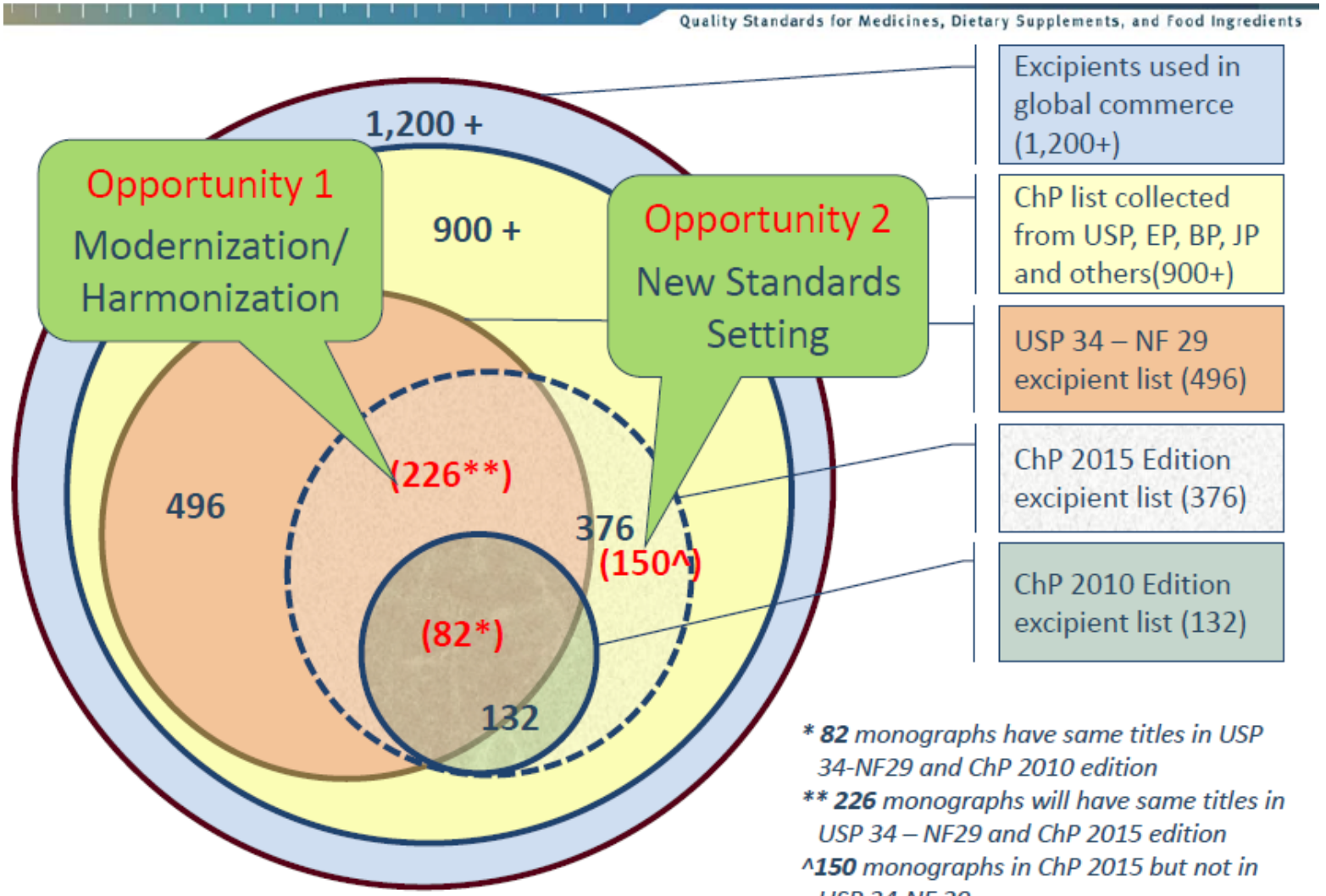
Pharmaceutical Excipients in MC- Funnel Model

