Captisol®: What gives European Pharmacopeia?!

Analytical Method Challenges for EP Monograph

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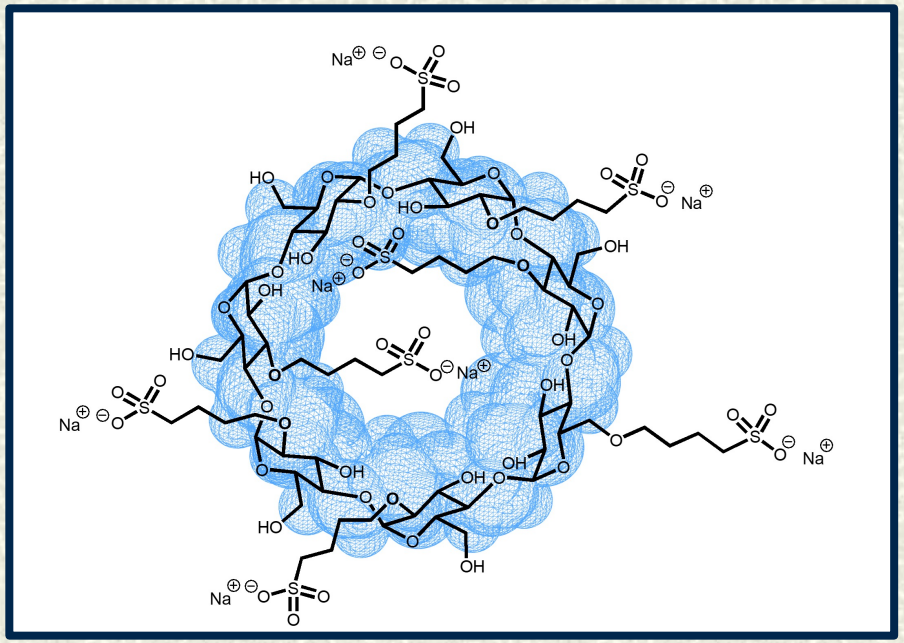
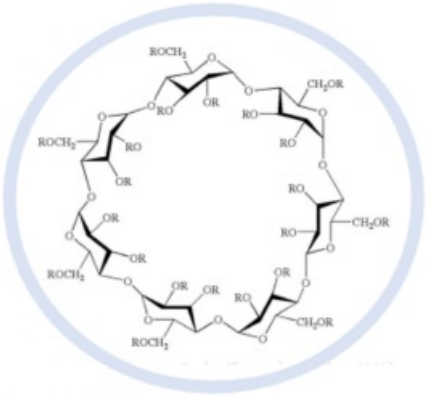
Captisol®



- **Proprietary Sulfobutylether-β-Cyclodextrin (bonded sugar molecules) with a process specific composition.**
- **Patented product. Synthesized by enzymatic degradation of starch.**
- **Enables an aqueous formulation for many water insoluble APIs.**

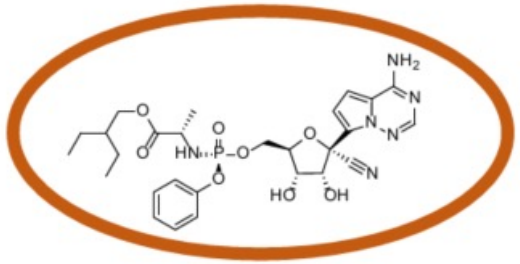
- **Applicable in several drug classes and drug product presentations such as oral, nasal, topical, lyophilized or liquid.**
- **SAFE. Several cosolvents and surfactants currently being used in the industry are toxic.**

