

## 2016 PROGRAM

### SUNDAY, SEPT 25<sup>TH</sup> 2016

5:30-6:30 PM

Registration

6:30-9:00 PM

**ASAPprime® Workshop**

6:30-6:45 PM

Welcome & Opening Remarks

Dr. Ken Waterman, President, FreeThink Technologies, Branford, CT, USA

6:45-7:15 PM

ASAPprime® 5.0: Introduction to Latest Version Release

Dr. Ken Waterman, FreeThink Technologies, Branford, CT, USA

The latest version of ASAPprime® will be released shortly. It will have a number of new features:

- Added the cross-validated  $R^2$  ( $Q^2$ )
- Ability to see all the isoconversion plots at once
- Warnings when data involve significant extrapolations at a condition
- Ability to store individual sorption isotherm data for excipients (blends)
- Ability to import Excel data by specifying individual columns
- Calculation of critical relative humidity by solubility
- Ordering of analyses to reduce systematic errors
- Adjustment of ASAP design based on long-term storage conditions
- Added excipients and packaging materials
- Ability to use ppm instead of just %
- More options for outputting tables and graphs
- Changed statistical handling of repeat measurements
- Compatibility for Windows through 10 (dropping XP)

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7:15-7:45 PM

ASAPprime® Case Study: Peptide Stability

Dr. Alisa Waterman, FreeThink Technologies, Branford, CT, USA

Peptides are small proteins that can be used as active pharmaceutical ingredients in drug products. This class of biologics shares some stability properties of small molecules. Solid bacitracin and bacitracin Zn were used as model peptides to examine the applicability of the Accelerated Stability Assessment Program (ASAP) to rapidly model shelf-life. The accelerated model-based predictions for ambient shelf-life and specific degradation product formation matched that observed in real time. The modeling also provides insight into the mechanism of stabilization of bacitracin by zinc complexation which appears to limit mobility at the active site.

7:45-8:15 PM

ASAPprime® Case Study: TBA

8:15-9:00 PM

Panel Discussion

Moderator: Dr. Steve Baertschi

Panelists: Dr. Ken Waterman, Dr. Sabine Thielges & Dr. Alisa Waterman

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klöckner pentaplast



## MONDAY, SEPT 26<sup>TH</sup> 2016

8:00-9:00 AM Registration & Continental breakfast

**9:00-10:30 AM SESSION I: THE SCIENCE OF ASAP & ITS APPLICATION IN DRUG DEVELOPMENT**

Chair: Dr. Steve Baertschi, Baertschi Consulting, Indianapolis, IN

9:00-9:45 AM “ASAP Theory and Fundamentals”  
Dr. Sabine Thielges, Novartis, Basel, Switzerland

ASAP (Accelerated Stability Assessment Protocol) is gaining acceptance across the pharmaceutical industry as a powerful tool for predicting the effects of temperature and humidity on pharmaceutical stability. In this presentation the theory and fundamentals of ASAP will be discussed, covering the science behind the protocol and some consideration for the implementation.

9:45-10:30 AM “Integration of ASAP in Early Drug Development using the FAST Approach”  
Dr. Chandan Bhugra, Boehringer Ingelheim, Ridgefield, CT

Using ASAP applies a scientific rationale for the chemical stability portion of drug product development beyond a simple “cook and look” approach and allows generation of chemical stability data supporting the early formulation development process to be greatly accelerated. Focused Accelerated Scientific Testing (FAST) formulation development approach allows significant reduction in timelines to First to Human trials. Combining ASAP stability testing with such a standardized formulation platform approach leads to large savings in time, resources and API. Without ASAP testing, stability becomes the rate limiting step in the drug product development program utilizing the FAST approach and adds significantly to the timeline. A standard ICH approach to stability testing cannot be suitable for a rapid early clinical formulation development program because the cycle time is too long (typically months). ASAP and a standardized approach also leads to systematic learning across projects. Instead of every single stability study being a new, surprising result, by standardizing excipients, it allows knowledge to be generated across projects and default approaches to be identified.