- MC monographs: aim to develop reference procedure for multisources of excipients. Same name with different composition
- Candidates: screened from excipients used in drug products

Excipients



Denominators



** **82** monographs have same titles in USP 34-NF29 and ChP 2010 edition*

*** **226** monographs will have same titles in USP 34 – NF29 and ChP 2015 edition*

*^**150** monographs in ChP 2015 but not in USP 34-NF 29*

Numerators (Prioritization)

- Is it on the Work Plans of both NF and ChP?
- Does a monograph exist in any pharmacopeia (lower in terms of risk/priority)?
- Does a monograph exist in NF or ChP?
- Does it need updating in NF or ChP?
- Exposure/tonnage
- Safety issue
- Ease of development
- Value/risk of economically motivated adulteration

34 Candidate Excipients for MCEA

- Aluminium Stearate
- Calcium Oxide
- Cholic Acid
- Dimethyl Ether
- Lauryl Alcohol
- Nutmeg Oil
- Potassium Stearate
- Rosin
- Sodium Bisulfite
- Sodium Caseinate
- Sodium Nitrate
- Sodium Oleate
- Sodium Polyacrylate
- Turpentine Oil
- Benzyl Hydroxybenzoate

- Benzalkonium bromide
- borneol
- Cetalkonium Chloride
- Chlorophyll
- Deoxysodiumcholate
- Disodium Hydrogen Phosphate Dodecahydrate
- Gallic Acid
- Larch Gum
- Laurel Oil
- Laurocapram
- Mercaptoacetic Acid
- Methy Myristate

- N,N-Dimethylformamide
- Nicotinamide
- Nicotinic Acid
- p-Chlorophenol
- Sodium Dihydrogen Phosphate
- sodium cholate
- Sodium Hydrosulfite

Performance-based Monographs (PBM) of Excipients: Key Words

- PBM
- Critical Quality Attributes (CQA)
- GC <10> and <12>

PBM

- Naming information, tests for CQAs, procedures acceptance criteria and acceptance criteria for these attributes.
- A framework for USP and other laboratories to build high technology Reference Procedures, which are intended to be source-independent.
- Reference Procedures use high-end analytical tools with multi-dimensional detectors to assure adequate control of a compendia article.

General Chapter <10>*Assessing Validation Parameters for Reference and Acceptable Procedures*

- GC<*10*> is currently adopted by the MC South Asia Expert Committee and exists on the MC website.
- It also is under final review by USP Expert Panel on Physical Analysis for adoption into the *USP-NF*.
- This GC fills a gap now existing in the ICH Q2A and B documents and USP's General Chapter <1225>. The gap is that these prior documents, although excellent, do not indicate the criteria for when a procedure is considered acceptable relative to its acceptance criteria.
- **GC <10> will be suitable for development of excipient in MC.**

General Chapter <10> and <12> Discussion

Also, General Chapter <12> *Drug Product Performance* has been reviewed by the MC South Asia Expert Committee and will be posted soon for public comment. This GC speaks not to topic of excipients but to drug product performance. USP's MC Reference Procedure for non-solution orally administered drug products must be incomplete in the absence of specific dissolution data from a manufacturer. Thus <12> indicates a 'best practices' approach for this information using the biopharmaceutical classification system (BSC) criteria.

Why is PBM in MC ?

An excipient will be of

- Different origin
- Different manufacturing processes
- Different grade
- ……..