Captisol ®: Increases Solubility

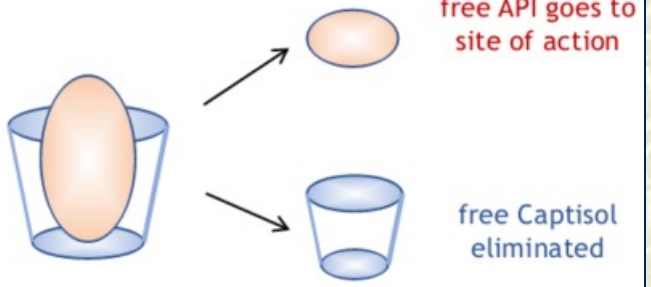


R = (—H)$_{21-n}$ or (—(CH$_2$)$_4$—SO$_3$Na)$_n$
where n = 6.0–7.1

Captisol

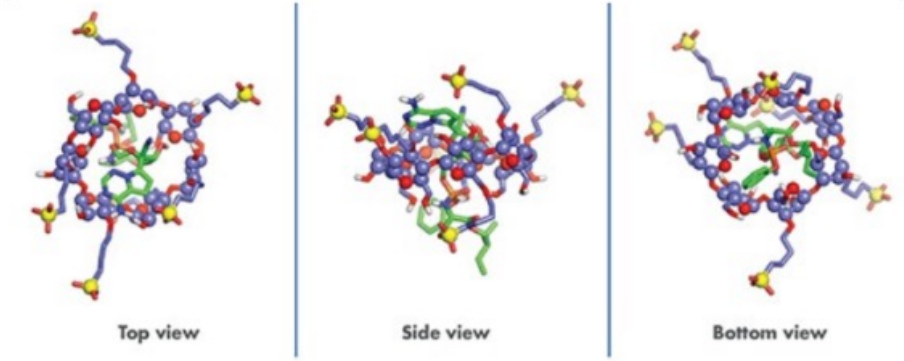


remdesivir



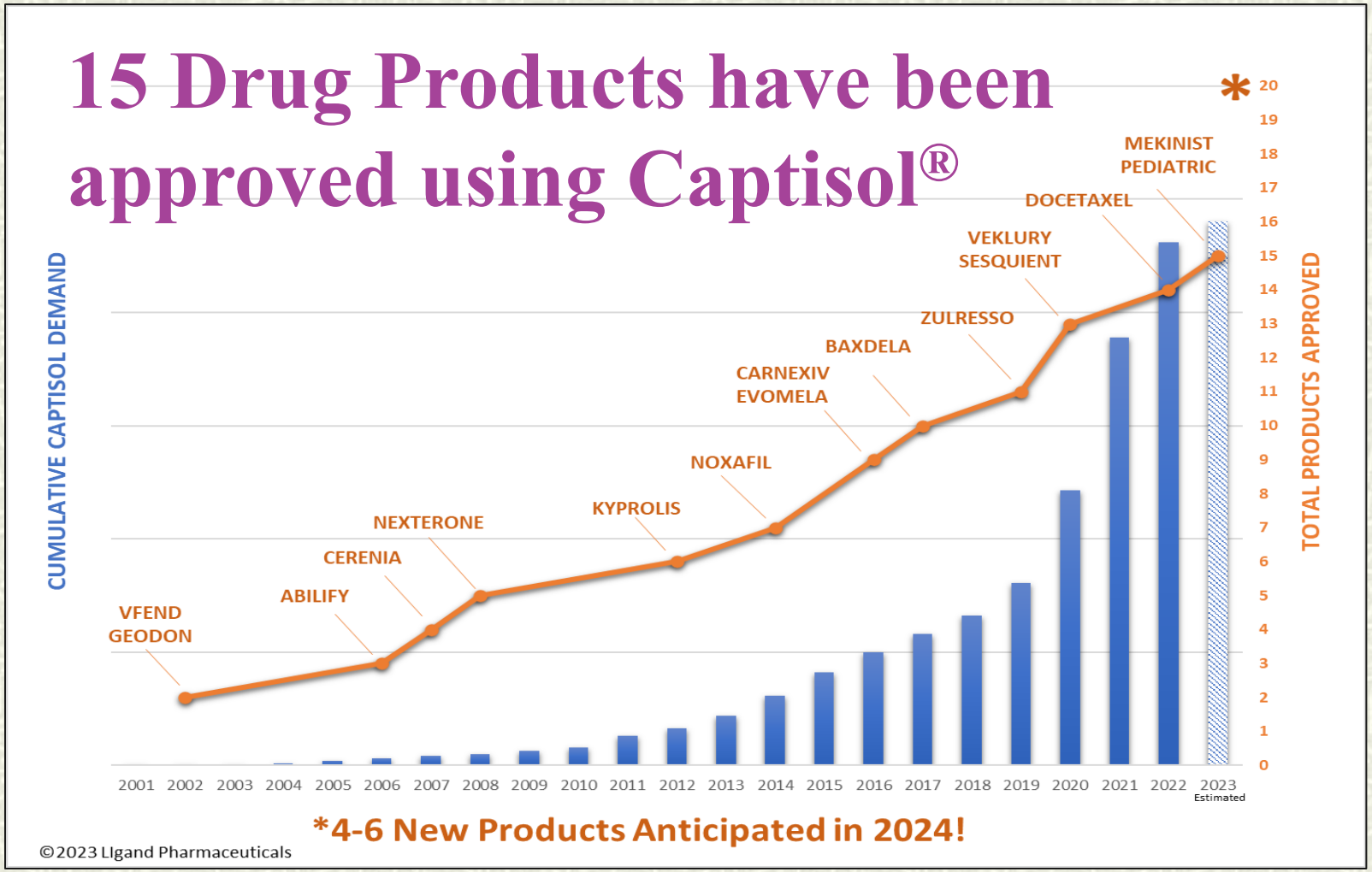
Each vial contains 100 mg of remdesivir, without (left) or with (right) Captisol (3 g). Internal demonstration performed by WuXi AppTec following a procedure adapted from Example 1 in US 2019 / 0083525 A1 Larson; Pub. Date: Mar. 21, 2019.

Simulation of complexation



Pipkin, et al., Drug Development and Delivery, June 2020, Vol. 20, No. 5, p 42-47

