



Das Beste herausholen – innovative Lösungen in der biopharmazeutischen Produktion

26. September 2019

Michael Dekner

Head of PS FFF



Better Health, Brighter Future

Takeda Austria

Top employer in the Austrian biopharmaceutical industry





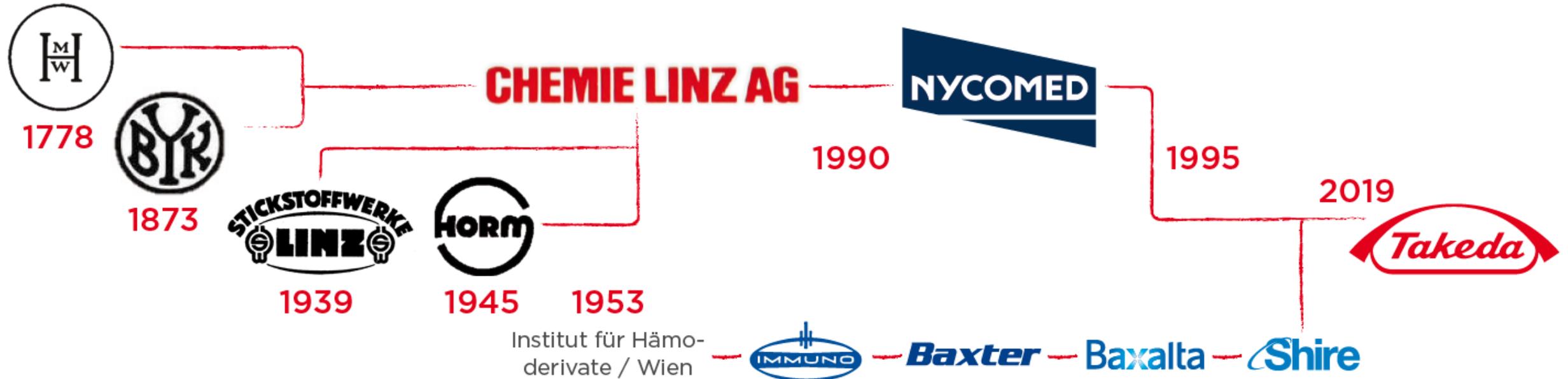
We have an innovative and maturing pipeline

	PHASE 1	PHASE 2	PHASE 3/FILED	APPROVED*	
ONCOLOGY	<p>TAK-981 SAMD Inhibitor Multiple cancers</p> <p>TAK-164 ImmunoGen GIC, SW, AOC GI cancer</p>	<p>TAK-573 Trop AIC/CD88 agonist KLN MM</p> <p>TAK-079 AIC/CD88 sub KLN MM, SA</p>	<p>TAK-788 NIM/NIG Inhibitor NSCLC</p> <p>TAK-931 CD7 Inhibitor MCR, BR, NSCLC</p>	<p>relugolix Muvoril GnRH antagonist Prostate Cancer (P) (Phase 1 in CD)</p> <p>TAK-924 (penciclovir) NA Inhibitor HS-MC/CMV/LS AML</p>	<p>NINLARO* Proton Pump Inhibitor GI, H. pylori, GERD, AOC KLN, PPI, Q14, AOC</p> <p>ADCRETIS* Smoothened G-protein CDK5/6C KLN, PPI, Q14, AOC</p> <p>ICLUSIG* BCR-ABL Inhibitor 3L Chronic Phase CML, Piv ALL</p> <p>ALUNBRIG* ALK Inhibitor 3L ALK+ NSCLC</p> <p>cabozantinib VEGFR/TYK2 Inhibitor 2nd line RCC, HCC (P)</p> <p>Niraparib Temozi PARP 1/2 Inhibitor Multiple cancer (P)</p>
GASTRO-ENTEROLOGY	<p>TAK-671 Serotonin 5-HT_{2B} Receptor Inhibitor Acute Pancreatitis</p> <p>TAK-018 Ezetimibe HMG-CoA reductase Cholesterol's Disease</p>	<p>Kuma052 PVP Biologic Multiple Osteo. Disease</p> <p>TAK-906 CD144 antagonist Gastroenteritis</p>	<p>TAK-954 Thyroglobulin 5-HT_{2B} agonist Enteral/feeding intolerance</p>	<p>TAK-721 (SHP621) BCS ICA</p> <p>TAK-647 (SHP647) MGCAM-1 mod ICD</p>	<p>ENTYVIO* anti-mAb MAG, anti-mAb, HLA, H, ULN/UL Anti-hepatitis</p> <p>Vonoprazan PCAB GORD PPI, partial resp. AAD</p> <p>ALOFSEL transcatheter stem cells Perforated Nucleus in CD</p> <p>GATTEK (SHP-2) Adult GSK, pediatric GSK</p> <p>RESOLOR prochlorperazine CC (L)</p>
NEUROSCIENCE	<p>TAK-653 Alone A antagonist TSD</p> <p>MEDI-1341 Anti-Zenica APP/tau/PS2 Parkinson's Disease</p> <p>WVE-120101 W/one mHTT SMP1, ASO Huntington's Disease</p>	<p>TAK-418 GSK-3 Inhibitor Parkinson's Disease</p> <p>TAK-925 Orally 2-agonist Neurology</p> <p>WVE-120102 W/one mHTT SMP1, ASO Huntington's Disease</p>	<p>TAK-041 SHP621 agonist CNS TB</p> <p>TAK-935 Oxid Therapeutic Oxid Inhibitor Rare Pediatric Epilepsia</p> <p>TAK-831 DAAC Inhibitor Headache, CNS HS</p>		<p>TRINTELLIX™ Lexapro Multimodal anti-depressant MDD (P)</p> <p>BUCCOLAM Solifenacin (SAL, SP)</p> <p>MYDAYIS AChE</p> <p>VYVANSE ADHD (P)</p>
RARE DISEASES	<p>TAK-611 (SHP611) SIC MED</p> <p>TAK-754 (SHP634) Gene Therapy Hemophilia</p>	<p>TAK-531 (SHP631) ERT Hunter CMG</p>	<p>TAK-607 (SHP607) SIC-1/antagonist Chronic Lung Disease</p> <p>TAK-609 (SHP609) Remyelin P1</p> <p>TAK-752 (SHP632) SLS</p>	<p>TAK-755 (SHP655) SIC/ADAMTS-18 CTP</p> <p>TAK-620 (SHP620) CMT Inhibitor in transgenic rat patients</p>	<p>FIRAZYR HAE (P)</p> <p>VONVENDI VMD</p> <p>TAKHZYRO Anti-tau/tau/tau HAE prophylaxis (P)</p> <p>OBIZUR Oral anti-fibrosis</p> <p>NATPARA Hypoparathyroidism (P)</p>
PLASMA-DERIVED THERAPIES				<p>HYQVIA Protein A, CDP</p> <p>ONRYZE 3C HAE prophylaxis, HAE prophylaxis (P), prophylaxis (P), AML</p>	
VACCINES	<p>TAK-021 EV71 Vaccine</p> <p>TAK-426 SARS-CoV-2 Vaccine</p>	<p>TAK-195 Gorilla Foundation Inactivated Polio Vaccine</p> <p>TAK-214 Nerveless Vaccine</p>	<p>TAK-003 Design Vaccine</p>		
OPHTHALMOLOGY	<p>TAK-639 (SHP639) Molecular</p>		<p>TAK-759 (SHP639) GSK</p>	<p>TAK-640 (SHP640) Infectious ophthalmology</p> <p>XIIDRA DRO (P)</p>	

