



# Das Beste herausholen – innovative Lösungen in der biopharmazeutischen Produktion

26. September 2019

Michael Dekner

Head of PS FFF

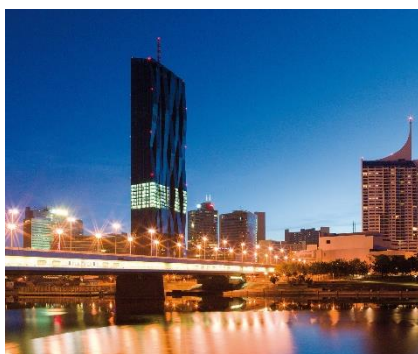


Better Health, Brighter Future



# Takeda Austria

Top employer in the Austrian biopharmaceutical industry





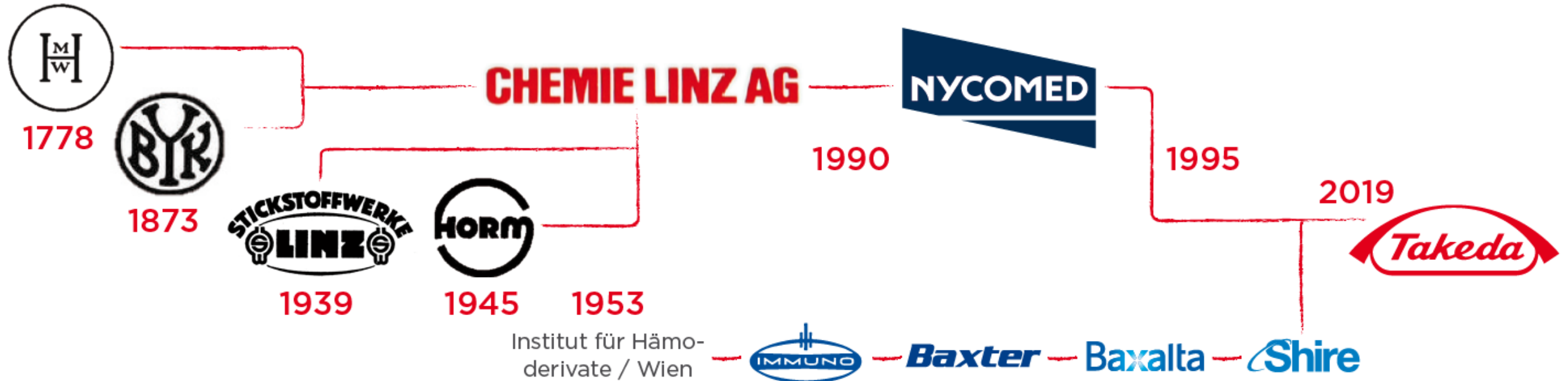
# We have an innovative and maturing pipeline