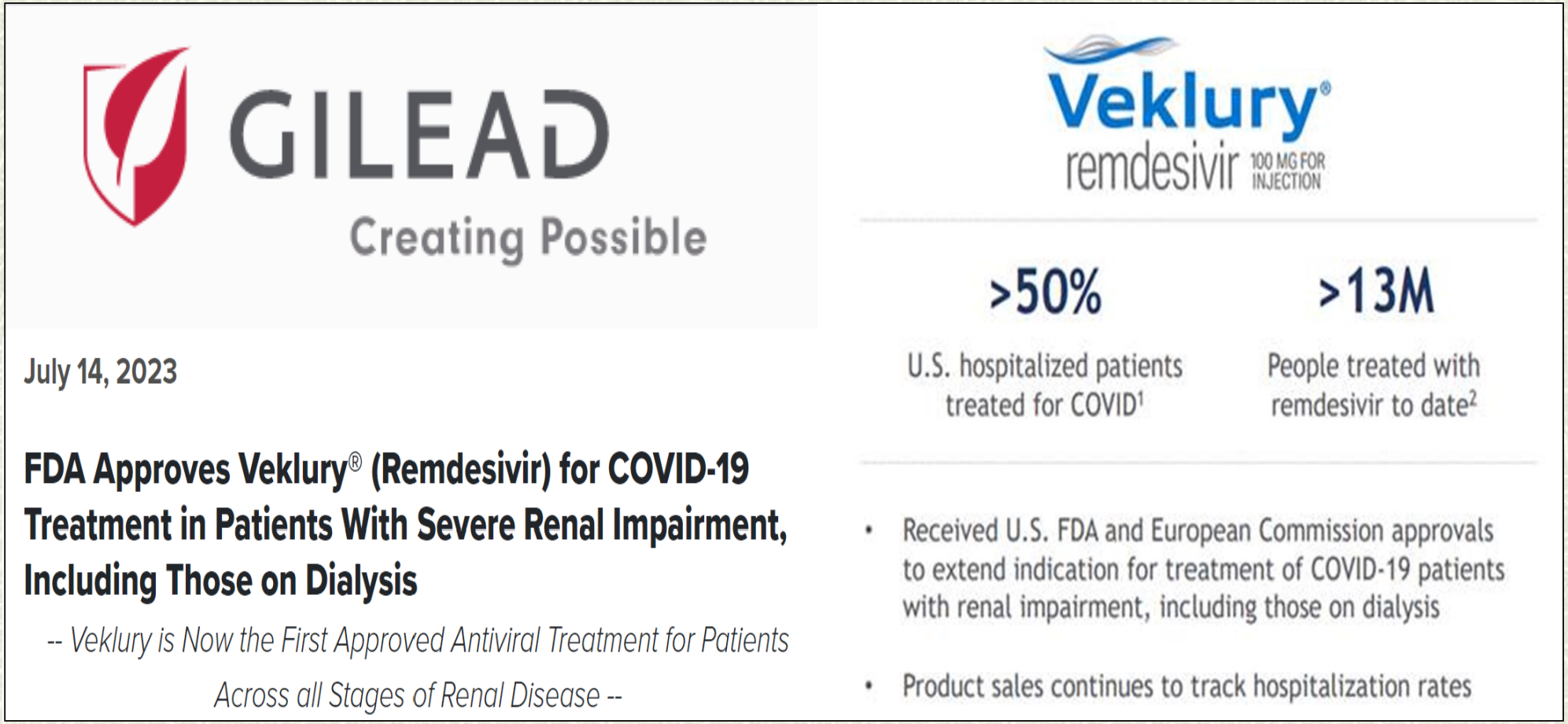
Pharmaceutical Industry Impact



Pharmaceutical Industry Impact

Singota – 14 Active Clients using Captisol® in their Formulation

Pharmaceutical Industry Impact: COVID



Captisol® Compendial Testing

USP (United States Pharmacopeia)

EP (European Pharmacopeia)

- Compilation of developed methods, supporting documents, databases, photographs, and other items to aide in the support of developing safe products.
- For the pharmaceutical industry and Singota, analytical tests prove the identity, efficacy, and safety of drugs. Universally beneficial across the world to develop safe products.
- Basic requirement for most regulatory submissions of materials used in manufacturing of pharmaceuticals.
- 24 Established Compendial Methods for Captisol®.

Captisol® Compendial Testing: EP Complexities

- USP (United States Pharmacopeia) – NF (National Formulary) monograph for Captisol (Betadex Sulfobutylether Sodium) was established based on the validated Captisol test methods and went into effect in 2012.
  - -Singota performed the Captisol USP-NF method comparison for Ligand in 2017.
- The Captisol team approached the EP (European Pharmacopeia) in 2018 to harmonize the USP method with the methods of the EP, but were unable to establish dialog with EP.
  - -In July 2019 the EP monograph for Sulfobutylbetadex sodium (2804) was implemented.
  - -Several new methods and columns were introduced with the EP monograph specifically NMR for determination of degree of substitution, impurity analysis, and reducing sugars.
  - -Additionally different specification ranges were adopted with the monograph including Assay, pH, degree of substitution, and impurity limits.
- Singota completed the EP monograph method transfer on behalf of Ligand in 2018.

Captisol ® Compendial Testing: COVID Stresses Compilations

- Early in the adoption of the EP monograph many were left without a means to perform impurity testing due to the discontinuation of the column described in the EP monograph.
- This issue required Singota and the Captisol® team to perform a method comparison validation between the EP and USP impurity methods.
- At a time when Captisol ® was in high demand for the Veklury COVID treatment, it was difficult to release batches for the European market.

edqm
European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé

COUNCIL OF EUROPE
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European Pharmacopoeia Commission Secretariat

RZ/PH/2020-03574L
CV/vn

Strasbourg, 22/07/2020

Subject: Sulfobutylbetadex sodium (2804) – Impurities A, C and D

Due to the unavailability of the recommended chromatography column (CD-Screen-IEC), users might face issues in applying the method for Impurities A, C and D in the *Sulfobutylbetadex sodium (2804)* monograph of the European Pharmacopoeia. As the column used during the validation of the method and recommended for use in the EDQM Knowledge Database is no longer available from the listed supplier, the test for Impurities A, C and D cannot be performed.

The European Pharmacopoeia is working to find a solution.

In the meantime, under these circumstances, users are permitted to use other test methods, subject to agreement of the competent authorities. These test methods may be in-house methods or methods from a third country pharmacopoeia and must be validated in accordance with accepted scientific practice. The same acceptance criteria (impurity limits) as given in the Ph. Eur. monograph must be applied.

You will be able to follow the progress of the monograph revision in the Knowledge Database. Moreover, if you have information to share with us (e.g. validated in-house method, successful use of a different column) and/or you wish to take part in the revision process, please do not hesitate to contact us via the EDQM HelpDesk.