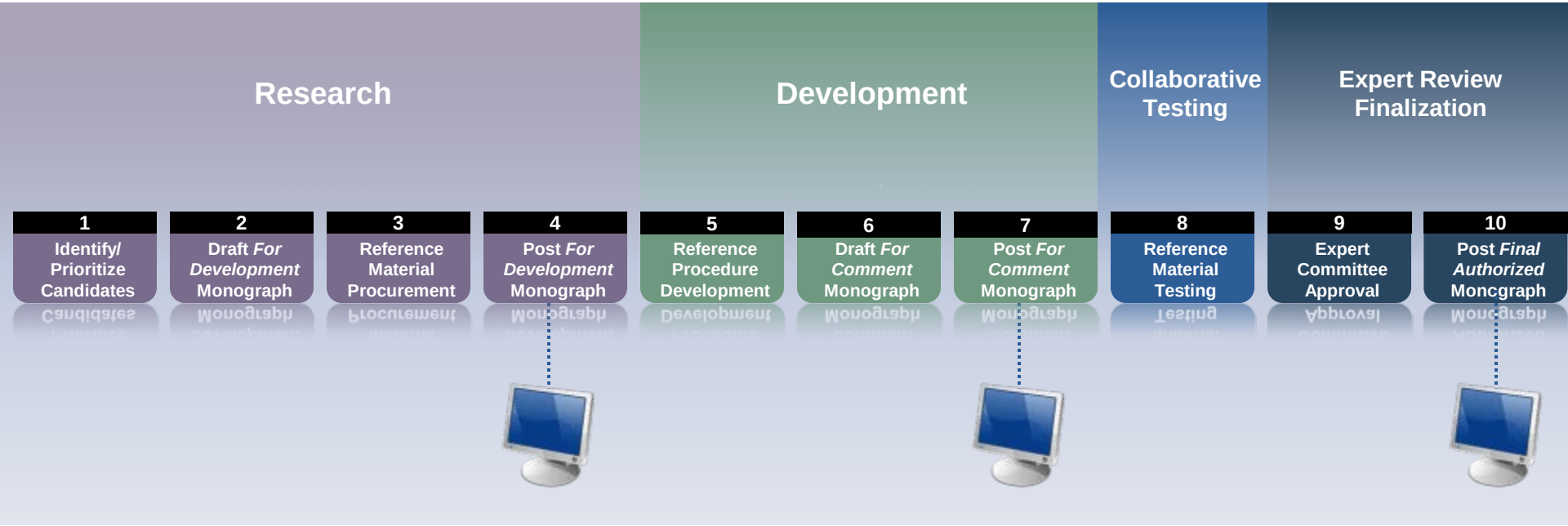
Example: Gelatin

- Type A, B
- Sourced from skin, bone, and fish bone
- Manufacturing condition: hydrolysis from days to weeks

Who Will Develop PBM: USP and CHPMOU

- USP lab
- China FDA provincial Institute for Drug Control: Zhejiang IDC, Guangdong IDC, Jiangsu IDC, et al