*With ongoing significant clinical development activities. Pipeline as of January 4, 2019 for Takeda and September 30, 2018 for Shire
As announced on October 27, 2018, Takeda has proposed a remedy to the European Commission of a potential divestment of SHP647 and certain associated rights

Orphan Drug Designation

Today's integration continues a legacy of great companies coming together in Austria to deliver the highest quality patient care



Takeda Österreich

Auf einen Blick


+4.000
Mitarbeiter



● BioLife Plasmazentren

● Takeda Produktionsstandort & Vertrieb

Takeda Österreich

Ein bedeutender Standort mit langer Tradition

TOP



Pharmaarbeitgeber in Österreich



Lange Tradition in Österreich

Heilmittelwerke, Chemie Linz, Immuno, Baxter, Nycomed, Shire



Verarbeitung von 3 Mio. Liter Plasma p.a.

Wien ist eines der größten Fraktionierungswerke weltweit



Pathogen Safety

Globales Center für Excellence für Pathogensicherheit



Zentrum für Gentherapie

in Orth an der Donau



Heimisches Forschungsteam
mit Weltruf in den Bereichen Hämatologie, Immunologie und Gentherapie



238 Jahre
Geschichte Takeda international



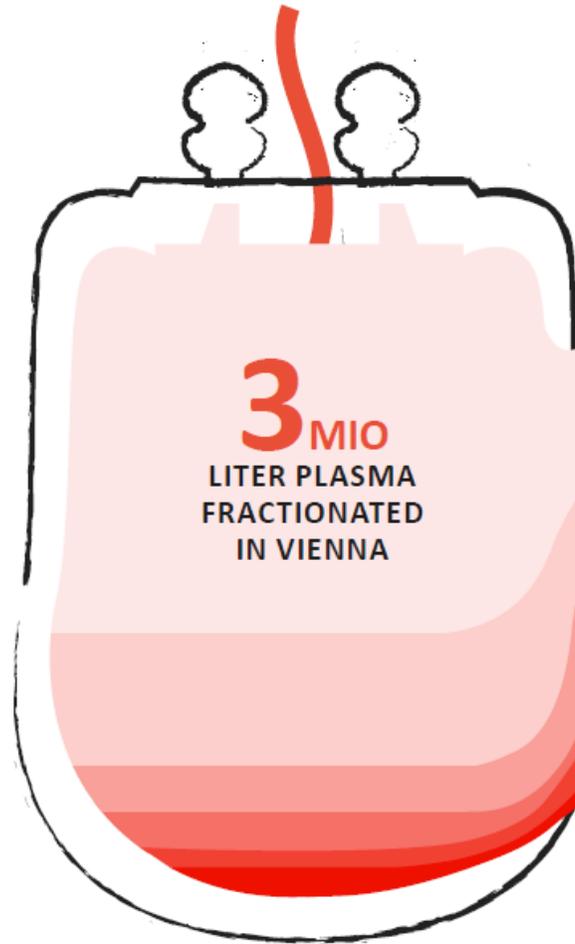
10 eigene Plasmaspendezentren in Österreich

Gesamte Wertschöpfungskette in Österreich

Forschung – Plasmaaufbringung – Plasmaverarbeitung – Verpackung – Versand in 100 Länder – Vertrieb in Österreich