10:30-11:00 AM Networking Break & Refreshments

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**11:00-12:30 PM**      **SESSION II: ASAP APPLICATIONS IN DRUG DEVELOPMENT & ITS USE AS PART OF A LEAN STABILITY REGULATORY STRATEGY**

Chair: Dr. Isamir Martinez, FreeThink Technologies, Branford, CT

11:00-11:45 AM      “The Use of ASAP from Early to Late Drug Development”  
Dr. Eduard Luss, Vertex Pharmaceuticals, Boston, MA

The presentation covers a brief overview of ASAP, experimental design and its advantages in pharmaceutical development when compared to other typical approaches. Also, ASAP implementation in early development projects is demonstrated, including regulatory implications during filing of the data. Potential use in late pharmaceutical development is also discussed.

11:45-12:30 PM      “ASAP Regulatory Strategy, Acceptance and Feedback”  
Dr. Elke Debie, Janssen Pharmaceuticals, (J&J), Beerse, Belgium &  
Ms. Helen William, AstraZeneca, Macclesfield, UK

During this presentation the use of ASAP stability in regulatory filings will be discussed. Companies have been utilizing ASAP tools to enable development. However, the perception is that the application of these tools has been inconsistent across the industry. Therefore, from within the IQ consortium a working group was launched to focus on the use of ASAP to optimize pharmaceutical development. From within the regulatory sub-team a survey has been sent out to 17 pharmaceutical companies. The industry survey was conducted to get a sense of to what extent ASAP stability was used in regulatory filings along with the regulatory experience. IQ consortium survey results will be shared during the presentation.

12:30-2:00 PM      Lunch

**2:00-3:30 PM**      **SESSION III: ASAP APPLICATIONS IN THE GENERIC & OTC INDUSTRIES**

Chair: Dr. Jennifer Lewis, FreeThink Technologies, Branford, CT

2:00-2:45 PM      “ASAP Applications in Generic Products”  
Dr. Bryan Wicks, Boehringer Ingelheim, OH, USA

The typical generic pharmaceutical business model requires ascertaining as much product understanding as possible in a drastically shortened development time. With ever changing regulatory requirements, product knowledge and robust development processes are critical in the manufacturing of a sustainable quality product. The generic industry benefits from tools that provide substantial scientific information relatively quickly relating to development, investigation and change control issues pertaining to long term life cycle issues of commercial products.

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The Accelerated Stability Assessment Program (ASAP) is a tool that has been recently applied within the generic industry. The ASAP approach has shown utility in generating valuable information within a minimal timeframe. In this presentation, a case study illustrating the application of ASAP for the evaluation of changes to an active pharmaceutical ingredient's (API) physical properties and the resultant impact on drug product stability will be discussed.

2:45-3:30 PM

“Teaching Old Drugs New Tricks: Applications of ASAP in OTC Product Development”  
Dr. Jonathan E. Clark, Procter & Gamble, Cincinnati, OH, USA

The Over the Counter (OTC) drug market is changing. USP OTC Drug Product monographs are evolving to contain better control of API degradation products. OTC products are complex formulations, often containing solvents, dyes, flavors, and sweeteners. The OTC category is ~\$40 billion and continues to grow annually. Deep understanding of these products and their stability is critical, as there are thousands of OTC drug products used by ~90% of American families.

To aid in our technical diligence, Procter & Gamble has implemented *ASAPprime*<sup>®</sup> as a tool for rapid evaluation of API vulnerability, packaging options, and overall formulation stability. *ASAPprime*<sup>®</sup> strategy and experimental execution for existing and new OTC products will be discussed. Discussion of synergies between *ASAPprime*<sup>®</sup> and novel physical models for evaluation of in-process stability will also be presented.

3:30-4:00 PM

Networking Break & Refreshments

4:00-5:30 PM

#### **SESSION IV: AMORPHOUS DRUG STABILITY**

Chair: Dr. Peter Persich, Janssen Pharmaceuticals (J & J), Beerse, Belgium

4:00-4:45 PM

“Modeling the Physical Stability of Amorphous Solid Dispersions”  
Dr. Rodney Ketner, Bend Research, a division of Capsugel, Bend, OR, USA

The use of amorphous solid dispersions to improve oral bioavailability has been known in the pharmaceutical industry for well over 40 years, with a large number of products advancing to commercialization in the past few years. Driven by an increasing percentage of poorly soluble drugs in pharmaceutical industry pipelines, fundamental understanding and the application of solid-dispersion technology have advanced substantially. This presentation briefly describes the formulation of amorphous solid dispersions (“spray-dried dispersions” or SDDs) and related technologies that have been used successfully to improve the oral bioavailability of low-solubility drugs. Stage-appropriate physical stability models that have been developed and verified for the prediction of long term stability for SDD formulations are described, as are applicability maps that identify the physical-property boundaries of drug molecules where “conventional” SDD technology is applied.

