XRPD in Pharmaceutical Industry

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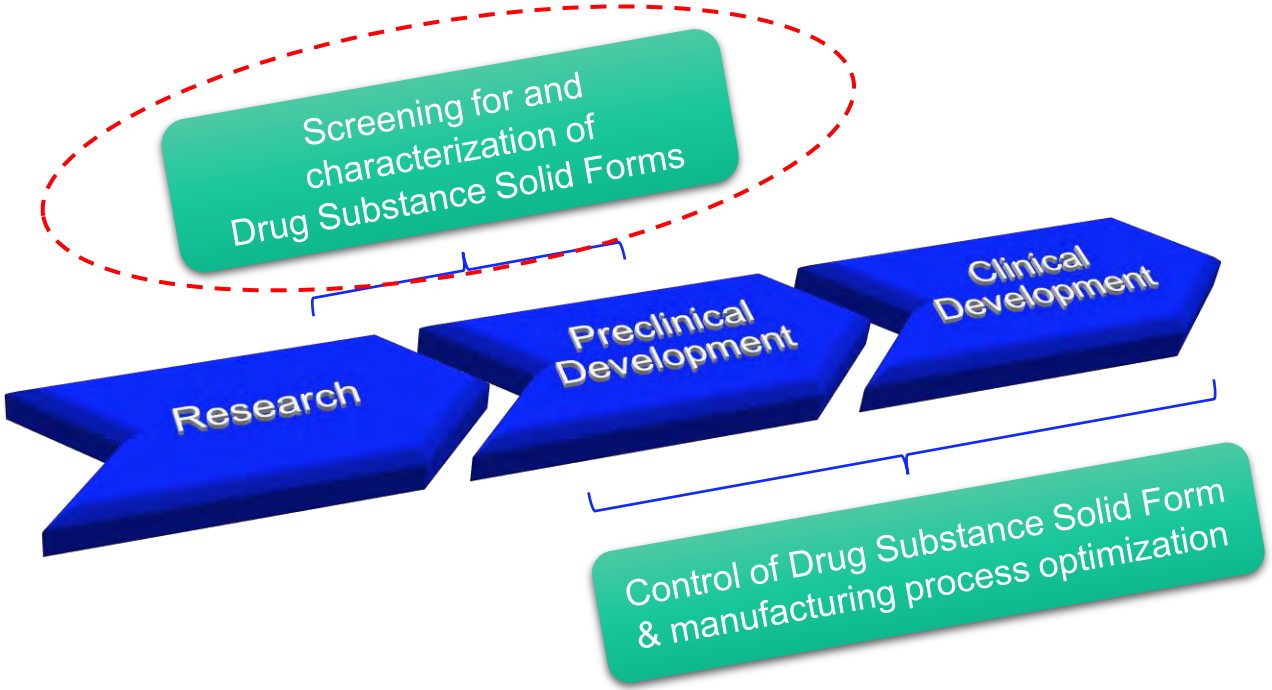
December 7th 2022

abbvie

NanED Workshop II, Mainz, Germany

XRPD in Pharmaceutical R&D



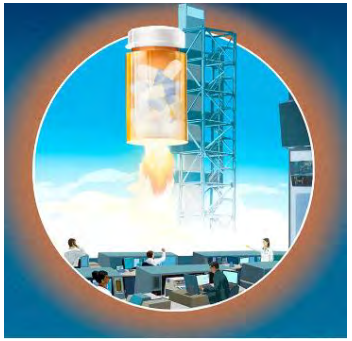
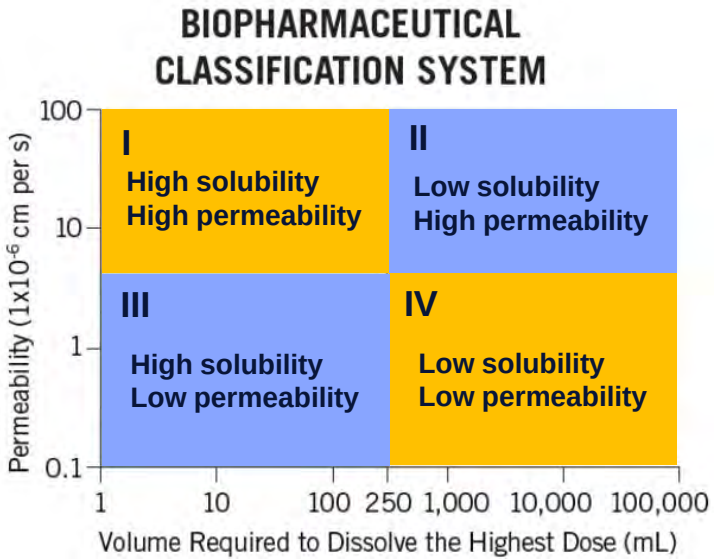