Multi-Product Site Wien

17 Plasmaprodukte aus Wien



ALBUMIN

α 1-GLOBULIN PULMONOLOGY

α 2-GLOBULIN
COAGULATION FACTORS

α 2-GLOBULIN COAGULATION
INHIBITORS/INACTIVATORS

β -GLOBULIN
BIOLOGICAL TISSUE SEALANT

γ -GLOBULIN ANTIBODY
CONCENTRATES

TAKEDA PLASMA-DERIVED PRODUCTS

PRODUCED
IN VIENNA

Flexbumin

Human Albumin

Aralast

Glassia

Hemofil M

Immunate

Immunine

Feiba

Prothromplex, Bebulin

Prothromplex T

Factor VII

Cinryze

ATIII Antithrombin

Ceprothin

Artiss

Tisseel

Thrombin

BabyBIG

Hyqvia

Cuvitru

Gammagard Liquid/Kiovig

Gammagard SD

X

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X

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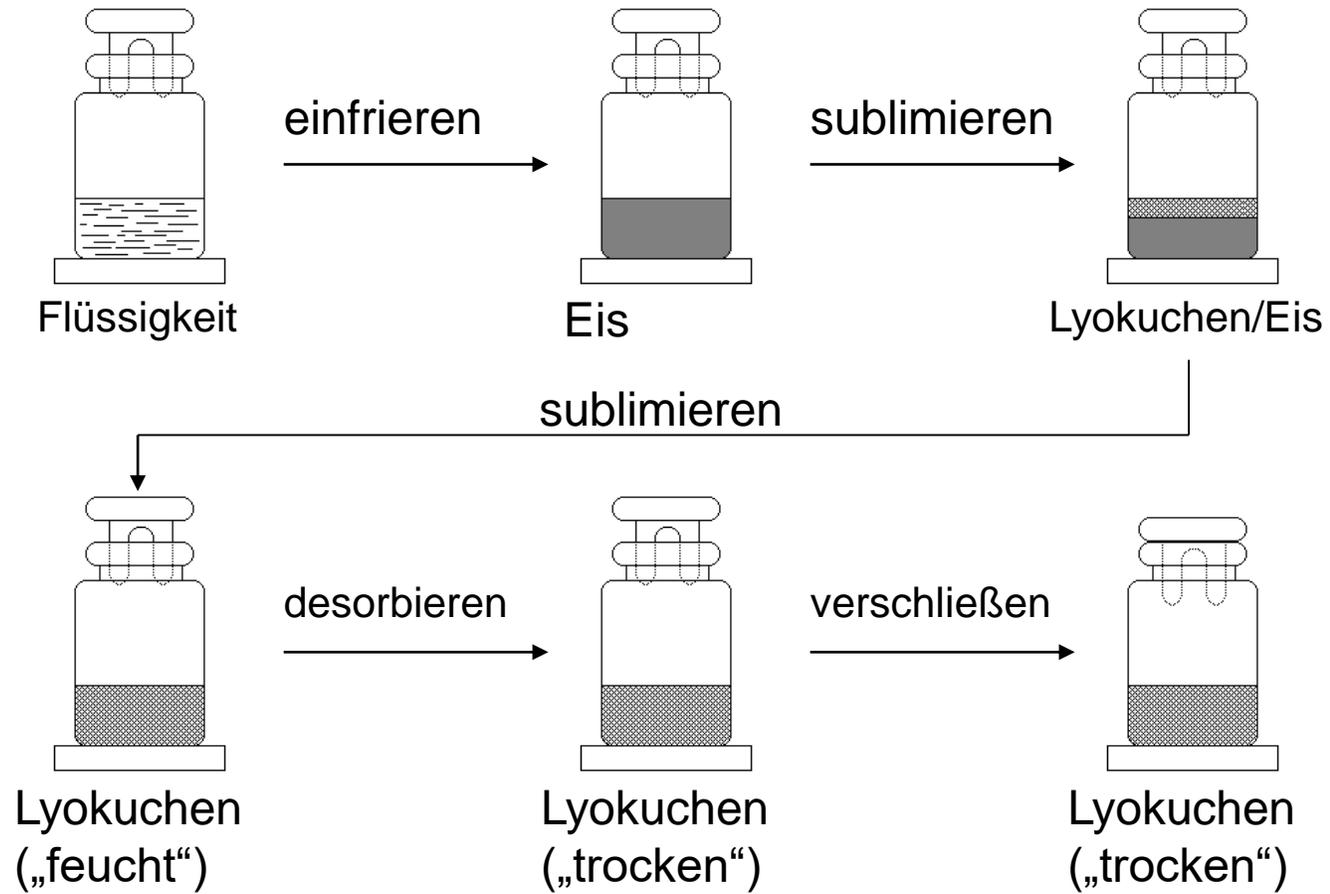
X

17 products made in Vienna and shipped in over 100 countries.