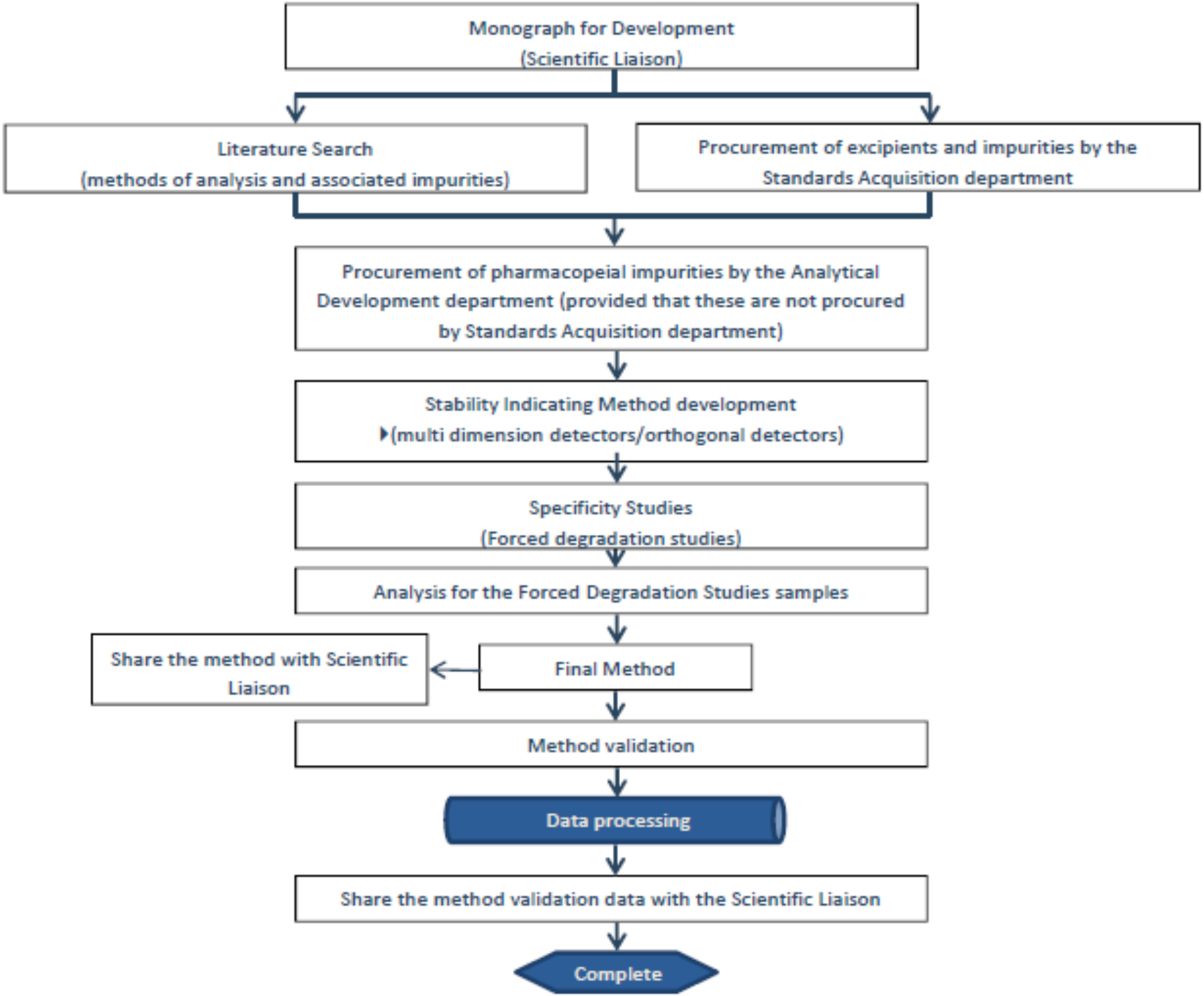
The Work Plan and Priority for USP *MC*



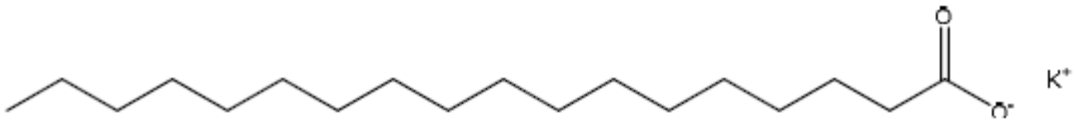
Monograph Development

- The Performance Based Monograph (PBM) must define the quality of the materials, and do not address the excipient functionality .
- Samples can collected from food or/and pharmaceutical grade.
- Multisouced samples will be used to develop PBM.

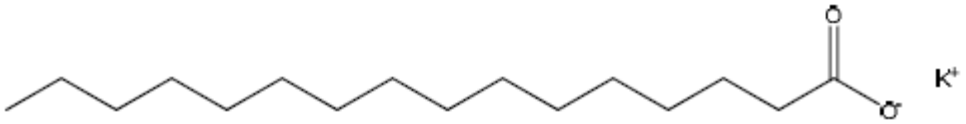
Reference Procedure Development


Monograph for Development
(Scientific Liaison)
Literature Search
(methods of analysis and associated impurities)
Procurement of excipients and impurities by the Standards Acquisition department
Procurement of pharmacopeial impurities by the Analytical Development department (provided that these are not procured by Standards Acquisition department)
Stability Indicating Method development
(multi dimension detectors/orthogonal detectors)
Specificity Studies
(Forced degradation studies)
Analysis for the Forced Degradation Studies samples
Final Method
Share the method with Scientific Liaison
Method validation
Data processing
Share the method validation data with the Scientific Liaison
Complete