Image from Deloitte.com

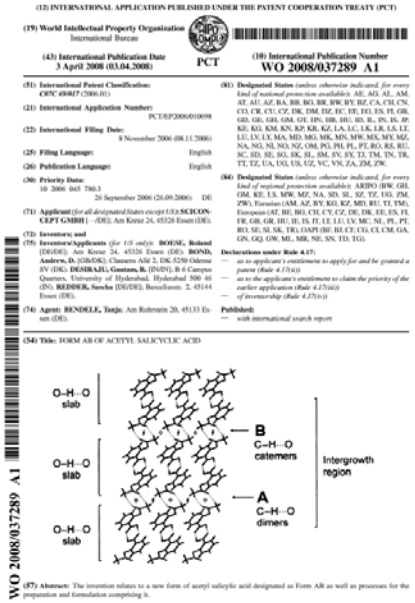
Why does the Drug Substance Solid Form matter?

- **Differences in properties, e.g. solubility, stability**



Scheme modified from semanticscolar.org

- **Patentability**


(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

PCT

(43) International Publication Date
3 April 2008 (03.04.2008)

(10) International Publication Number
WO 2008/037289 A1

(54) Title: FORM AB OF ACETYL SALICYCLIC ACID

O–H···O slab
O–H···O slab
O–H···O slab
B C–H···O catemers
A C–H···O dimers
Intergrowth region

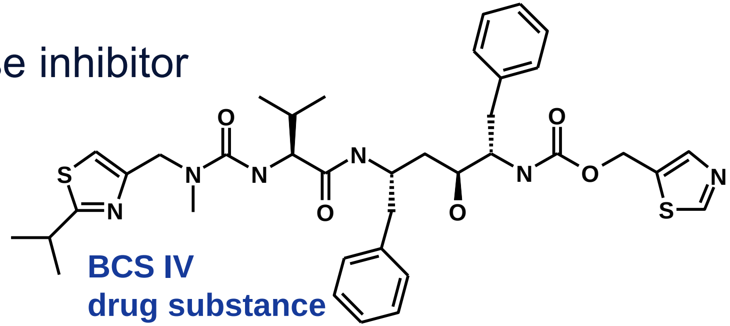
WO 2008/037289 A1

Patent application ‘Form AB of Acetyl Salicylic acid‘ published in 2008

Initial Aspirin® patent filed ~1900

Case Study – Norvir®

HIV protease inhibitor
Ritonavir



BCS IV
drug substance

Chicago Tribune
3rd August 1998

Manufacturing problems hit anti-Aids drug

Sarah Boseley
Health Correspondent

Chicago Tribune
19th September 1998

Chicago Tribune

Abbott still seeking Norvir answer

Chicago Tribune - Saturday, September 19, 1998
Andrew Zajac

Abbott Laboratories investigators still can't find the source of a mysterious manufacturing line problem that is about to dry up the supply of the capsule form of Norvir, the company's well-regarded anti-AIDS drug.

Supplies of capsulized Norvir will run out within the next month, unless the production glitch can be identified and remedied, a company spokeswoman told Reuters Friday.