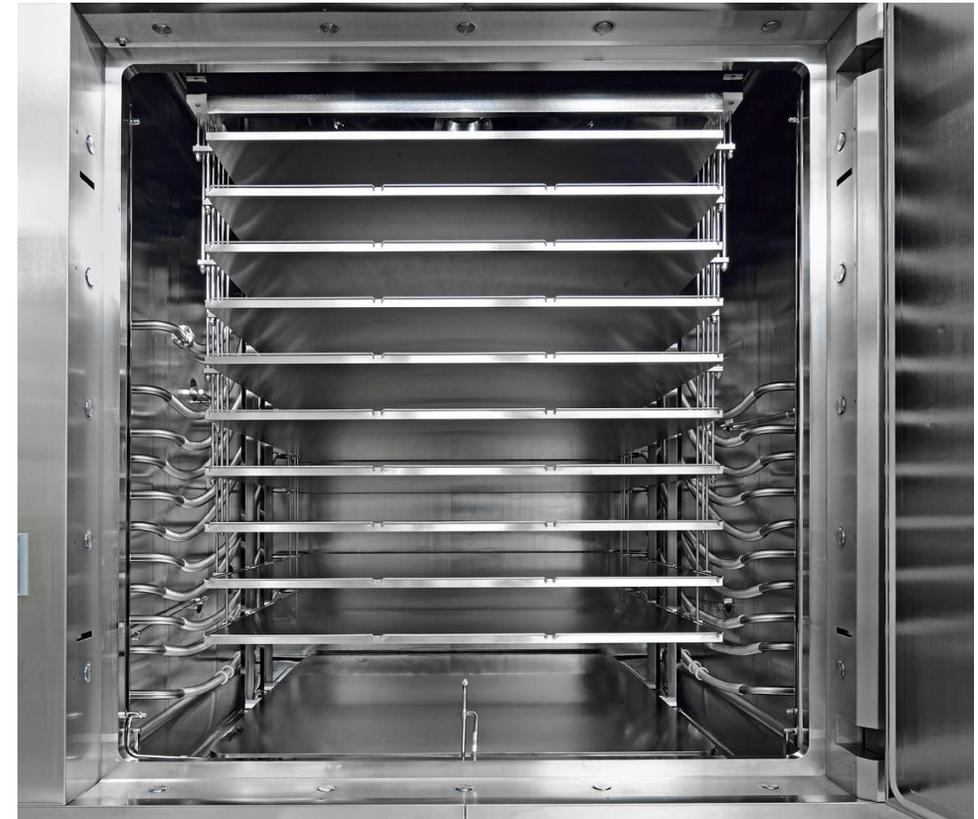
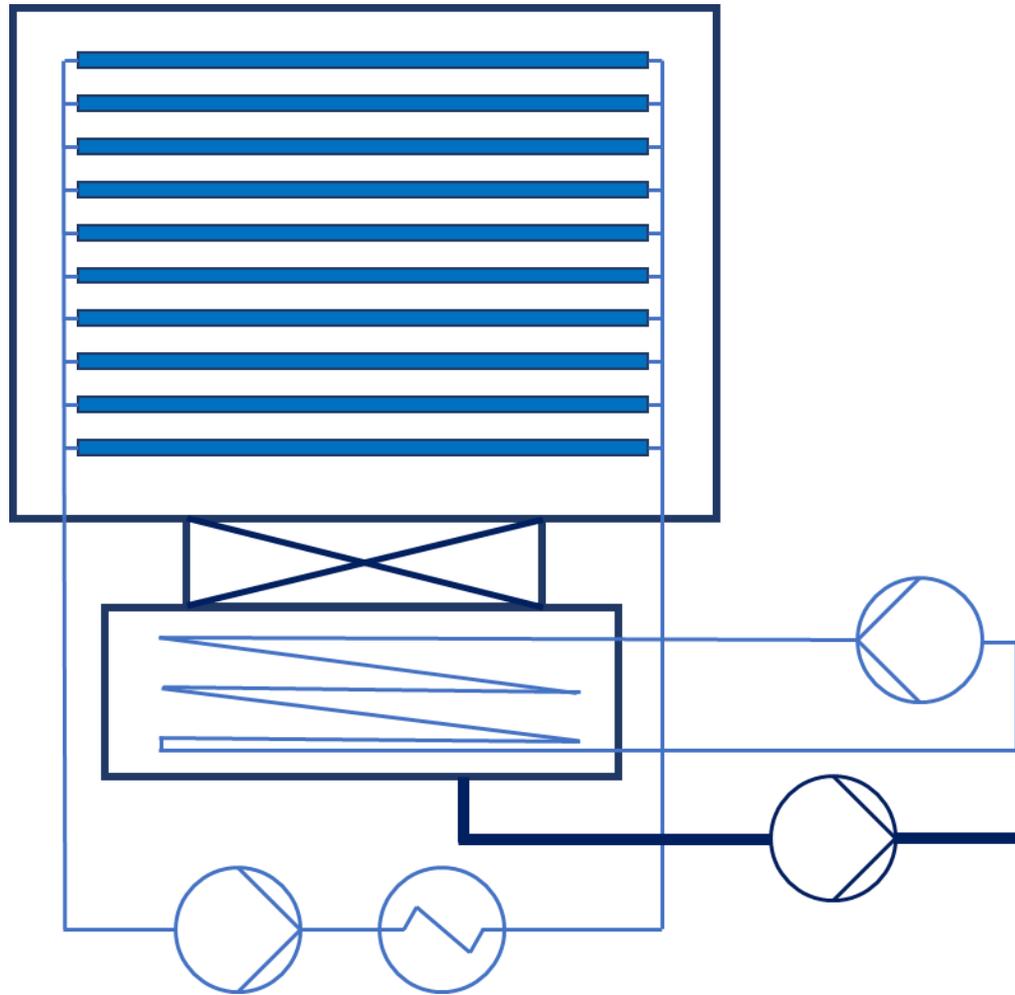
„**Lyophilization** is defined as a **stabilizing process** in which the **substance** is first **frozen** and then the quantity of the **solvent** is **reduced** first by sublimation (primary drying) and then by desorption (secondary drying) to values that will **no** longer support **biological growth** or **chemical reactions**.“

Thomas A. Jennings, Lyophilization

Vorgänge im Produkt

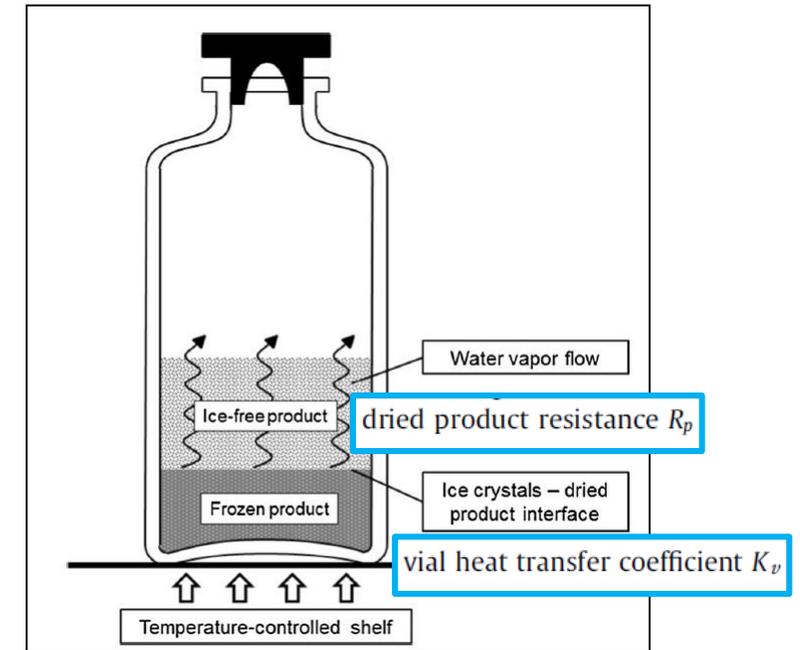
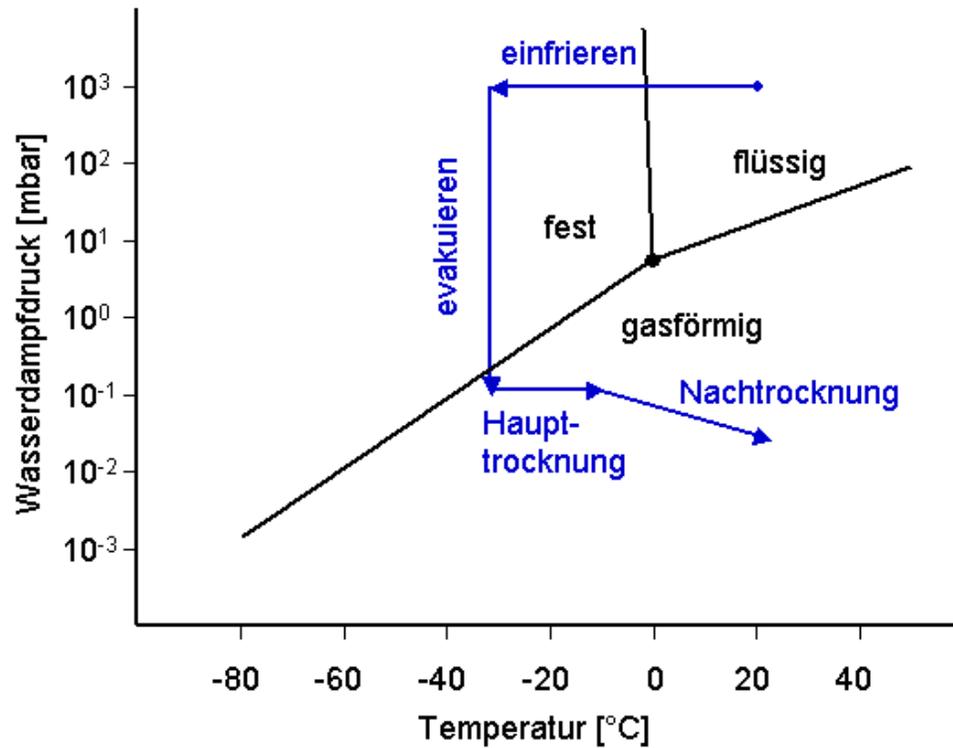