	PHASE 1	PHASE 2	PHASE 3/FILED	APPROVED*
<b>ONCOLOGY</b>	<p><b>TAK-981</b> SAMD Inhibitor Multiple cancers</p> <p><b>TAK-164</b> ImmunoGen G1C, S1N, AOC S1, S10A</p> <p><b>TAK-573</b> Trop A1C, C10B, S10A, S10B, S10C, S10D, S10E, S10F, S10G, S10H, S10I, S10J, S10K, S10L, S10M, S10N, S10O, S10P, S10Q, S10R, S10S, S10T, S10U, S10V, S10W, S10X, S10Y, S10Z</p> <p><b>TAK-788</b> N1P, N1Q Inhibitor NSCLC</p>	<p><b>TAK-228</b> (apanartib) mTORC1/2 Inhibitor Endometrial cancer</p> <p><b>TAK-659</b> S1P, R1, 2 Inhibitor DMCL, Solid Tumors</p> <p><b>TAK-931</b> A1C Inhibitor NSCLC, S10C, S10D, S10E, S10F, S10G, S10H, S10I, S10J, S10K, S10L, S10M, S10N, S10O, S10P, S10Q, S10R, S10S, S10T, S10U, S10V, S10W, S10X, S10Y, S10Z</p>	<p><b>relugolix</b> Muvion G1C, S1N, AOC Prostate Cancer (P) (Phase 1 in C)</p> <p><b>TAK-924</b> (pivonelestat) NA Inhibitor NS-MDS/CMML/3 AML</p>	<p><b>NINLARO*</b> Proton Pump Inhibitor Gastroesophageal Reflux Disease (GERD) Multiple Cancers (P)</p> <p><b>ADCRETIS*</b> Smad2/3 Inhibitor C10B, C10C S1, S10A, S10B, S10C, S10D, S10E, S10F, S10G, S10H, S10I, S10J, S10K, S10L, S10M, S10N, S10O, S10P, S10Q, S10R, S10S, S10T, S10U, S10V, S10W, S10X, S10Y, S10Z</p> <p><b>ICLUSIG*</b> BCR-ABL Inhibitor S1, Chronic Phase CM, P1+ ALL</p> <p><b>ALUNBRIG*</b> A1C Inhibitor S1, A1A, NSCLC, S1, A1A, NSCLC</p> <p><b>cabozantinib</b> V10P, V11L Inhibitor 2<sup>nd</sup> Line RCC, RCC (P)</p> <p><b>Niraparib</b> PARP Inhibitor Multiple Cancer (P)</p>
<b>GASTRO-ENTEROLOGY</b>	<p><b>TAK-671</b> Serotonin Receptor Inhibitor Acute Pancreatitis</p> <p><b>TAK-018</b> Disease Risk associated Crohn's Disease</p>	<p><b>Kuma052</b> PVP Biologic Multiple G1C, Disease</p> <p><b>TAK-906</b> G1C, G1D Inhibitor Gastroenteritis</p> <p><b>TAK-954</b> Thyroglobulin Inhibitor S1, H111, S10A, S10B, S10C, S10D, S10E, S10F, S10G, S10H, S10I, S10J, S10K, S10L, S10M, S10N, S10O, S10P, S10Q, S10R, S10S, S10T, S10U, S10V, S10W, S10X, S10Y, S10Z</p>	<p><b>TAK-721</b> (SHP21) S1C S1A</p> <p><b>TAK-647</b> (SHP47) NS-CAM-1 Inhibitor S1C</p>	<p><b>ENTYVIO*</b> mTOR Inhibitor NS-CAM-1 Inhibitor S1, S10A, S10B, S10C, S10D, S10E, S10F, S10G, S10H, S10I, S10J, S10K, S10L, S10M, S10N, S10O, S10P, S10Q, S10R, S10S, S10T, S10U, S10V, S10W, S10X, S10Y, S10Z</p> <p><b>Vonoprazan</b> K1A S10D, P1, partial resp. ASD</p> <p><b>ALOFSEL</b> Immunomodulator S1, stem cells Peritoneal Metastasis in CD</p> <p><b>GATTEK</b> (S1P-2) Adult S1C, pediatric G1C</p> <p><b>RESOLOR</b> proprionitrile CC (S1)</p>
<b>NEUROSCIENCE</b>	<p><b>TAK-653</b> M10K Inhibitor S1D</p> <p><b>MEDI-1341</b> A1C Inhibitor S1, S10A, S10B, S10C, S10D, S10E, S10F, S10G, S10H, S10I, S10J, S10K, S10L, S10M, S10N, S10O, S10P, S10Q, S10R, S10S, S10T, S10U, S10V, S10W, S10X, S10Y, S10Z</p> <p><b>WVE-120101</b> W10e mHTT S1P1, S10A Huntington's Disease</p>	<p><b>TAK-418</b> G1C Inhibitor S10A, S10B, S10C, S10D, S10E, S10F, S10G, S10H, S10I, S10J, S10K, S10L, S10M, S10N, S10O, S10P, S10Q, S10R, S10S, S10T, S10U, S10V, S10W, S10X, S10Y, S10Z</p> <p><b>TAK-925</b> Orphan Drug S10A, S10B, S10C, S10D, S10E, S10F, S10G, S10H, S10I, S10J, S10K, S10L, S10M, S10N, S10O, S10P, S10Q, S10R, S10S, S10T, S10U, S10V, S10W, S10X, S10Y, S10Z</p> <p><b>TAK-680</b> (SHP60) Hemolytic Conditions</p> <p><b>WVE-120102</b> W10e mHTT S1P1, S10A Huntington's Disease</p>	<p><b>TAK-935</b> Orphan Therapeutic Orphan Inhibitor Rare Pediatric Epilepsia</p> <p><b>TAK-831</b> DAAC Inhibitor Hemolytic, CNS HS</p>	<p><b>TRINTELLIX™</b> L10A, L10B Multimodal anti-depressant M10 (P)</p> <p><b>BUCCOLAM</b> S10A, S10B, S10C, S10D, S10E, S10F, S10G, S10H, S10I, S10J, S10K, S10L, S10M, S10N, S10O, S10P, S10Q, S10R, S10S, S10T, S10U, S10V, S10W, S10X, S10Y, S10Z</p> <p><b>MYDAYIS</b> A10D</p> <p><b>VYVANSE</b> A10D (P)</p>
<b>RARE DISEASES</b>	<p><b>TAK-611</b> (SHP611) S1C M10</p> <p><b>TAK-754</b> (SHP654) Gene Therapy Hemophilia</p>	<p><b>TAK-531</b> (SHP531) ERT Hunter CMG</p>	<p><b>TAK-607</b> (SHP607) S1C-1/2 Inhibitor Chronic Lung Disease</p> <p><b>TAK-609</b> (SHP609) Hemolytic (P)</p> <p><b>TAK-752</b> (SHP652) S1A</p>	<p><b>TAK-755</b> (SHP655) S1C/1/2 Inhibitor S1C/1/2 CTP</p> <p><b>TAK-620</b> (SHP620) Orphan Inhibitor S10A, S10B, S10C, S10D, S10E, S10F, S10G, S10H, S10I, S10J, S10K, S10L, S10M, S10N, S10O, S10P, S10Q, S10R, S10S, S10T, S10U, S10V, S10W, S10X, S10Y, S10Z</p> <p><b>FIRAZYR</b> S10A (P)</p> <p><b>VONVENDI</b> V10D</p> <p><b>TAKHZYRO</b> Anti-folate/m10A S10A prophylaxis (P)</p> <p><b>OBIZUR</b> Orphan Surgery</p> <p><b>NATPARA</b> Hypoparathyroidism (P)</p>
<b>PLASMA-DERIVED THERAPIES</b>				<p><b>HYQVIA</b> Protein P10, C1P</p> <p><b>CINRYZE</b> S1C S10A prophylaxis, S10A prophylaxis (P), protein S10A (S10), S10A</p>
<b>VACCINES</b>	<p><b>TAK-021</b> S10A Vaccine</p> <p><b>TAK-426</b> S10A Vaccine</p>	<p><b>TAK-195</b> G1C, S10A Foundation Inactivated Polio Vaccine</p> <p><b>TAK-214</b> S10A Vaccine</p>	<p><b>TAK-003</b> Design Vaccine</p>	
<b>OPHTHALMOLOGY</b>	<p><b>TAK-639</b> (SHP639) S10A</p>	<p><b>TAK-759</b> (SHP659) S10A</p>	<p><b>TAK-640</b> (SHP640) Inhibitor m10A, m10B</p>	<p><b>XIIDRA</b> S10A (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