The loss of the capsule will leave patients reliant on a liquid form of Norvir, which is in plentiful supply and effective, but foul-tasting.

Abbott reported problems making Norvir (ritonavir) capsules on July 27. The North Chicago-based company said a manufacturing flaw produced crystals that altered the way the capsules dissolved.

None of the flawed drug was distributed.

Norvir is used by about 60,000 AIDS patients.

Physicians recommend masking the taste of liquid Norvir by taking it with chocolate products such as cake or a milkshake.

Norvir, with $170 million in sales in 1997, is the fourth best-selling protease inhibitor, a category of drug used to combat HIV, usually in concert with other compounds, among them AZT.

Protease inhibitors block the production of enzymes in the human immunodeficiency virus, and their use in "cocktails" of HIV drugs is thought to be a major factor in the decline in AIDS deaths in the U.S.

Researchers at this year's World AIDS Conference in Geneva reported that Norvir increased the effectiveness of related drugs, resulting in a more potent treatment of HIV.

Abbott maintains a Web site, http://www.norvir.com, on the drug.

Protease inhibitors are a $2.2 billion market, and Norvir was projected to yield about $250 million in revenue this year.

When the production problem was reported, Abbott said it did not believe the difficulty would affect the revenue target for the drug.

1996 **First approval of Norvir®**

Δt = 2 years

1998 **New polymorph occurs, originally produced phase no longer stable: continuation of capsule production impossible**

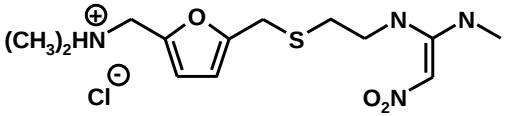
Δt > 1 year

06-12/1999 **Approval of re-formulated Norvir®**

2022 **New Ritonavir polymorph discovered and published**

Case Study – Zantac®

Ranitidine HCl
H_2-Antihistamine



BCS III
drug substance

FINANCIAL TIMES, 9. 4. 1991

COMPANIES & MARKETS

© THE FINANCIAL TIMES LIMITED 1991 Tuesday April 9 1991

Glaxo fights for Zantac patent

By Charles Leadbeater, Industrial Editor, in London

GLAXO, Britain's biggest pharmaceutical company, yesterday fired the first shot in a battle over the patents on Zantac, its ulcer treatment which is the world's best-selling drug.

The company has started legal action in the US against Genpharm Pharmaceuticals, a Canadian manufacturer of generic drugs, alleging infringement on one of the two main patents covering Zantac.

Genpharm, which is based in Toronto, has filed an abbreviated new drug application with the US Food and Drugs Administration seeking to manufacture a generic form of Zantac.

The applications set the scene for a protracted legal battle over one of the most lucrative drugs in the world. The outcome of the dispute will have a crucial bearing on Glaxo's future.

Zantac last year accounted for about half Glaxo's turnover of £2.8bn ($4.9bn). About 55 per cent of Zantac sales are in the US. The total sales of Zantac are equivalent to the entire pharmaceutical turnover of Pfizer, the US group which is one of the world's top 10 drug manufacturers.

A successful challenge from a generic drug producer could have a dramatic effect on Glaxo's revenues and profits in the later half of the decade. It has been relying on profits from the ulcer treatment to fund a heavy research and development programme into new drugs. Generic drugs quickly eat into markets for brand-named drugs once patent protection breaks down or expires. In the past, it has taken only two years for generic drugs to capture half the market. Genpharm's challenge to the Zantac patent comes far earlier than many analysts had expected. The complex legal dispute will centre on two patents which cover ranitidine, the substance from which Zantac is manufactured.

The initial so-called Form 1 patent expires in the US in 1996. However, Glaxo argues that this patent covers forms of ranitidine which it has never manufactured or marketed. Glaxo says the relevant Zantac patent is the Form 2 which expires in 2002. It covers a crystalline form of ranitidine. Glaxo, which has been preparing for a challenge to Zantac for years, is expected to unveil one of the most sophisticated patent protection programmes yet seen from a drug company.