Gefriertrocknung konventionell



<http://www.hof-pruefsysteme.de/en/communication/important-downloads/news-archive/article/hof-sonderanlagenbau-geht-zu-den-top-100.html>

Physik der Gefriertrocknung



T_c collapse temperature (maximum allowable product temperature during primary drying)

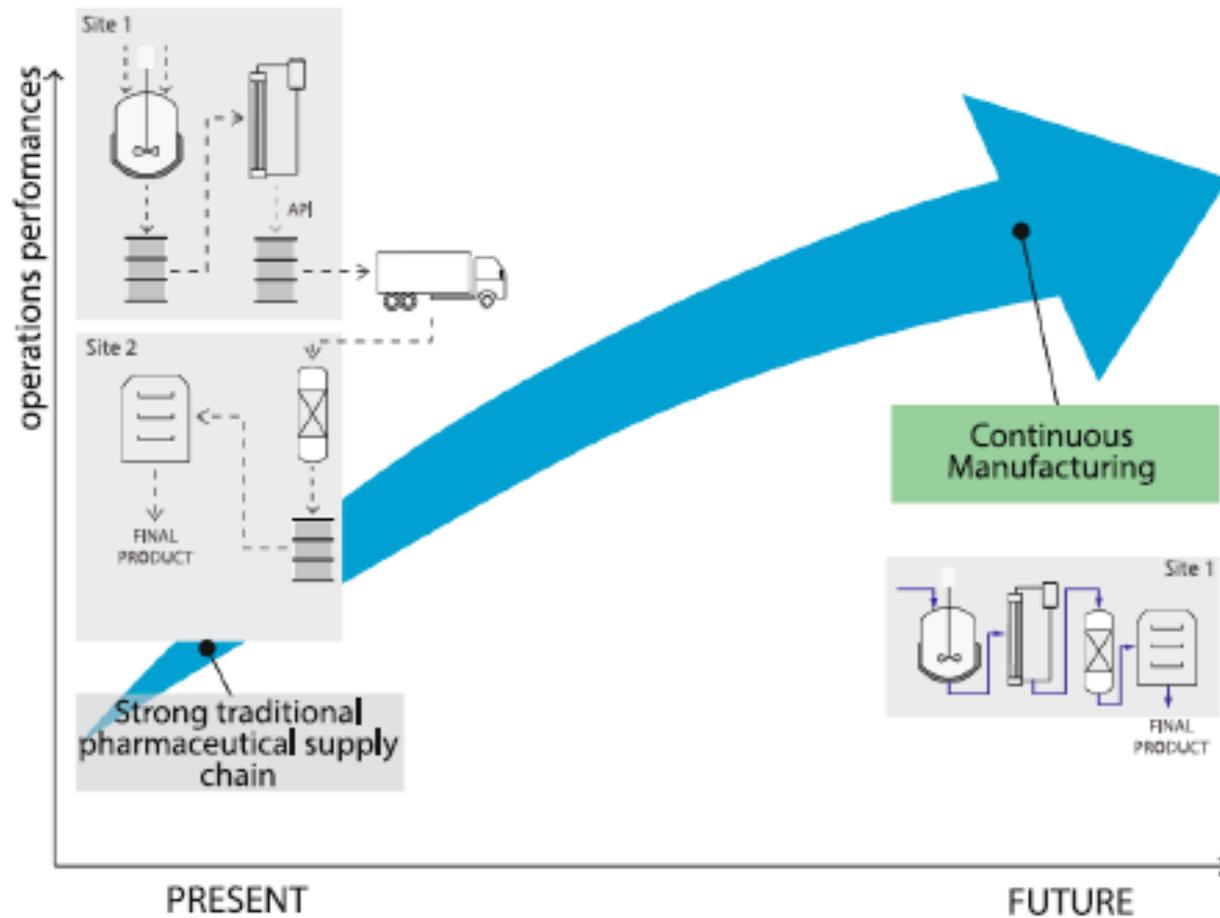
Uncertainty analysis as essential step in the establishment of the dynamic Design Space of primary drying during freeze-drying



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Warum kontinuierlich



- Flexibilität
- Scale-up weniger komplex
- Real-time Analyse
- Geringerer Platzbedarf

Achieving continuous manufacturing in lyophilization: Technologies and approaches

Roberto Pisano^{a,*}, Andrea Arsiccio^a, Luigi C. Capozzi^a, Bernhardt L. Trout^b