Proposal for Potassium Stearate: defination



Potassium Stearate



Potassium Palmitate

Potassium Stearate

Potassium Stearate is a mixture of solid organic acids and consists of variable proportions of potassium stearate ($C_{18}H_{35}KO_2$) and potassium palmitate ($C_{16}H_{31}KO_2$). It contains NLT 40.0% potassium stearate, and the sum of potassium stearate and potassium palmitate is NLT 90.0%. Potassium stearate contains small amounts of the potassium salts of other fatty acids.

Identification

The two critical components of potasium stearate are potassium and a mixture of stearate and palmitate.

Potassium Identification

- <191> includes chemical tests for salts and counter-ions. The move to Ion Chromatography would be beneficial
  - **A. IDENTIFICATION TESTS—GENERAL,** *Potassium* **<191>**

Ester Identification

- This is covered by the Stearate-to-Palmitate Ratio procedure in the Assay and is not included here.

Assay

- Because of the importance of the stearate composition, the Stearate-to-Palmitate Ratio is included as the Assay. The same procedure can be used to quantify the free fatty acids in the impurities section

• **Stearate-to-Palmitate Ratio**
Standard solution: USP Stearic Acid RS and USP Palmitic Acid RS in an appropriate diluent
Sample solution: Potassium Stearate in an appropriate diluent
Analytical system: Use a procedure validated as described in *MC* general chapter *Assessing Validation Parameters for Reference and Acceptable Procedures* <10>.
System performance requirements
Precision: Meets the requirements. [Note—Use 97.0%–103.0% as the lower and upper values, and normalize to 100% before calculating the *Acceptance criteria*.]
Accuracy: Meets the requirements. [Note—Use 97.0%–103.0% as the lower and upper values, and normalize to 100% before calculating the *Acceptance criteria*.]
Specificity: Meets the requirements
Range: Meets the requirements
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the ratio of stearate to palmitate.
Acceptance criteria: NLT 40% stearate; the sum of stearate and palmitate is NLT 90% of all fatty acids.

Impurities

Impurities include

- • **Elemental Impurities <232>:** Proceed as directed in the chapter.
- • **Residual Solvents <467>:** Proceed as directed in the chapter.
- • **Limit of Free Fatty Acids**

The first two are consistent for all monographs in the MC and the USP-NF.

The Free Fatty Acids limit is consistent with all other Stearate Monographs.

- If possible the reference procedure should be the same for all fatty acid monographs.
- The proposed derivatization-GC procedure is acceptable, but has characteristics that limit its usefulness as a Reference Procedure

Introduction for the Committee

- Committee of Medicines Compendium-East Asia
- Approved by Council of Experts Executive Committee in Jan 12, 2012
- 10 members: 2 from universities, 2 from local IDCs, 2 from R&D institutes (1 from TCM), 1 from excipient manufacturer, 3 from pharmaceutical industries.

Responsibilities of the Committee and Procedure to Create a Standard

- **Review the PBM monograph** and a Reference Procedure, prior to posting on the MC website.
- Review the validation data for the Reference Procedures, produced in USP laboratories. This data also is posted on the website.
- After a 90-day comment period, the Expert Committee will **review any comments** and decide if any changes should be incorporated into the monograph.
- Once the changes are incorporated, the Expert Committee will **vote on the standard**.
- Upon Expert Committee approval, the standard becomes a "**Final Authorized Standard**."

Updated Progresses: From China Provincial IDC

- Benzyl Paraben: Jiangsu IDC
- Sodium Nitrate：Hunan IDC
- Dimethyl Ether: Guangdong IDC
- Rosin: Guangdong IDC
- It is proposed that the data will submitted before Sept.