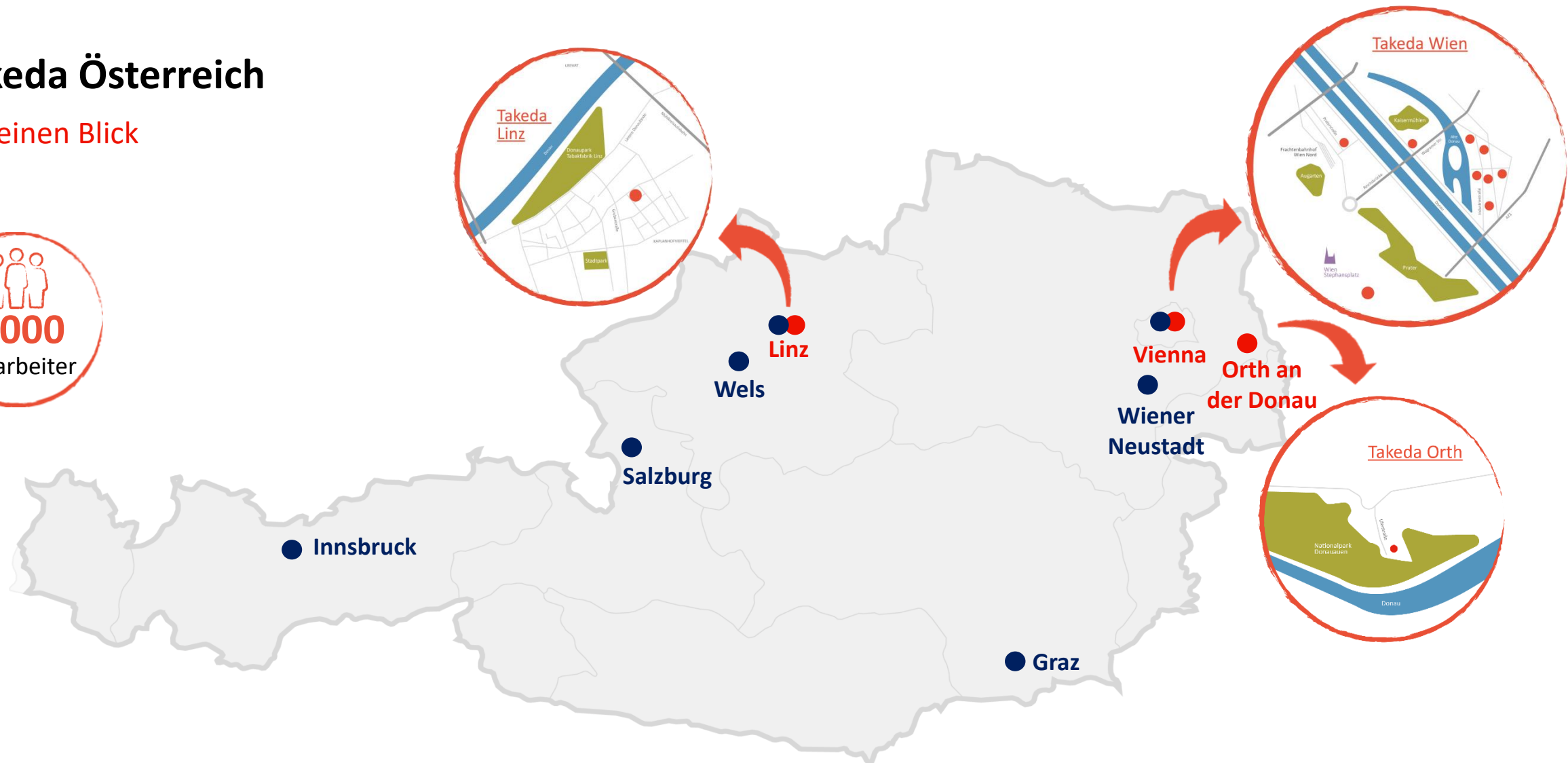




# Takeda Österreich

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



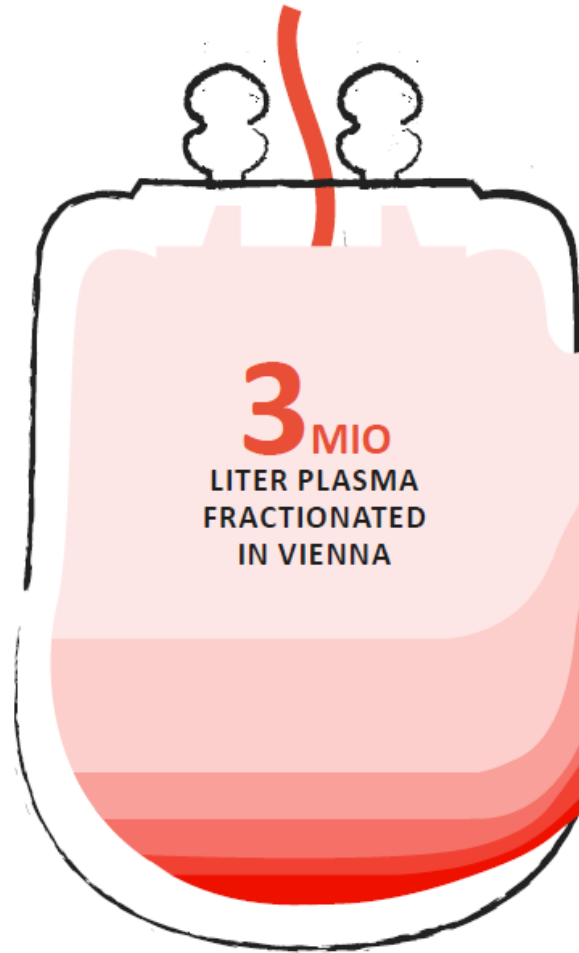
**10** eigene Plasmaspendezentren in Österreich

**Gesamte Wertschöpfungskette in Österreich**

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

# Multi-Product Site Wien

17 Plasmaprodukte aus Wien



**3** MIO  
LITER PLASMA  
FRACTIONATED  
IN VIENNA

ALBUMIN

$\alpha$ 1-GLOBULIN PULMONOLOGY

$\alpha$ 2-GLOBULIN  
COAGULATION FACTORS

$\alpha$ 2-GLOBULIN COAGULATION  
INHIBITORS/INACTIVATORS

$\beta$ -GLOBULIN  
BIOLOGICAL TISSUE SEALANT

$\gamma$ -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

X

X

X

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X

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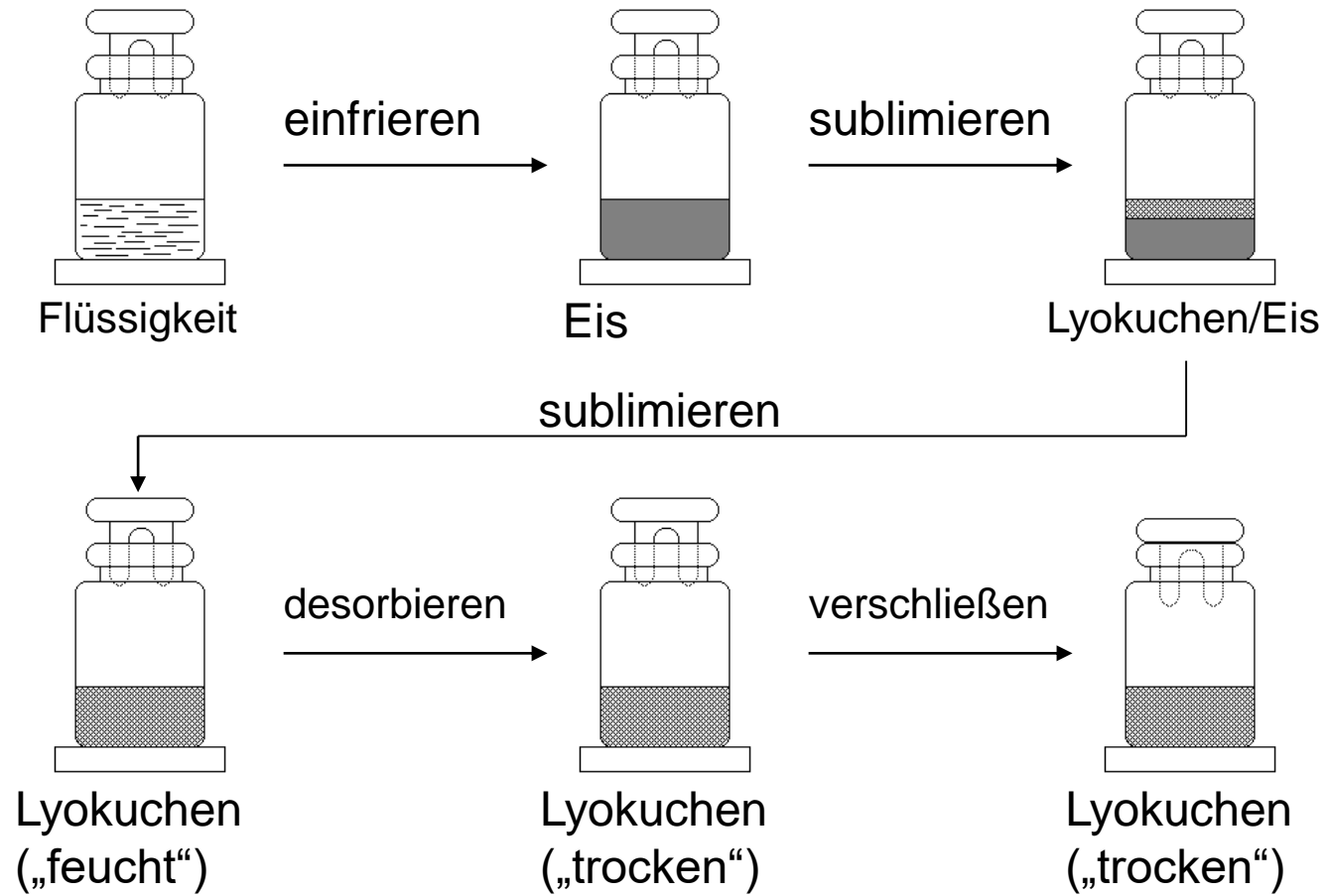
17 products made in Vienna and shipped in over 100 countries.