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4:45-5:30 PM

*“In Silico, Thermodynamic and Kinetic Stability of Amorphous Solid Dispersions”*  
Dr. Jeffrey Tan, Eli Lilly and Company, Indianapolis, IN, USA

Amorphous solid dispersion is an important formulation platform for the delivery of poorly soluble drugs. The solubility enhancement is achieved by disruption of the highly ordered crystalline lattice into a disordered amorphous state that is thermodynamically less stable. This necessitates a comprehensive understanding of the thermodynamic and kinetic factors that can drive phase separation and ultimately crystallization of the amorphous material that will significantly impact in vivo performance of the drug product. This presentation will discuss the application of drug-polymer binary phase diagrams as formulated by Flory-Huggins to assess thermodynamic stability and the use of accelerated stress-testing methodologies to assess crystallization kinetics of amorphous solid dispersions.

5:30-6:00 PM

Discussion Q&A & Closing Remarks, Day 1

6:00-7:00 PM

Networking Event: Wine and Cheese Social

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## TUESDAY, SEPT 27<sup>TH</sup> 2016

8:00-9:00 AM Registration & Continental breakfast

### 9:00-9:45 AM **SESSION V: IN-USE STABILITY**

Chair: Dr. Sabine Thielges, Novartis, Basel, Switzerland

9:00-9:45 AM "In-Use and Excursions: Stability Beyond ICH"

Dr. Ken Waterman, FreeThink Technologies, Branford, CT, USA

While there is a regulatory expectation that in-use shelf-life will be determined for multiuse packaging, there is little definition of what that testing entails. In-use conditions can be from opening of a package (e.g., breaking a heat-induction seal (HIS) on a bottle) or constituting a product (e.g., dispersing a powder in water). Similarly, scientific justification for acceptability (with few specifics) is required when shipping or storage conditions exceed specifications. The impact in both situations is effectively modeled based on accelerated data and understanding of the importance for a given product of both temperature and humidity. Examples are shown illustrating this accelerated modeling approach for: (1) sudden drops in temperature, (2) tablets removed daily after a bottle seal is broken, (3) powder constituted after storage, and (4) high temperature excursion for tablets.

### 9:45-12:15 PM **SESSION VI: DRUG DEGRADATION CHEMISTRY**

Chair: Dr. Kenneth Waterman, FreeThink Technologies, Branford, CT, USA

9:45-10:30 AM "Drug Degradation Mechanisms"

Dr. Steve Baertschi, Baertschi Consulting, Indianapolis, IN, USA

Developing an understanding of the degradation pathways available to drug substances and associated formulated products is an important part of establishing the "intrinsic stability" characteristics of a drug. This talk will focus on several case studies of degradation mechanisms, highlighting the importance of a "chemistry-guided" approach that includes structure elucidation of degradation products, utilization of kinetics, analytical tools, and experiments that are designed to uncover critical mechanistic aspects. The mechanistic insights gained from this approach will be used to illustrate how such understanding can reveal the reactive sites in the drug molecule, potential analytical pitfalls, and implications for stabilization through formulation design and packaging.

10:30-11:00 AM Networking Break & Refreshments

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11:00-11:45 AM

“Analysis of unstable degradation impurities and their quantification without isolation using multiple linear regression”

Dr. John Campbell, GlaxoSmithKline, Philadelphia, PA, USA

This presentation discusses a novel methodology developed for calculating the relative response factors (RRFs) of two highly unstable degradation impurities without isolation using only HPLC-UV data. Subsequent correction of HPLC peak areas with the experimentally-determined RRFs allowed for accurate quantification of the degradants and demonstrated mass balance in forced degradation samples.