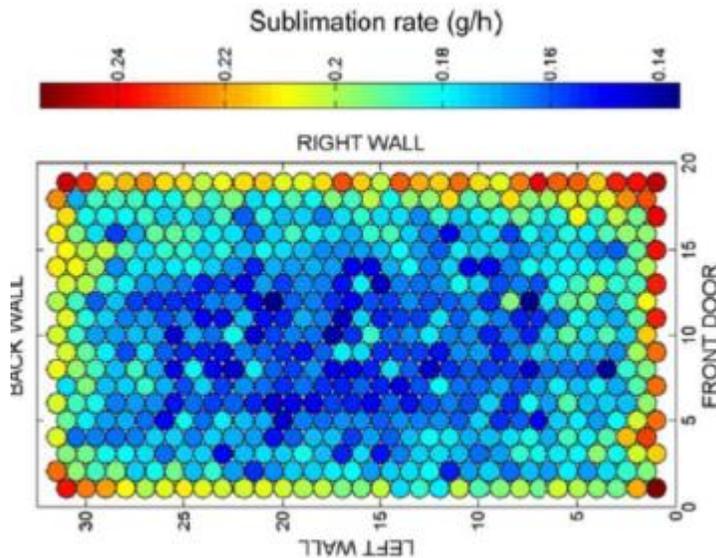
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Von Batchprozessen zu kontinuierlichen Prozessen

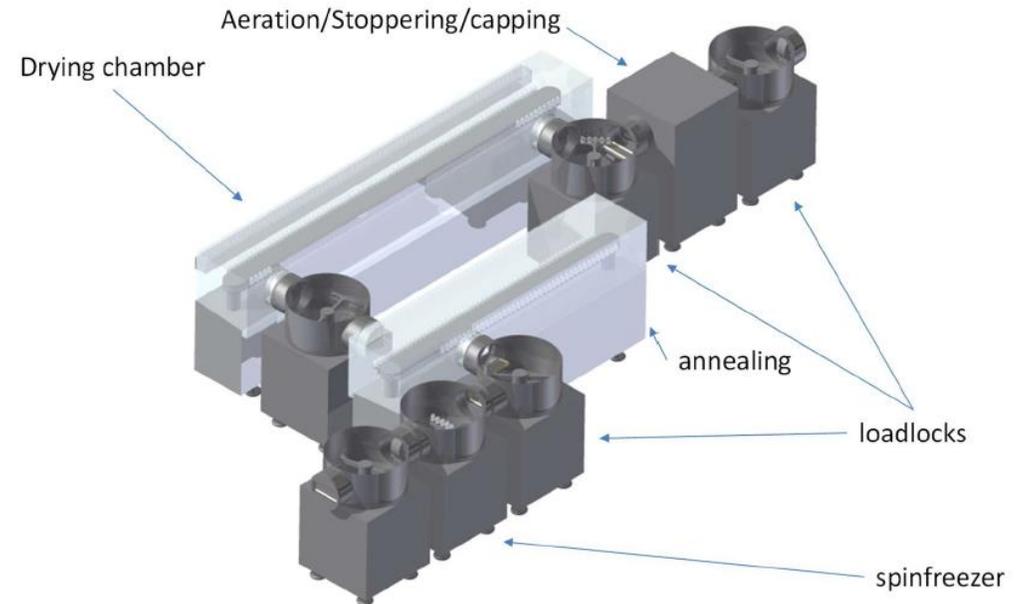
Gefriertrocknung im Batchverfahren

- Inhomogene Eisnukleation
- Inhomogenes Trocknungsverhalten
- Transfer und Scale-Up herausfordernd
- Lange Prozesszeiten



Kontinuierliche Gefriertrocknung

- Homogene Eisnukleation
- 100% Kontrolle über JEDES Vial
- Einfacher Transfer und Scale-Up (Out)
- Kurze Prozesszeiten

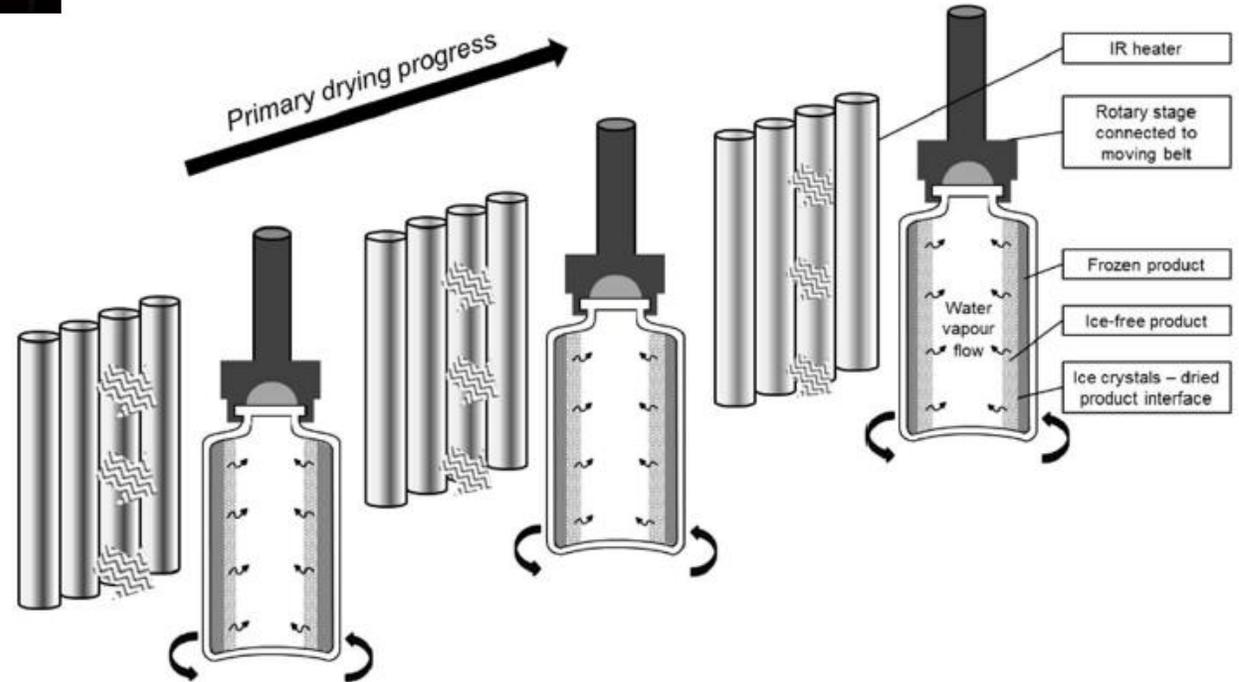
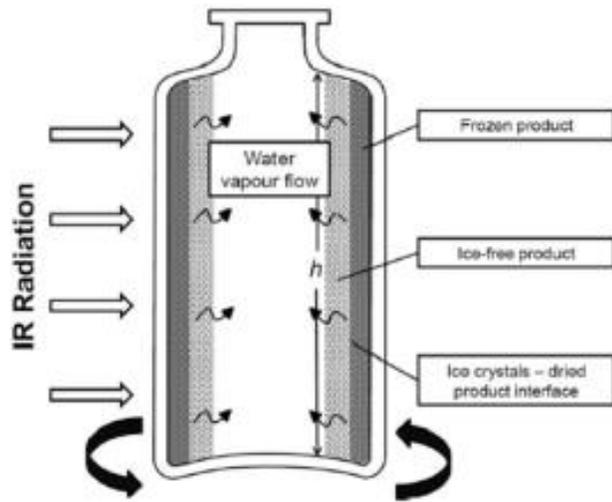
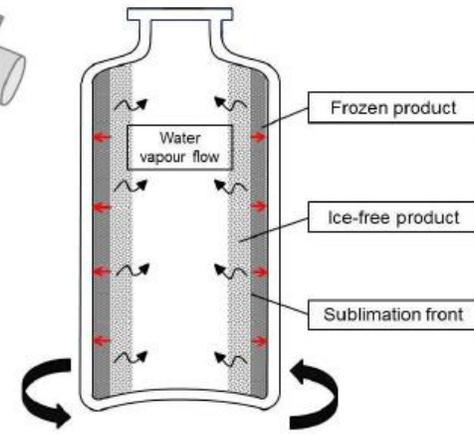
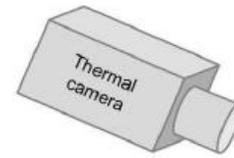