„**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**.“

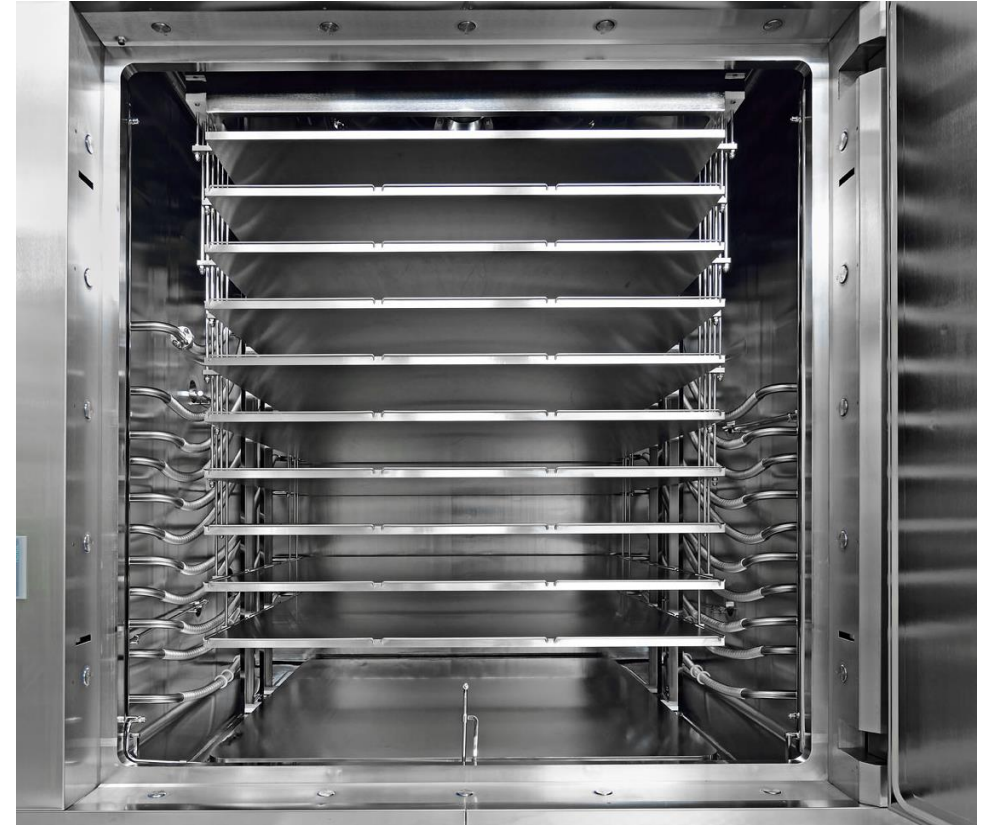
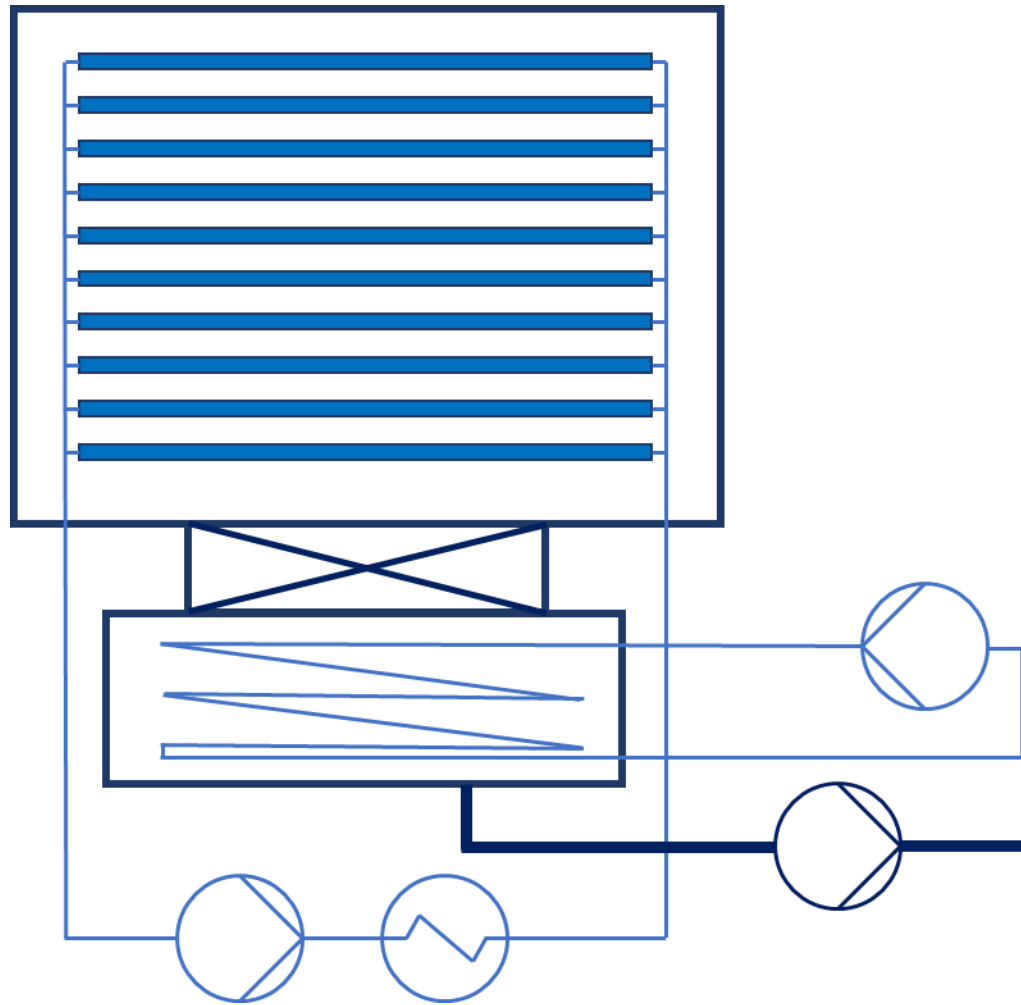
Thomas A. Jennings, Lyophilization