11:45-12:30 AM

“Stress Testing in Solid State: Towards a Realistic Degradation Profile”

Dr. Peter Persich, Janssen Pharmaceuticals, (J&J), Beerse, Belgium

Stress testing is an important and convenient tool to predict degradation profiles and to understand drug decomposition processes. A thoroughly-assessed degradation profile allows the smooth development of stability-indicating methods, robust formulations, and overall control strategies. In this respect, the selection of adequate and conclusive forced degradation conditions is one of the major challenges. The presented case studies will exemplify general strategies as well as novel approaches to study degradation pathways and to obtain realistic degradation profiles.

12:30-1:45 PM

Lunch

1:45-3:15 PM

## **SESSION VII: MOISTURE AND ITS IMPACT ON STABILITY**

Chair: Dr. Steve Baertschi, Baertschi Consulting, Indianapolis, IN

1:45-2:30 PM

“Understanding Importance of Water Sorption Isotherm Shape, Hysteresis, and Models on Pharmaceutical Materials”

Dr. Daniel Burnett, Surface Measurements Systems, Allentown, PA, USA

This educational seminar will focus on the interactions of water vapor and understanding physicochemical water sorption isotherms on pharmaceutical ingredients. Moisture and/or humidity has significant importance for pharmaceutical and biopharmaceutical solid state R&D for drug discovery, pre-formulation and formulation development of active drug compounds, excipients, binders, and other materials. In particular, practical examples of using the DVS for sorption mechanism determination and modeling, hydrate detection, amorphous phase detection and quantification, and vapor-induced transformations will be discussed. Also, the combination of moisture sorption experiments with parallel techniques like video microscopy and Near-IR or Raman spectroscopy will be introduced, including examples on pharmaceutically-relevant materials. Finally, diffusion and kinetic studies will highlight the application of moisture sorption techniques for studying moisture barrier and packaging applications.

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2:30-3:15 PM

“Case Studies in Drug Packaging: Supporting Stability by Addressing Specific Preservation Challenges.”

Mr. Valère Logel, Clariant Healthcare Packaging, Paris, France

Selecting the appropriate packaging to preserve drug products always requires calibration to the conditions specific to the application. In some instances, preservation of moisture-sensitive drug products is achieved by combining commonly available packaging components with the appropriate off-the-shelf desiccants. In other instances, conventional packaging configurations are not enough to address specific molecular instability, to achieve prolonged shelf life or to cover unique conditions of use. In such cases, additional situational analysis and packaging technologies should be considered to optimize drug preservation during shelf life or end-use. This discussion will examine specific cases where chemical and/or physical stability of drug products combined with application-specific requirements may necessitate advanced packaging solutions. The problem circumstances and the package solutions designed to address them will be explained.

3:15-3:45 PM

Networking Break & Refreshments

3:45-5:00 PM

## **SESSION VIII: ADDITIONAL STABILITY TOPICS**

Chair: Dr. Peter Persich

3:45-4:30 PM

“ASAP for Non-Traditional Factors: Dissolution, Disintegration & Color”

Dr. Kenneth Waterman, FreeThink Technologies, Branford, CT, USA

The Accelerated Stability Assessment Program (ASAP) approach of assigning storage times to hit the dissolution failure point at a range of temperatures and relative humidities (RH) below the critical relative humidity (CRH) at each storage condition can be used to model the dissolution and disintegration stability of immediate-release tablet products. For two such products, ambient condition stability could be determined based on a modified Arrhenius equation using the inverse of the failure times in place of rate constants. This use of failure times, rather than a rate of change, was critical for modeling dissolution and disintegration stability because the onset of the failures was sudden. In both cases, dissolution and disintegration failures were correlated with each other, but with greater storage times needed to effect destabilization for dissolution than disintegration.

Color change is modeled well by ASAP, with the challenge of changing qualitative descriptions to quantitative using colorimeter measurements. In addition, specification limits need to be established. Even such changes in appearance as spots can be effectively quantitated and modeled with ASAP. With these in place, ASAP can be used to determine such factors as formulation variation, packaging selection and climate zone sensitivity.

4:30-5:00 PM

Discussion Q&A & Closing Remarks, Day 2

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