Progresses From USP China MC Lab: 8 PBMs Published for Development

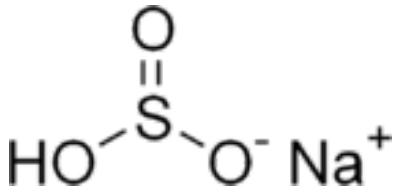
- Sodium Bisulfite
- Potassium Stearate
- Aluminum Stearate
- Sodium Oleate
- Cholic Acid
- Nutmeg Oil
- Sodium Caseinate
- Turpentine Oil

Progresses from USP China MC Lab

- 4 Projects are ongoing in the lab
  - Sodium Bisulfite – the first draft for comment monograph is expected to be completed by USP-China lab and published for public comment in June/July
  - Potassium Stearate
  - Aluminum Stearate
  - Sodium Oleate

Sodium Bisulfite

- Sodium Bisulfite consists predominantly of the sodium salts of Bisulfite.
- The molecular formula is $NaHSO_3$
- The molecular weight is 104.6.

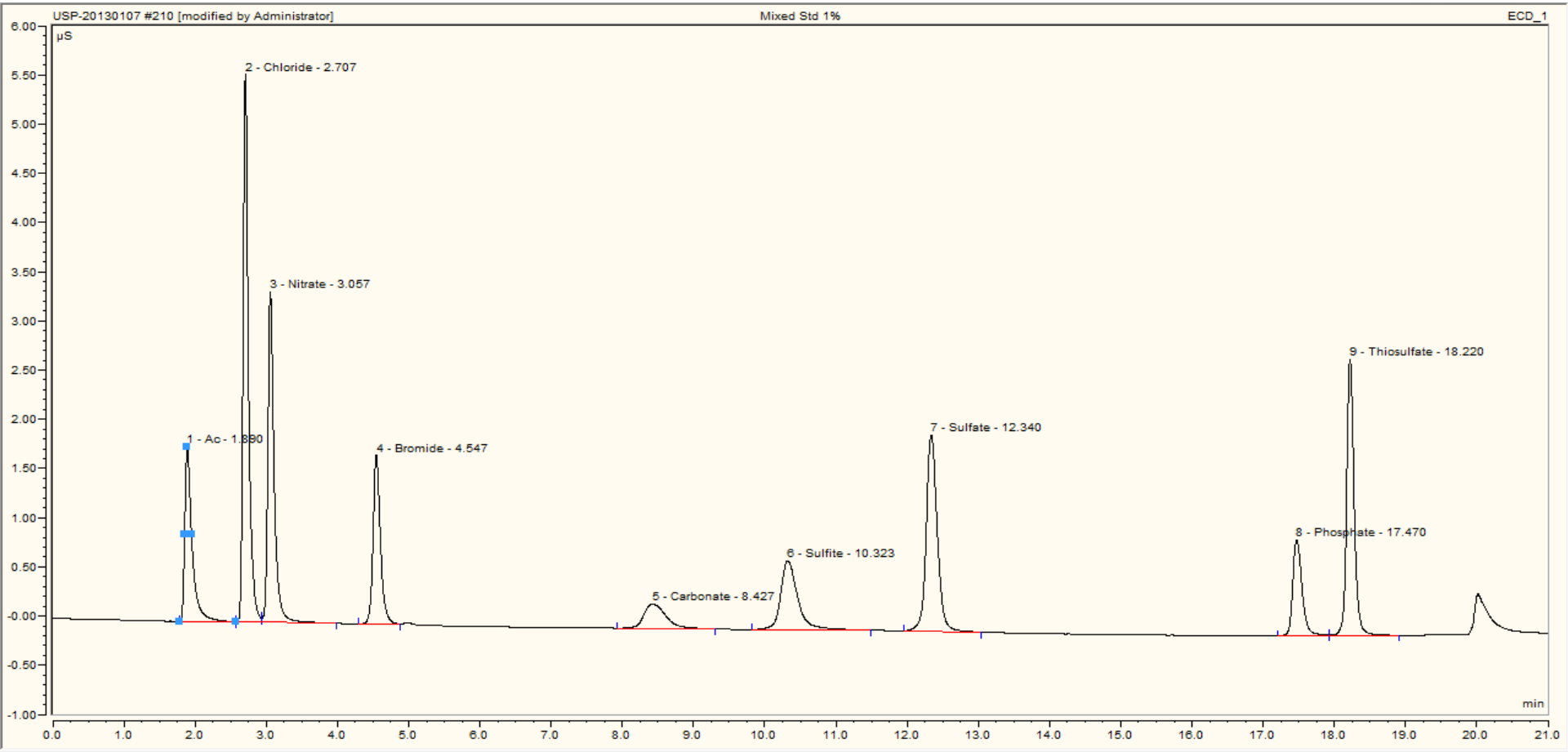


  - A common reductant