# Vorgänge im Produkt

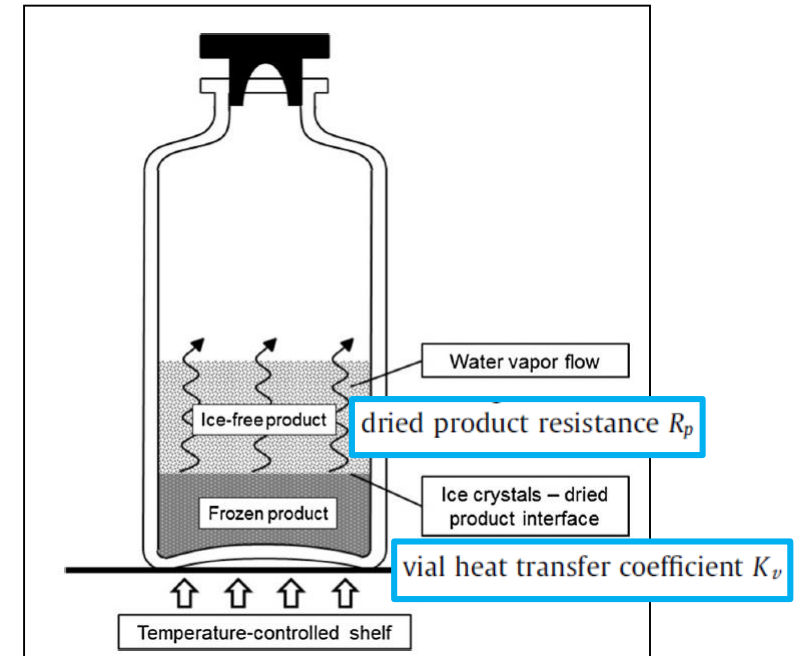
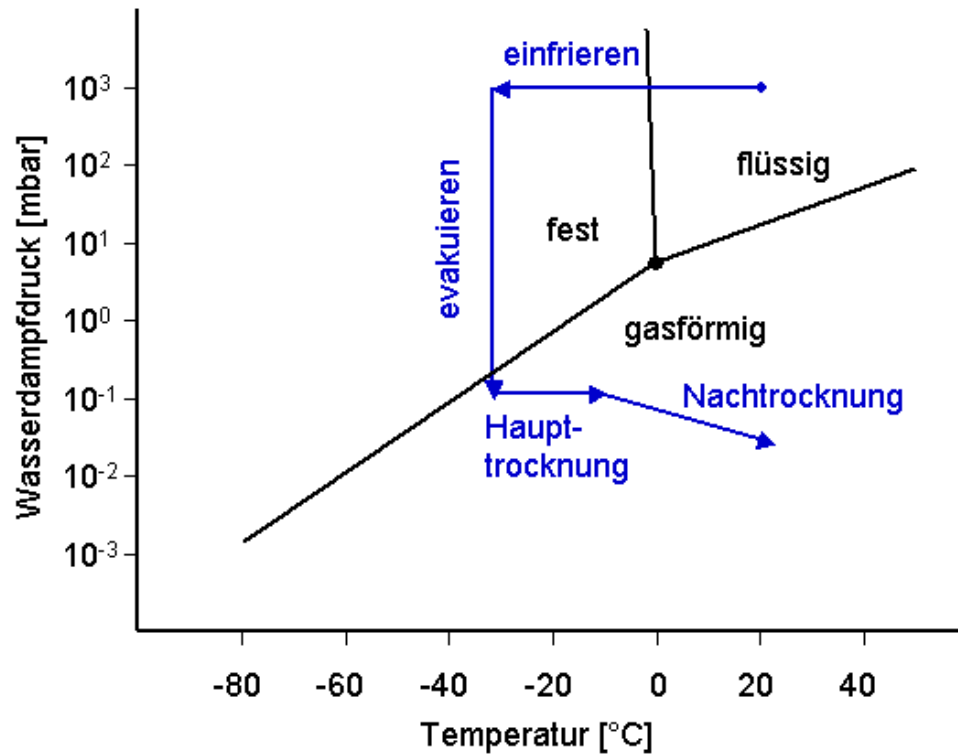