Genpharm would not comment on the dispute. However, London analysts regard it as a serious generic drug producer. It is used to fighting patent battles, and analysts believe it may be backed by larger generic producers such as American Cyanamid or Ciba-Geigy.

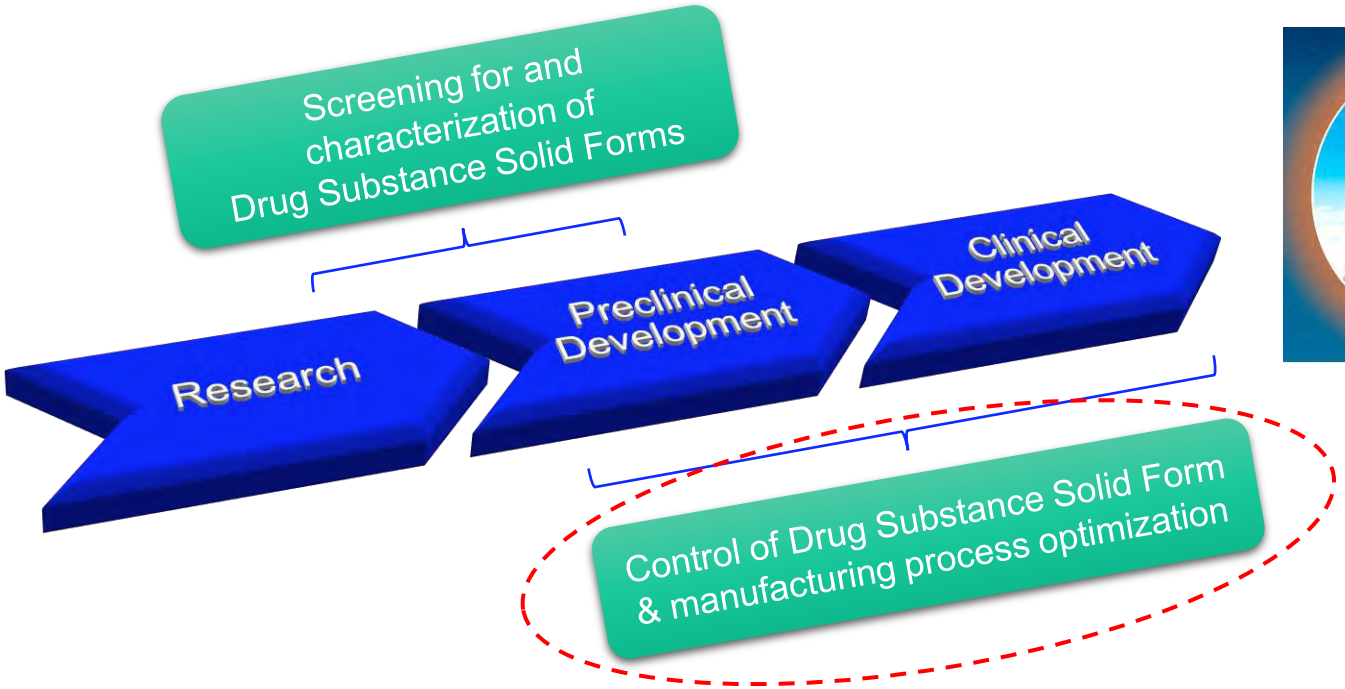
1981 First patent on Zantac® filed (1 drug substance phase known)