Gefriertrocknung kontinuierlich

Spin-freezing



Drying



Der Plasma Fraktionierungsprozess

The plasma fractionation process is based on the method of
Cohn *et al.* 1940's

Plasma



5 Parameter system

- pH
- Temperature
- Ethanol concentration
- Conductivity
- Protein concentration

Separation methods

- Centrifugation
- Filtration



Edwin Joseph
Cohn, Ph. D.
© 2002 The Educational
Broadcasting Corporation.

Das 5 Parameter System der Ethanol Fraktionierung

EtOH Konzentration:

Im Cohn Fraktionierungsschema zwischen 0 und 40%.

Durch Dehydratisierung werden Proteine unlöslich und präzipitieren in der EtOH – Wasser – Mischung.

pH:

Proteine präzipitieren leichter am Isoelektrischen Punkt, jenem pH Wert einer Lösung an dem die Primärladung eines Proteins Null ist.

Temperatur:

Muss zwischen 0 und -10°C gehalten werden, um Denaturierung zu verhindern.

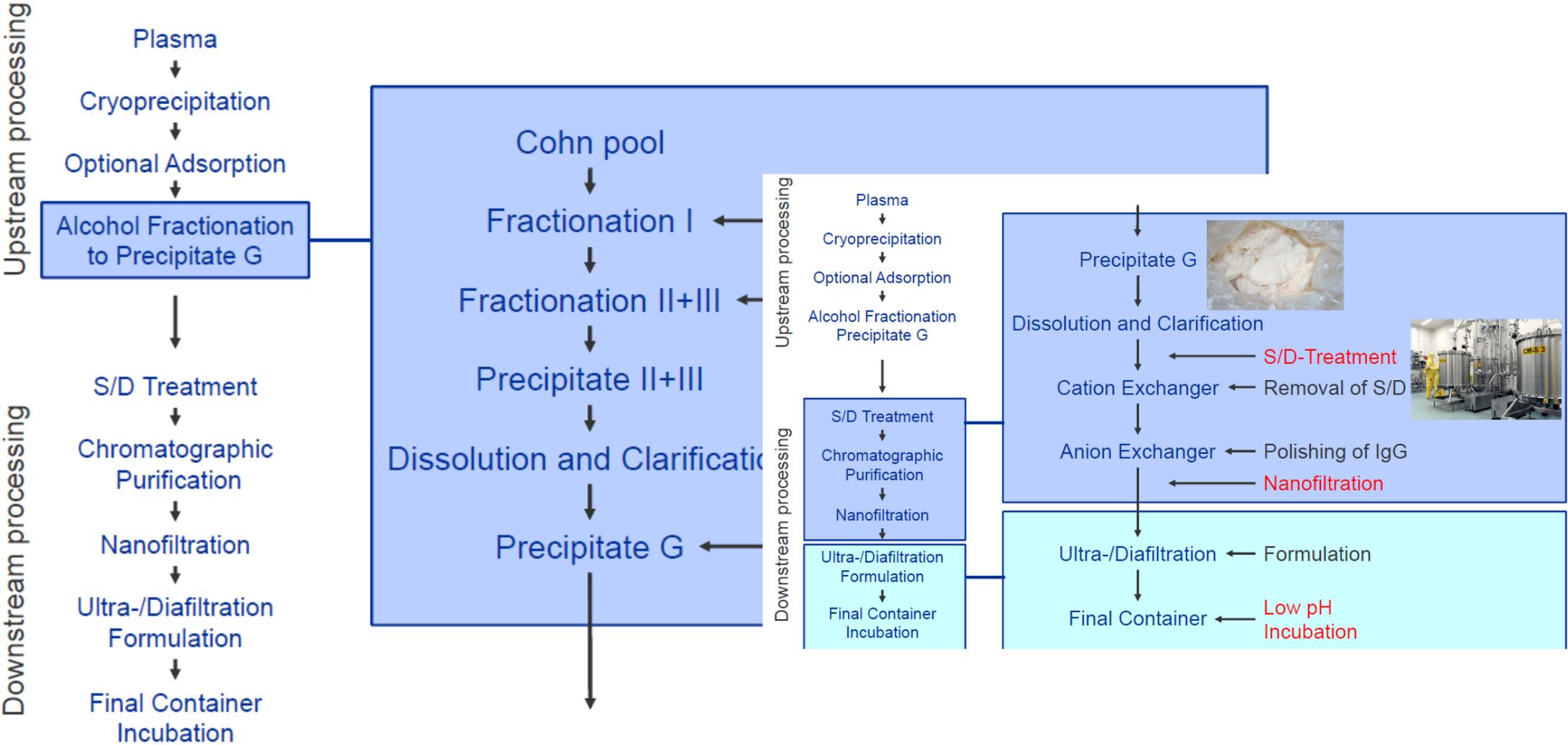
Protein Konzentration:

Je höher die Konzentration desto besser die Präzipitation.