# Gefriertrocknung konventionell



<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



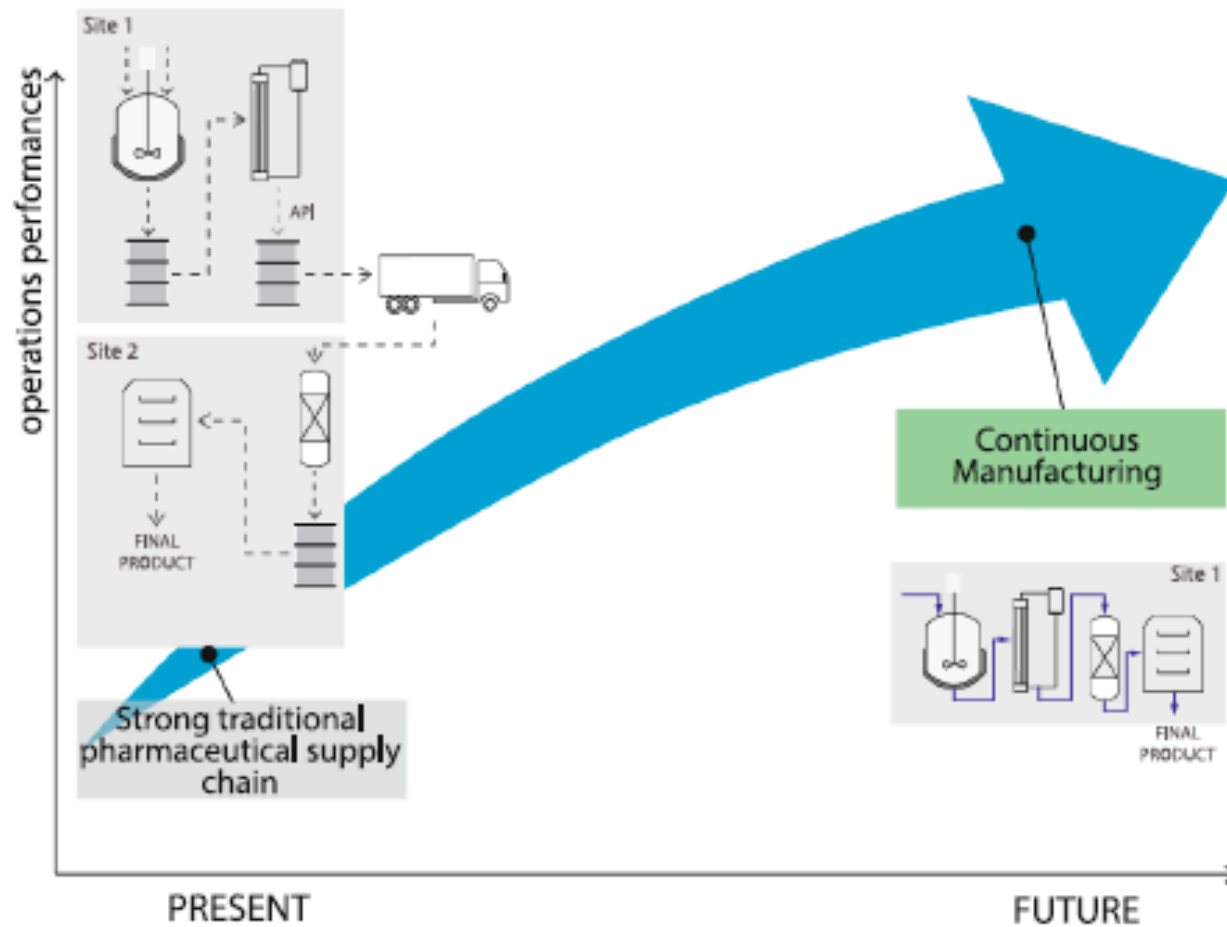
Séverine Thérèse F.C. Mortier<sup>a,b</sup>, Pieter-Jan Van Bockstal<sup>b</sup>, Jos Corver<sup>b</sup>, Ingmar Nopens<sup>a</sup>, Krist V. Gernaey<sup>c</sup>, Thomas De Beer<sup>b,\*</sup>

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<sup>c</sup>CAPEC-PROCESS Research Center, Department of Chemical and Biochemical Engineering, Technical University of Denmark, Building 229, 2800 Kgs. Lyngby, Denmark





# Warum kontinuierlich



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

Achieving continuous manufacturing in lyophilization: Technologies and approaches

Roberto Pisano<sup>a,\*</sup>, Andrea Arsiccio<sup>a</sup>, Luigi C. Capozzi<sup>a</sup>, Bernhardt L. Trout<sup>b</sup>

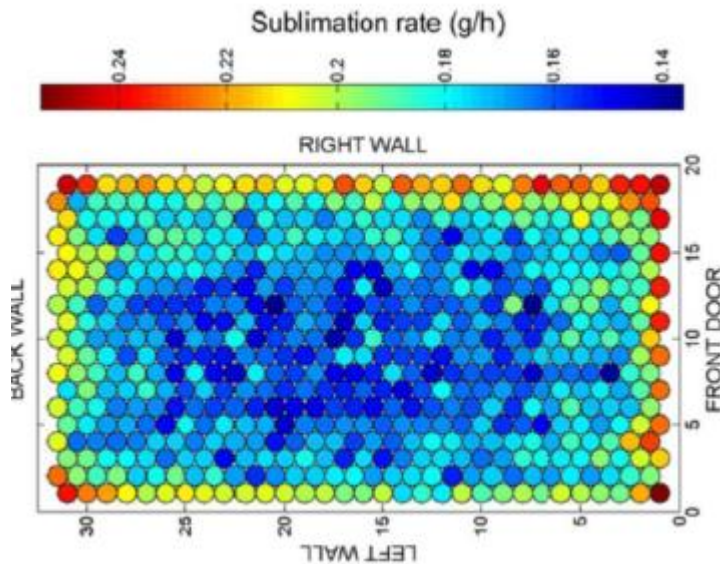
<sup>a</sup> Department of Applied Science and Technology, Politecnico di Torino, Torino 10129, Italy

<sup>b</sup> Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge, MA 02139, United States