    - Readily reacts with dissolved oxygen
  - The related compound
    - Sodium metabisulfite
      - is used in almost all commercial wines to prevent oxidation and preserve flavor.
  - Sodium bisulfite is sold by some home winemaking suppliers for the same purpose. In fruit canning, sodium bisulfite is used to prevent browning (caused by oxidation) and as an antimicrobial agent.

Sodium Bisulfite- Method Development

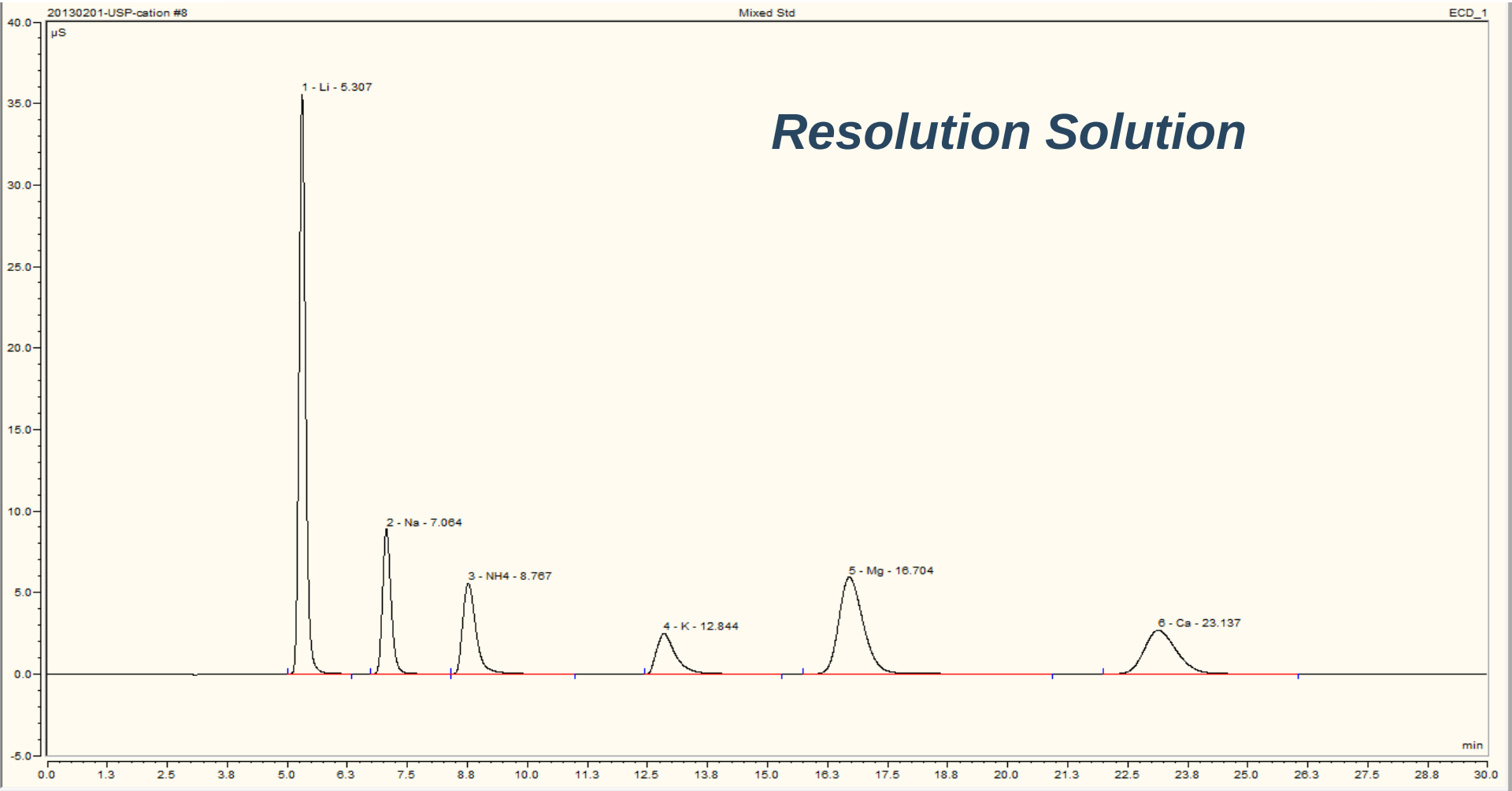
- Ion chromatography:
  - An IC method was developed to evaluate the Sodium Identification / Assay / Purities with Cation mode
  - An IC method was developed to evaluate the Bisulfite Identification / Assay / Purities with Anion mode
- Unique Innovation:
  - IC-Inhibitor combined with LC-MS to identify anions.