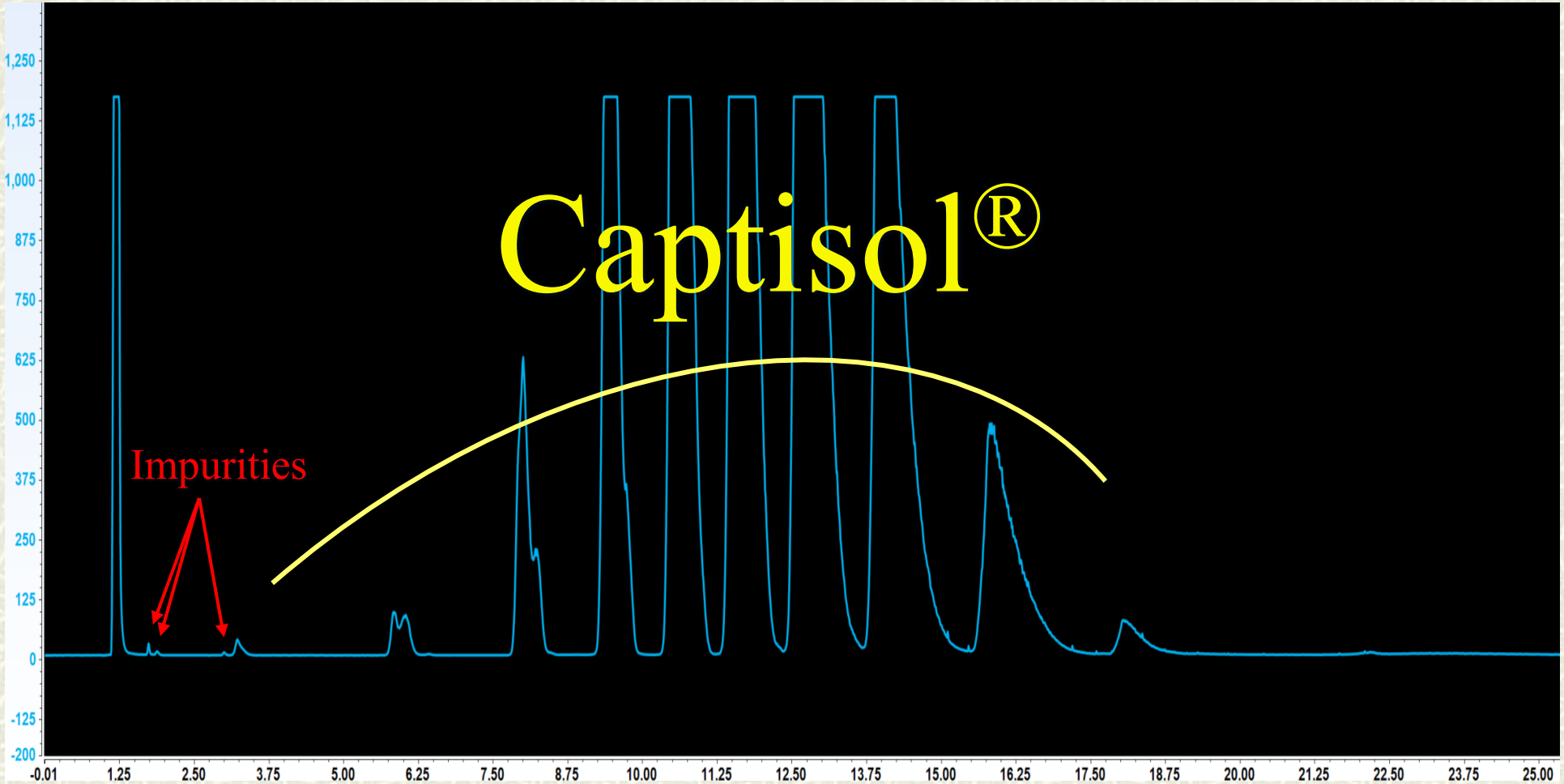
Please accept our apologies for any inconvenience.

Current EP Monograph: Impurities A, C, and D Analysis

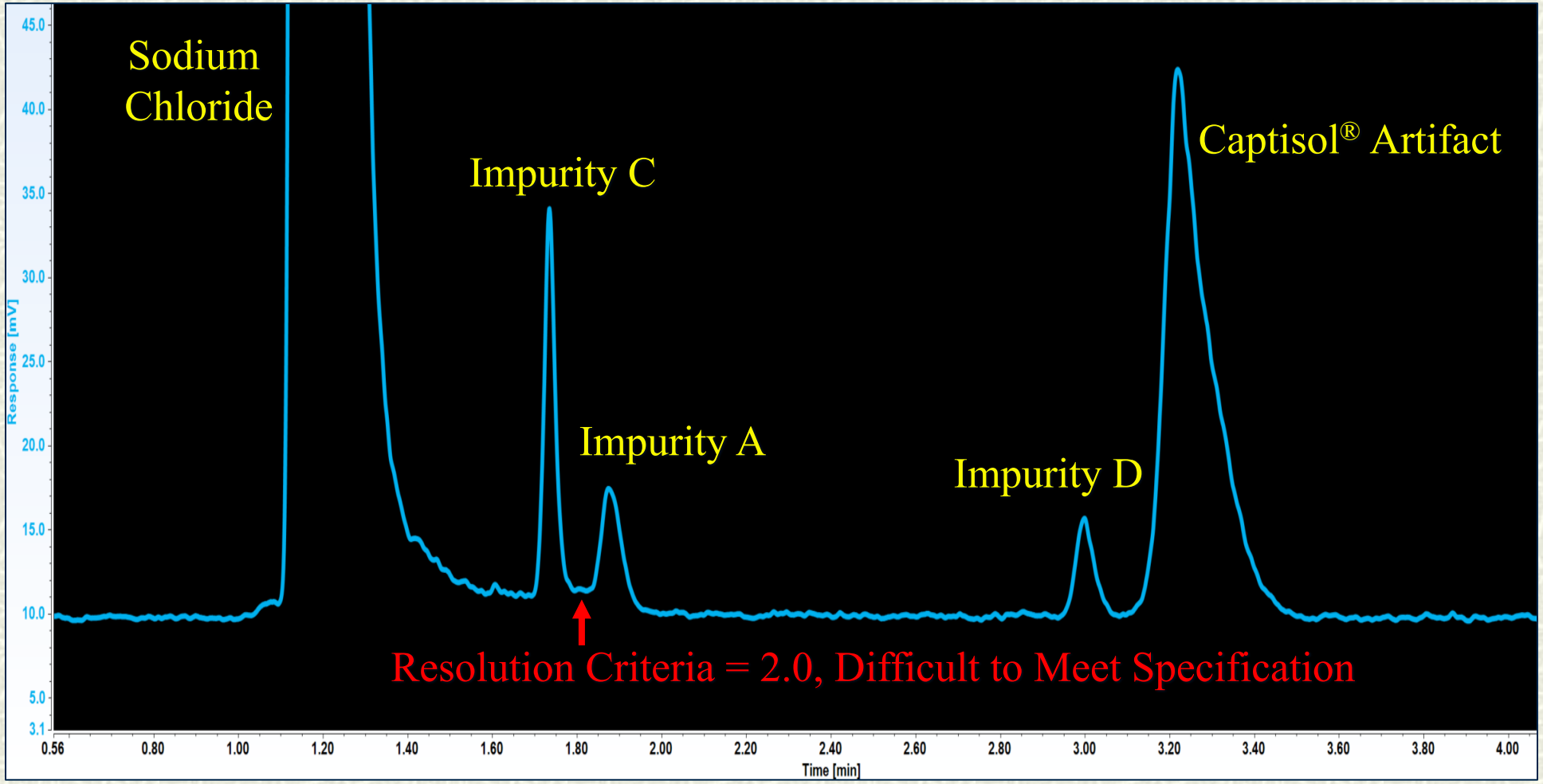
Limit Test by HPLC – Evaporative Light Scattering Detection (ELSD)