Batch 3B13 contained a new phase (2): Increasing problems to reproduce old phase

Glaxo patents polymorph 2 and produces Zantac with polymorph 2

1991 Genpharm and Novo developed a generic containing old polymorph 1

XRPD in Pharmaceutical R&D



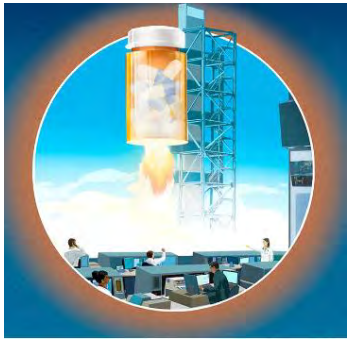
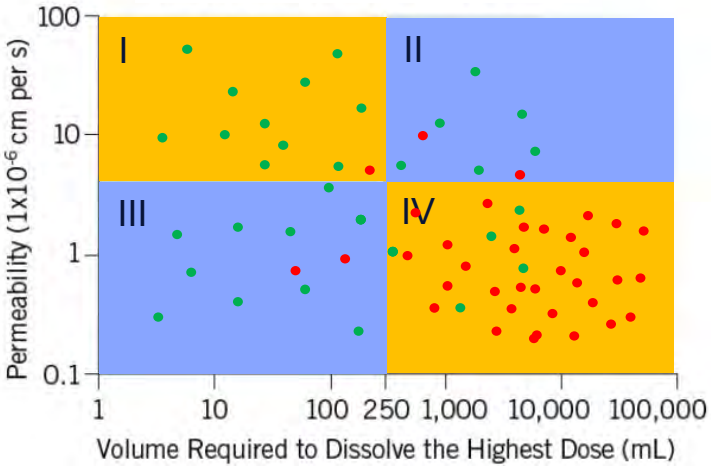


Image from Deloitte.com

Amorphous Solid Dispersions (ASDs)

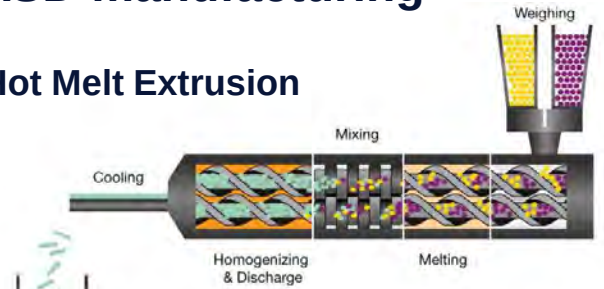
- **BCS class distribution of of drug subtances developed decades ago vs. nowadays**