Resolution Solution for Anion Identification /Specificity: Mixture of Anion Single Impurities



No. n.a.	Peakname n.a.	Ret.Time min	Peak Width min	Height µS	Type	Resolution (USP)	Asym. (EP)	Plates (USP)
1	Ac	1.890	0.17	1.779	BMB	5.57	2.02	2095
2	Chloride	2.707	0.13	5.565	BM	2.56	1.47	7154
3	Nitrate	3.057	0.15	3.360	MB	9.15	1.50	7110
4	Bromide	4.547	0.18	1.711	BMB	10.85	1.23	10115
5	Carbonate	8.427	0.53	0.249	BMB	4.05	1.40	3974
6	Sulfite	10.323	0.40	0.703	BMB	6.00	1.36	10595
7	Sulfate	12.340	0.27	1.993	BMB	20.44	1.11	33094
8	Phosphate	17.470	0.23	0.974	BM	3.64	1.34	91777
9	Thiosulfate	18.220	0.18	2.811	MB	n.a.	1.17	161830
Average:			0.2487	2.1271		7.78	1.40	36416

Resolution Solution for Cation Identification/Specificity: Mixture of Cation Single Impurities



No. n.a.	Peakname n.a.	Ret.Time min	Area µS*min	Rel.Area %	Peak Width min	Height µS	Type	Resolution (USP)	Asym. (EP)	Plates (USP)
1	Li	5.307	5.608	35.181	0.24	35.553	BMB	6.27	1.19	7695
2	Na	7.064	1.827	11.463	0.32	8.868	BMB	4.24	1.23	7878
3	NH4	8.767	1.777	11.147	0.49	5.558	BMB	6.88	1.50	5225
4	K	12.844	1.137	7.134	0.70	2.480	BMB	4.76	1.70	5394
5	Mg	16.704	3.508	22.009	0.92	5.937	BMB	5.97	1.25	5257
6	Ca	23.137	2.083	13.066	1.23	2.670	BMB	n.a.	1.24	5628
Average:					0.6500	10.1774		5.62	1.35	6180

Perspectives

- More candidates are under screen.
- Hopefully, MC monographs will be treated as the highly global standards for excipients.

Thank You