- Impurity A = Beta-Cyclodextrin, Limit - 0.1% Peak Area
- Impurity C = Hydroxybutanesulfonic Acid, Limit - 0.05% Peak Area
- Impurity D = Bis(Sulfobutyl) Ether Sodium, Limit - 0.05% Peak Area
- Column = CD-Screen-IEC, 4 x 150mm, 3µm
  - A very finely divided silica gel, chemically modified at the surface by the bonding of 4-dimethylaminobenzylcarbamide groups.

Current EP Monograph: Impurities A, C, and D Analysis



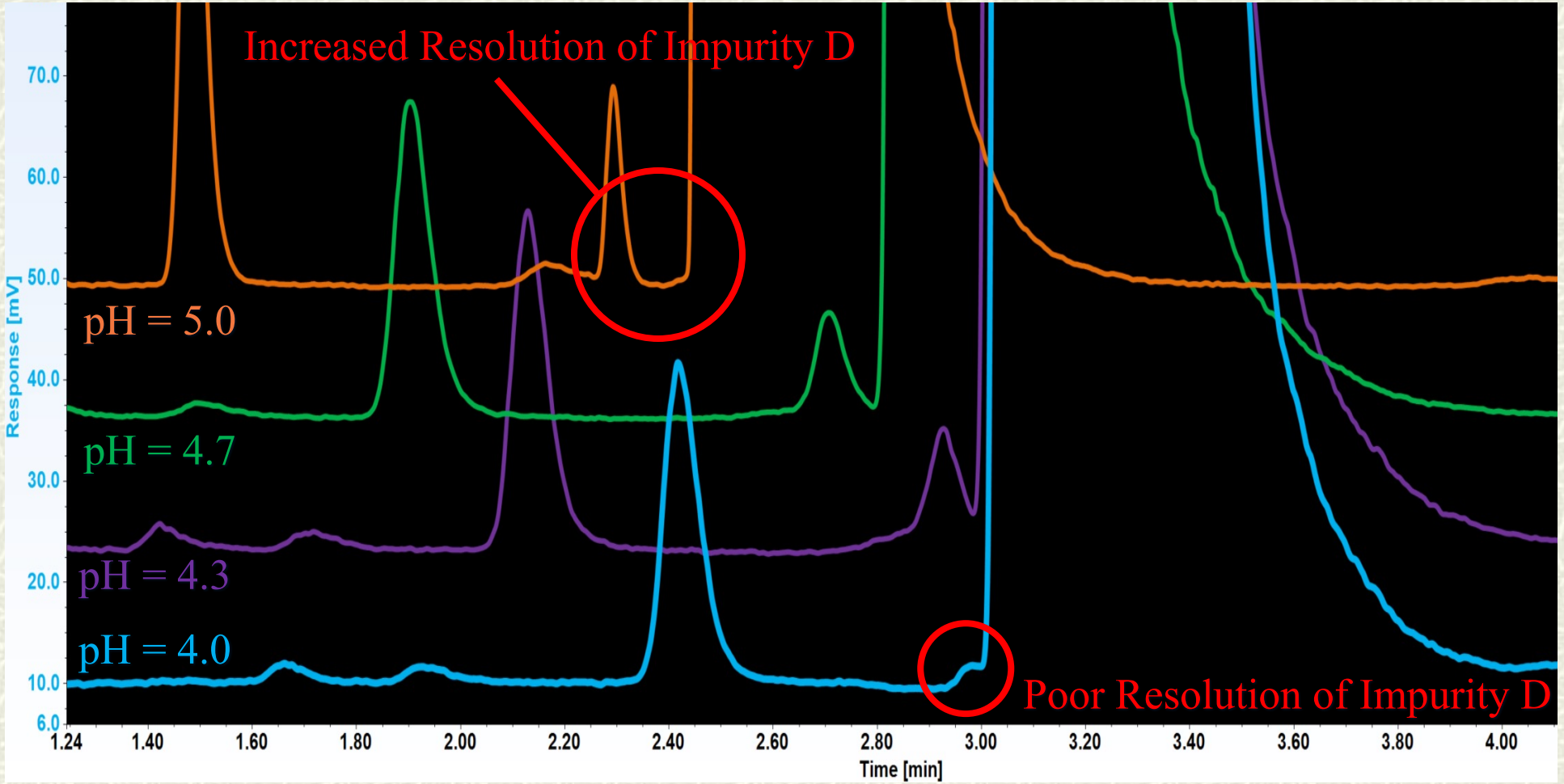
Current EP Monograph: Impurities - System Suitability



Current EP Monograph: Impurities Method Problems

- **Not Easily Transferred to Low Pressure System (HPLC/Quaternary Pump) or High Pressure System (uHPLC/Binary Pump)**
- **Variable pH of Mobile Phase Impacts Resolution**
- **Requires Resourceful Integration to Meet Resolution Criteria**
- **Column Stationary Phase – Breaks Down Rapidly**
- **Single Source from Bio-Sol-Dex Ltd. (Based Budapest, Hungary)**

New EP Monograph:
Impurities – Resolution Issues



New EP Monograph: Singota/Ligand - Troubleshooting

Improvement?