# Von Batchprozessen zu kontinuierlichen Prozessen

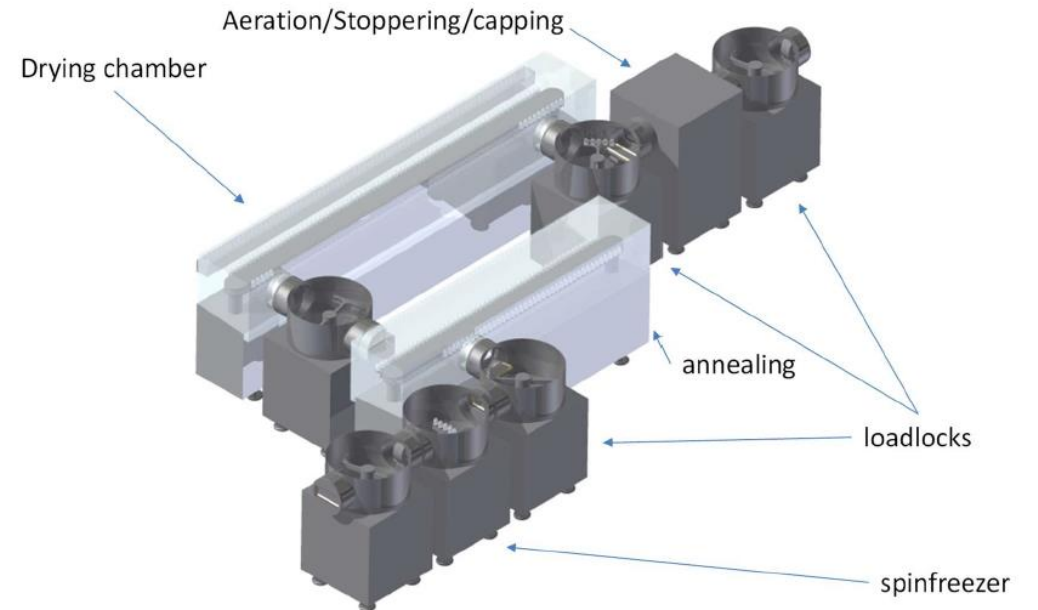
## Gefriertrocknung im Batchverfahren

- 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

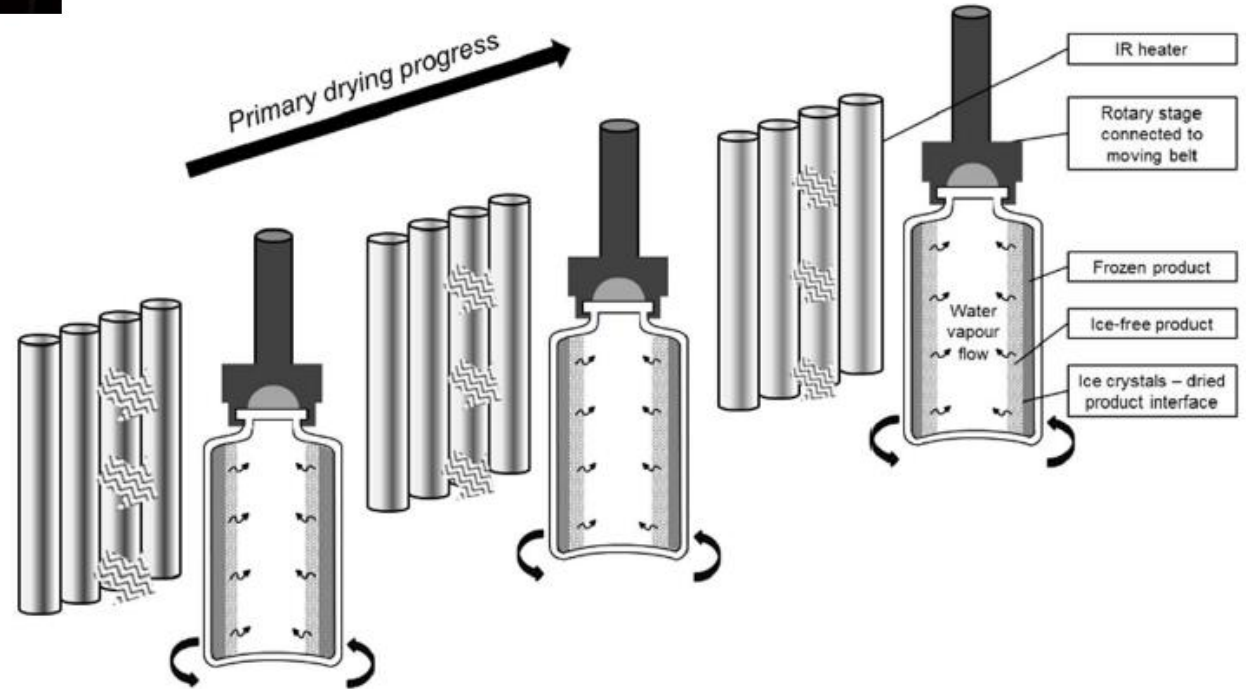
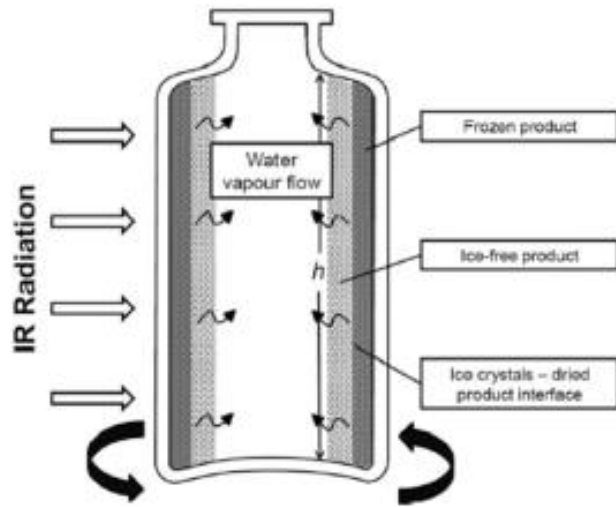
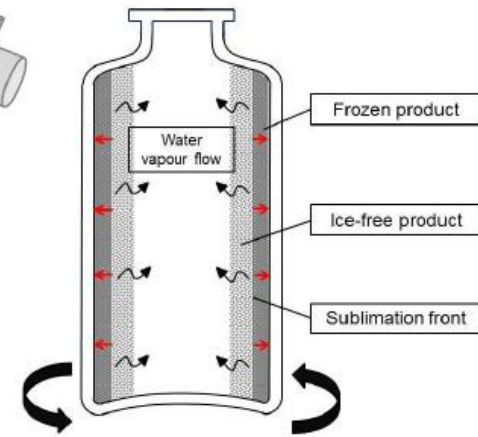
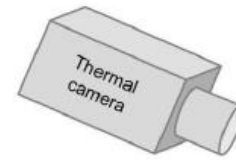