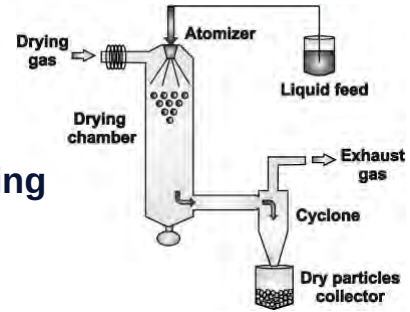
Scheme modified from semanticscolar.org

- **ASD manufacturing**

Hot Melt Extrusion

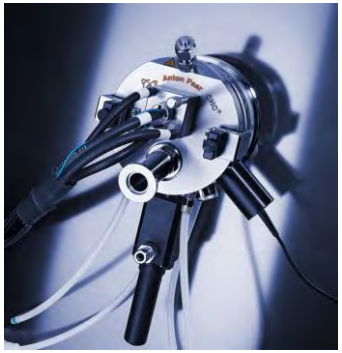


Spray Drying



Scheme from PACMOORE.com

Drug Substance Dissolution during HME



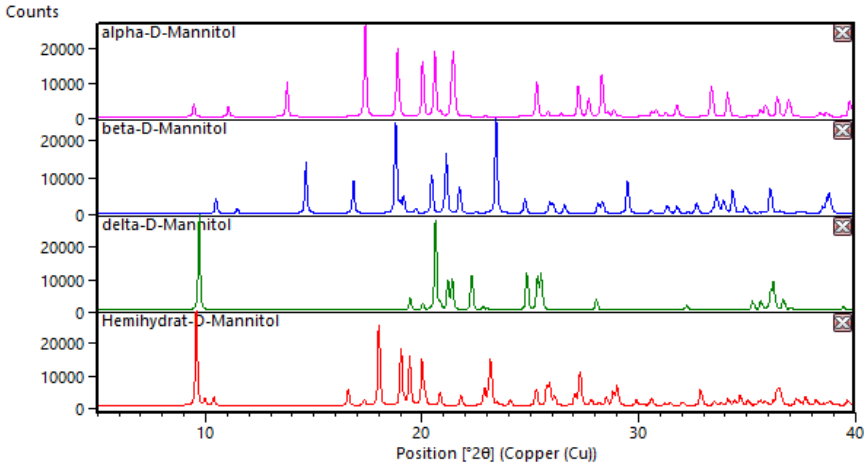
V.K. Seiler, F. Theil, N. Nagel, H. van Lishaut, Adding a New Dimension to the Amorphous Solid Dispersion Phase Diagram: Studying Dissolution Kinetics of Crystalline Drugs in a Polymer Matrix Using Temperature Dependent XRPD and DSC, J. Pharm. Sci. 111(9), 2496-2504, 2022.

Lyophilized Drug Products

Composition of freeze-dried biopharmaceuticals

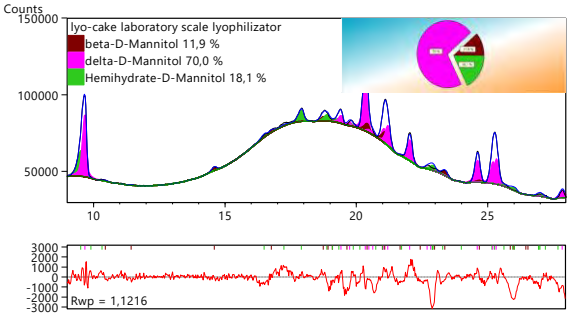
Formulation component	Examples
Drug Substance	Antibody
Buffer	Phosphate, histidine
Bulking Agent	Mannitol, glycine
Lyoprotectant	Disaccharides, sucrose, trehalose
Tonicity modifier	NaCl
Surfactant	Polysorbate 80

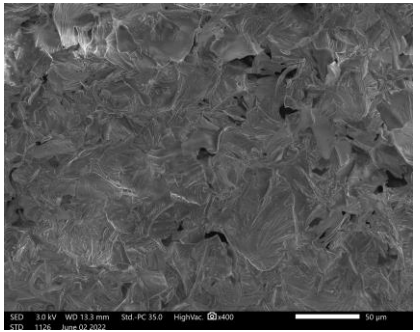
D-Mannitol crystalline phases:



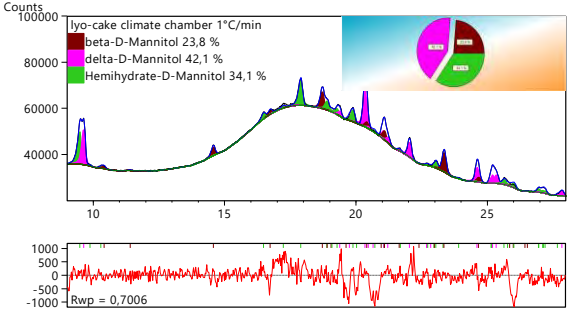
Freeze Dryer vs. XRPD Climate Chamber

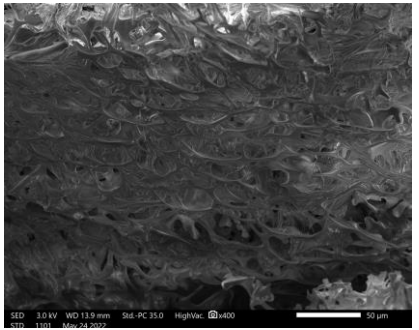
Freeze Dryer





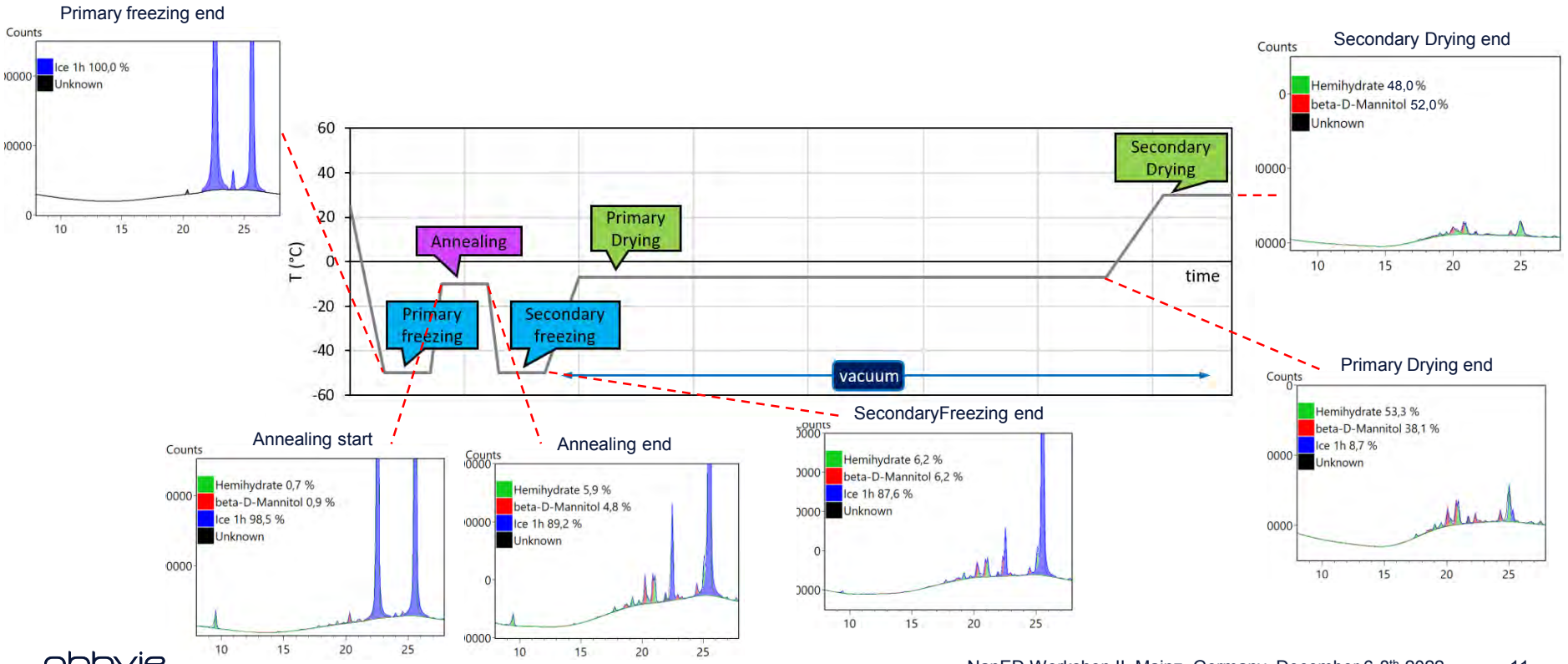
XRPD
Climate Chamber





V. Seiler, S. Weber, M. Börner, M. Witting, S. Daller, N. Nagel, In-situ investigation of solid phase evolution during lyophilization of mannitol-based antibody formulations using an XRPD climate chamber, Eur. J. Pharm. Sci., submitted 2022.

Lyophilization Process Investigation



Conclusion

XRPD is a key analytical technique to identify, characterize and control solid forms of drug substances and excipients. It can furthermore be imployed to optimize industrial processes, e.g. by investigating…

a) drug substance dissolution during hot melt extrusion of amorphous solid dispersions.

b) phase evolution during freeze drying of mannitol-based lyophilisates of biologics.

⇒ Efficient identification of best process parameters

I thank all colleagues who contributed to the process optimization examples!

Vanessa Seiler, Stefan Weber, Markus Börner, David Geßner, Ariane Julke, Frank Theil, Holger van Lishaut, Madeleine Witting, Sarah Ehlers

Thank you for your attention!

What questions do you have?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