- **Improved Column + Stationary Phase and Sourcing**

- **Poor Dilution Scheme for Analytical Preparation**
- **Variable pH (AGAIN) - Not Considered**
- **Heart Cutting to Minimize Sodium Chloride Interference**
- **No Resolution Criteria Set**

New EP Monograph: Singota/Ligand - Solutions

- Singota and Ligand providing technical notes to EP
- Singota performed comparison validation, successfully proving orthogonal method capability.
- Adopted USP Impurities Methods – Higher Limits
  - Analysis by HPLC – Ion Chromatography (IC)
  - Impurity A by Electrochemical Detection (ECD)
  - Impurities C and D by Conductivity Detection (CD)

Current EP Monograph: Reducing Sugars Analysis

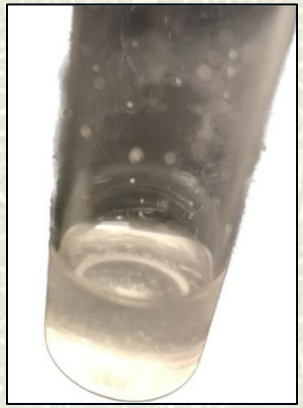
Limit Test by UV-Vis at 482 nm

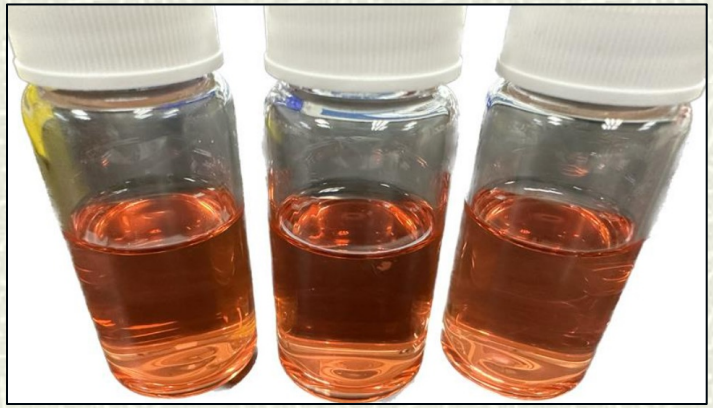
Oxidation-reduction differential kinetic reaction

- **Reagent Solution = Triphenyltetrazolium Chloride (THTCl) in MeOH.**
- **Reference Standard = Glucose in DMSO, NaOH, Reagent Solution.**
- **Reaction Rate = Determined by Ratio of THTCL to Sugar.**
- **Result = Sample absorbance is less than Reference Standard. Measured after 1 hour.**
- **Not a required USP Monograph Test Method.**

Current EP Monograph: Reducing Sugars Problems

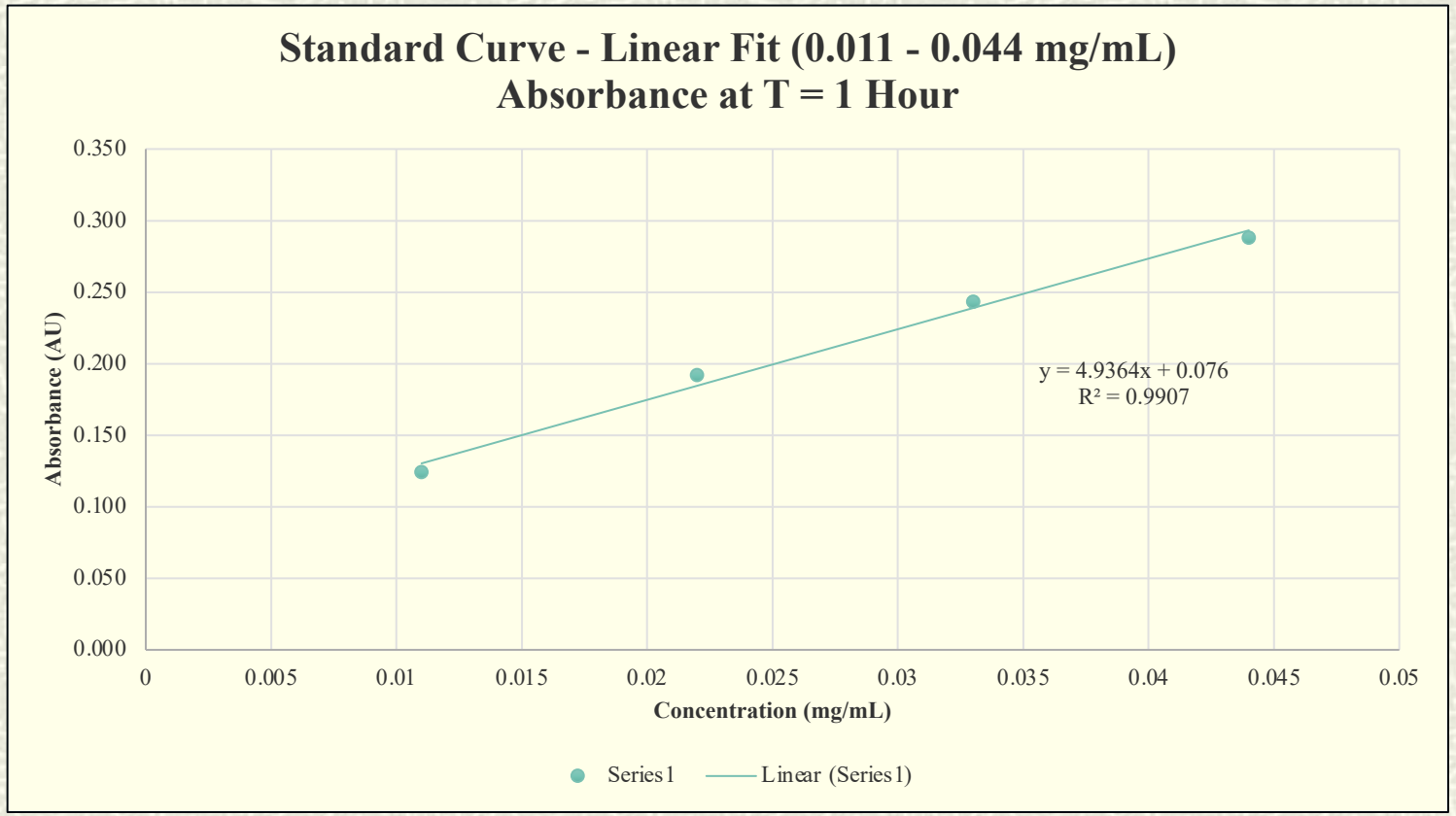
- **Results not Passing with samples absorbing higher than the Reference Standard.**
- **From analyst to analyst, sample to sample Absorbances Vary.**
- **Insolubility of the Samples due to organic solvents.**
- **No precision of duplicate sample preparation due to poor reaction rate and low absorbance.**