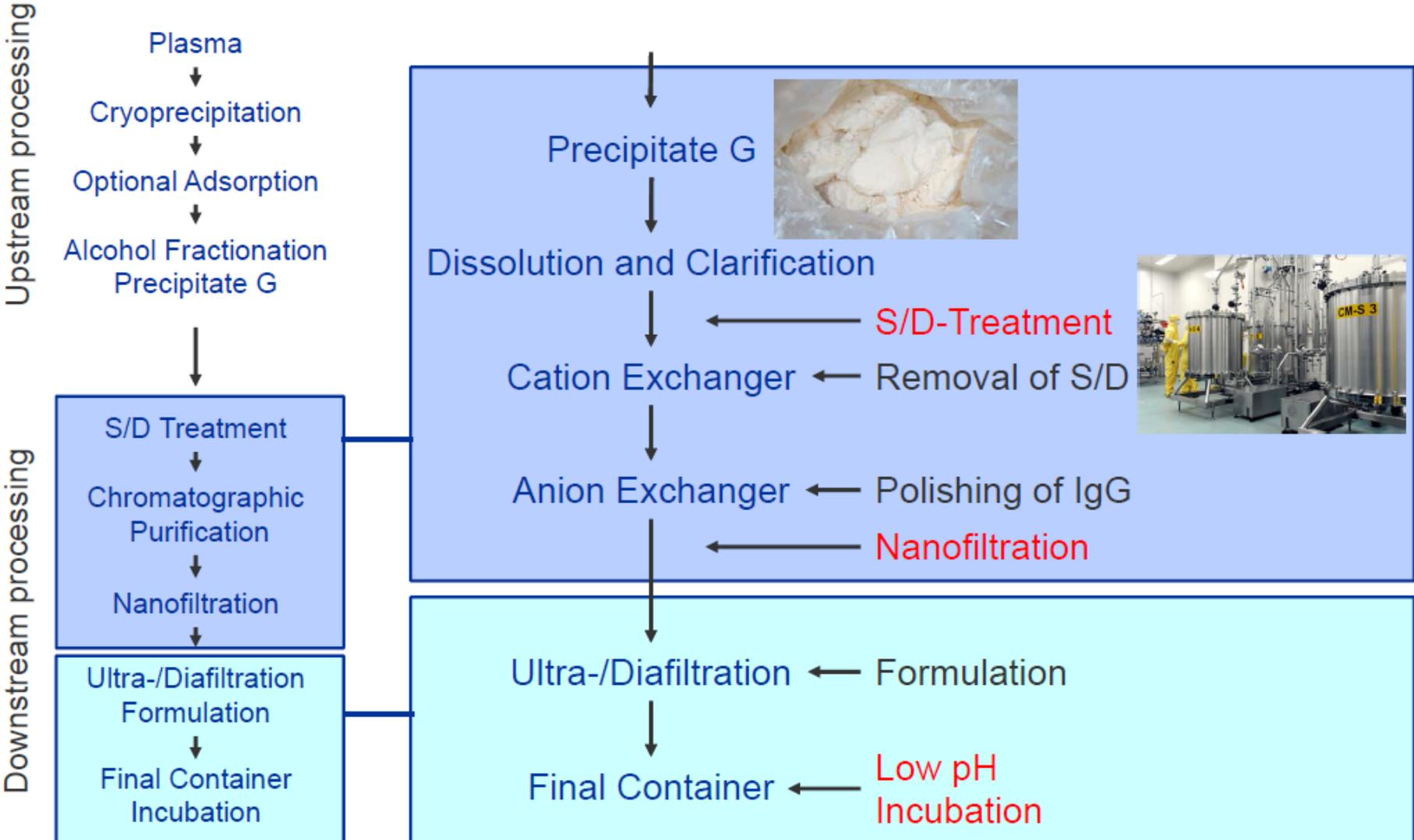
Leitfähigkeit:

Beinflusst die Löslichkeit der Proteine

Ethanol Fraktionierung



Downstream - Purification



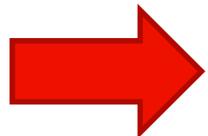
Wirkstoff aus Plasma ohne Ethanol Fraktionierung durch Direct Capture

Approach

- Capture IgG out of Plasma, Cryo Poor Plasma or Cohn Pool
- Utilize commercially available affinity resins
- Major challenge: column load, impurities, conditions

Results

- 80% footprint reduction with Direct Capture
- Direct Capture IgG subclass distribution comparable to standard distribution
- Process intensification to optimize performance and to reduce process steps
- Equipment investment and run costs significantly lower due to downsizing



process based on direct capture promising for emerging market and fast to clinic scenarios

Beispiel: Direct Capture für e.g. IgG

Process Development

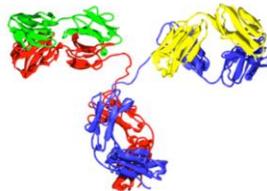
PoC

Scale Up (Piloting)

Ready
for
GMP

Approach Prozessentwicklung:

- Auswahl des geeignetsten Ausgangsmaterials
- Feasibility study
- Proof of concept study
- Scale up / Piloting
- Industrialization



Plasma intermediate
Starting Material

Affinity Chroma

Polishing

Nanofiltration

Ultrafiltration

Drug Substance



Vielen Dank!



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