# Gefriertrocknung kontinuierlich

Spin-freezing



Drying





# Der Plasma Fraktionierungsprozess

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

## Plasma



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

## 5 Parameter system

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

## Separation methods

- Centrifugation
- Filtration



# 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.

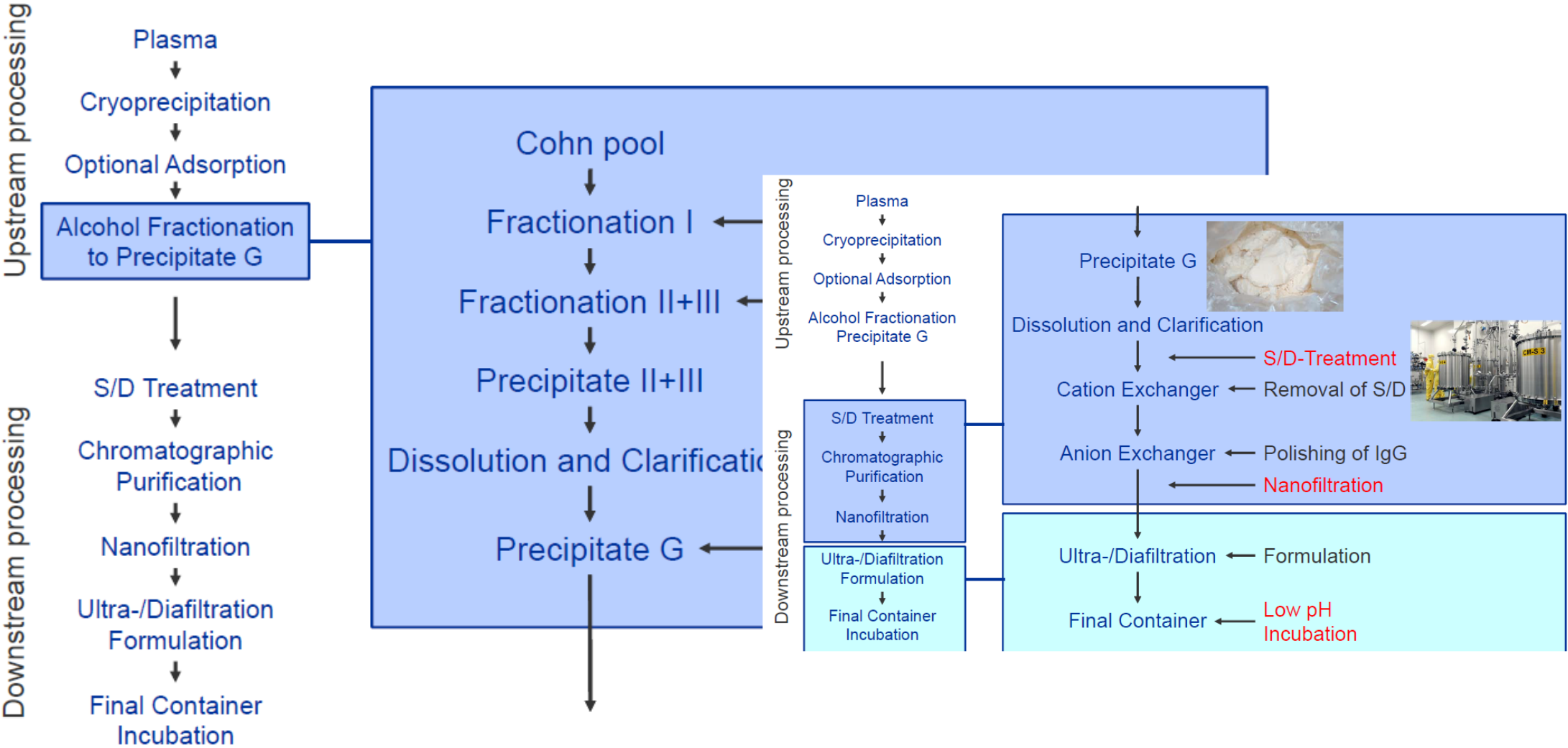
## **Protein Konzentration:**

Je höher die Konzentration desto besser die Präzipitation.

## **Leitfähigkeit:**

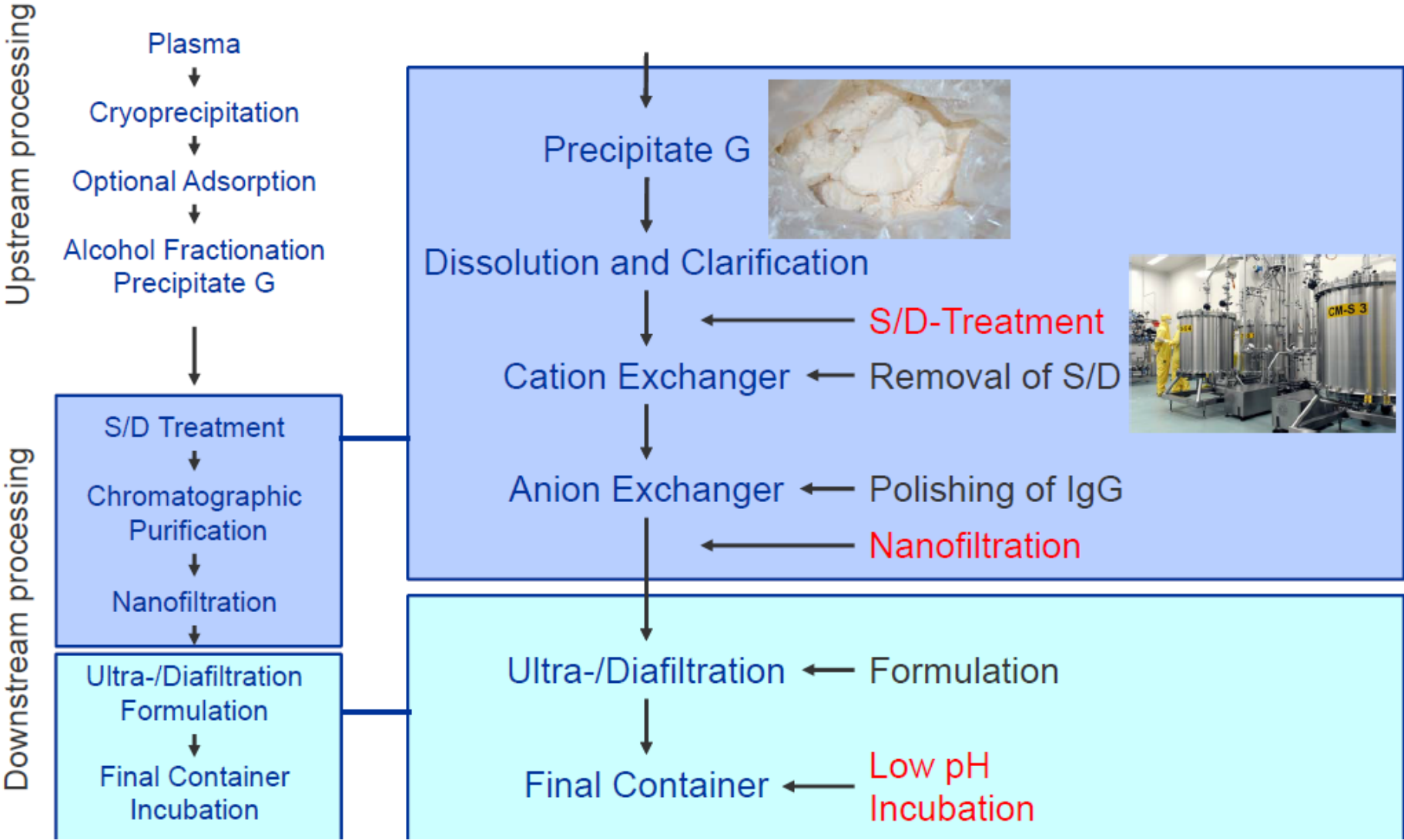
Beinflusst die Löslichkeit der Proteine

# Ethanol Fraktionierung





# Downstream - Purification



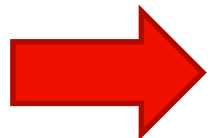
# Wirkstoff aus Plasma ohne Ethanol Fraktionierung durch Direct Capture

## 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

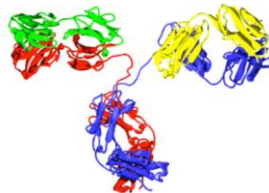
PoC

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!



Michael Dekner

Head of PS FFF

[michael.dekner@takeda.com](mailto:michael.dekner@takeda.com)