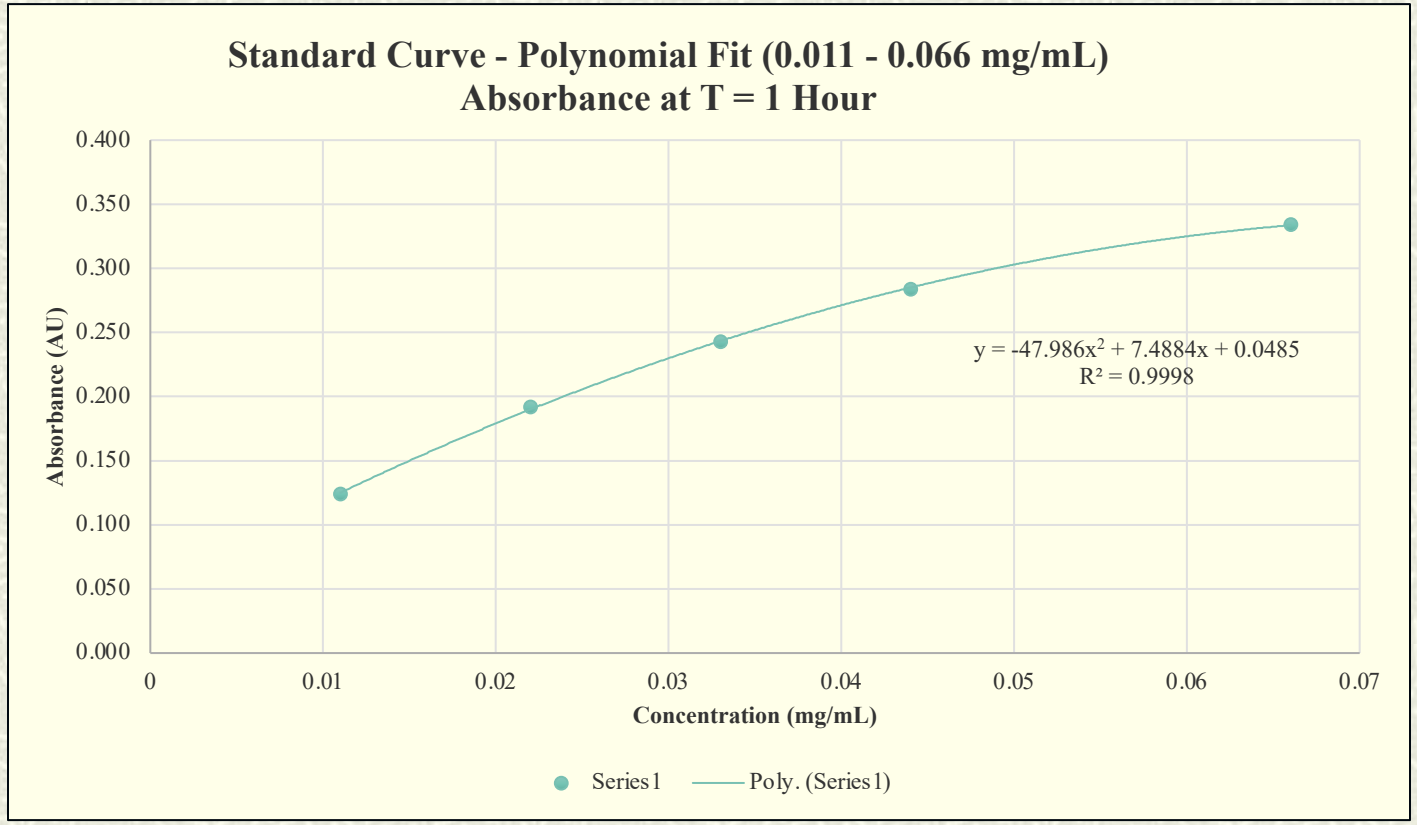
Current EP Monograph: Reducing Sugars Investigation

- Singota has spent extensive lab time understanding and perfecting this method.
- Produced standard curve to quantify - appears linear.



Current EP Monograph: Reducing Sugars Investigation

- One additional higher standard point produces a linear fit of $R^2 = 0.95$ outside the typical > 0.98.
- Only linear at lower concentrations and does not intercept zero, due to loss of sensitivity.
- Current reaction rate reaches endpoint and plateaus. Leading to inconsistent results.



Current EP Monograph: Reducing Sugars Problems

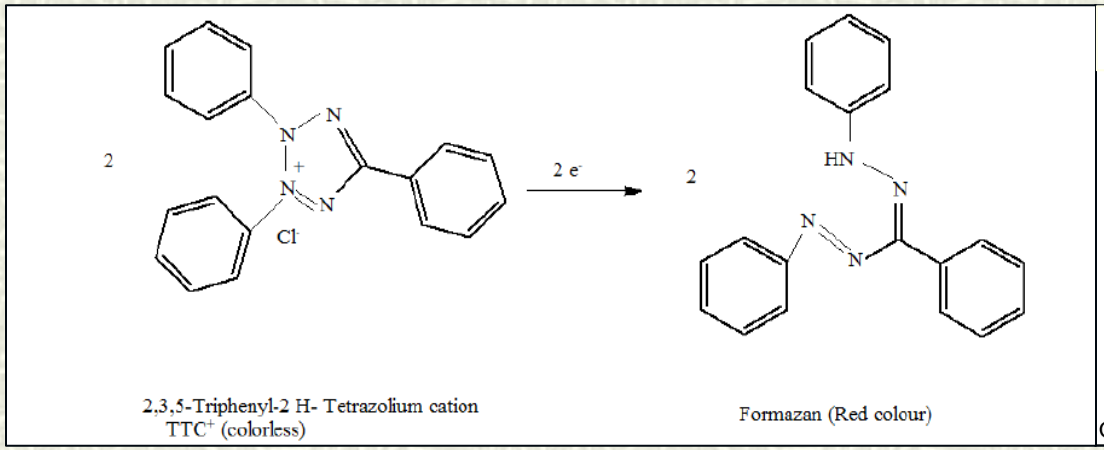
- **Reagent Solution degrades after a few hours. Leads to increased absorbance over time. If Reference Standard(s) and Samples not prepared at the same time, absorbances will vary.**
  - **Example being if the Reference Standard is prepared in the morning and the Sample is prepared in the afternoon, then the sample absorbance will be higher and fail.**
- **Current method reaction takes 2-3 hours to complete, not 1 hour. Modifying the ratio of reagent to glucose increases the reaction rate, providing reproducible results.**
  - **Current Ratio = 1:334**
  - **Target Ratio = 1:100**
- **Insoluble Samples lead to higher absorbance than the solubilized Reference Standard.**

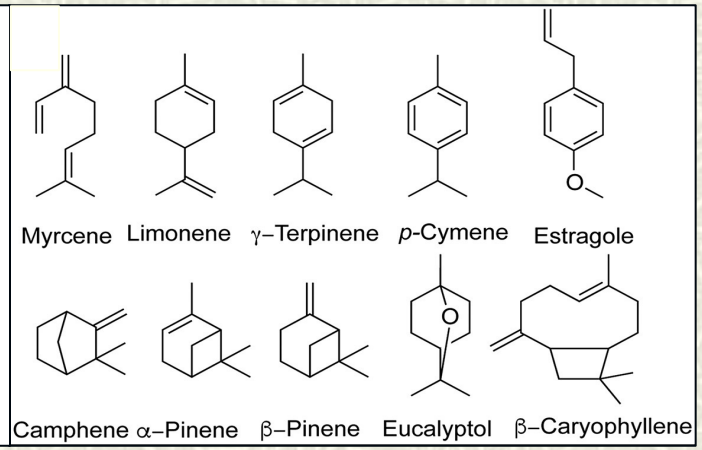
New EP Monograph: Reducing Sugars Solutions

- Reagent Solution concentration and volume scaled to slow degradation.
- Require Reference Standards and Samples be prepared at the same time within 20 minutes.
- Modified the ratio of reagent to glucose, providing reproducible results.
  - Current Ratio = 1:334
  - Target Ratio = 1:100
  - New Ratio = 1:166

New EP Monograph: Reducing Sugars Solutions

- **Filter both Reference Standard and Sample preparations prior to analysis.**
- **Develop an extraction method?!**
- **There also may be some inclusion of Formazan (final measured complex after the oxidation-reduction reaction) with Captisol®. Captisol® includes aromatic essential oil structures which are similar to Formazan.**





Flavour & Fragrance J, Volume: 32, Issue: 5, Pages: 340-346, First published: 05 June 2017, DOI: (10.1002/ffj.3395)

EP Monograph: Recent Journey - Difficult

- Captisol® was first used in an approved product in 2002 and established as a safe excipient worldwide through Pfizer's antifungal, Vfend.
- Approximately 200 commercial batches have been manufactured, so why after 20 years did this excipient have to now comply with new methods and specifications when it was already deemed safe?
- Current methodologies for Captisol® USP-NF Monograph do not have any issues, easily qualified.
- Is there a reason to keep an excipient from being used during emergency situations like COVID?
- Prior to 2019, considered safe in Europe.

Captisol®: Singota – Continues to Support

- Continues to support release testing for all Captisol®, including developmental technologies and commercial release testing.
- Supporting current and future Clients that have been recommended to use Singota from our Ligand friends.

- Contributions made to pending updates of the Captisol® methodologies for the USP-NF and EP Monographs.
- Singota continues to offer clients formulation development using Captisol® and testing of products with Captisol®.

Acknowledgments

- Ligand Team
  - Vince Antle, PhD – Senior Vice President, Technical Operations and QA
  - James Pipkin, PhD – Vice President, New Product Development
  - Jessica Beach – Associate Director, Captisol Customer Support
  - Lian Rajewski – Senior Investigator
- Singota Team
  - Will Powers – Senior Director of Business Development
  - Mihaela Simianu, PhD – Vice President of R&D and Operations

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