Uniquely Venofer®
Introduction 2nd day

Targeted iron therapy.
Our NBCD mission

Create and globally introduce appropriate science based approval and post approval standards for non biological complex drugs to ensure patient safety and benefit
NBCD Strategic Framework

Scientific Evidence

Establish strong scientific evidence to understand and support position

Awareness

Create awareness for NBCD:
• Not all iron are same
• Iron products are non biological complex drugs
• Iron products require appropriate regulatory pathways

Approval Standard

Ensure appropriate regulatory approval standards are applied

Risk Management

Establish mechanisms to track specific IS brands post approval
Evidence: BINIR research program in regulatory science

Characterization of complex

- Differentiation to other iv iron complexes and ISS
- Strengthen scientific base for new Pharmacopoeia monographs

Interaction with RES

- Provide further mechanistic data (uptake) supporting the difference of iron products
- Provide mechanistic understanding to optimize future drug design

Collaboration with experts

- Strengthen KOL network in regulatory science
NBCD Strategic Framework

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- Establish strong scientific evidence to understand and support position

**Awareness**
- Create awareness for NBCD:
  - Not all iron are same
  - Iron products are non biological complex drugs
  - Iron products require appropriate regulatory pathways

**Approval Standard**
- Ensure appropriate regulatory approval standards are applied
- Ensure appropriate drug evaluation standards are applied

**Risk Management**
- Establish mechanisms to track specific IS brands post approval

Healthcare Authorities
Industry
Hospital Pharmacists
Physicians
## Awareness program for NBCD Multichannel concept targeting key stakeholders

<table>
<thead>
<tr>
<th>Healthcare Authorities</th>
<th>Physicians</th>
<th>Hospital Pharmacists</th>
<th>Industry</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Scientific conferences</strong></td>
<td><strong>CME</strong></td>
<td><strong>Publications</strong></td>
<td><strong>Social media</strong></td>
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<tr>
<td>• Joint symposia with FDA and EMA members</td>
<td>• Meeting reports</td>
<td>• Reviews</td>
<td>• AAPS Blog</td>
</tr>
<tr>
<td></td>
<td>• Presentations at ASEAN Group</td>
<td>• Reviews</td>
<td>• GaBI editorial section</td>
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<td></td>
<td>• Clinical studies</td>
<td>• Wikipedia</td>
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<tr>
<td><strong>Hospital Pharmacists</strong></td>
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<tr>
<td>• ASHP (US)</td>
<td>• Reviews</td>
<td>• Clinical studies</td>
<td>• AAPS Blog</td>
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<tr>
<td>• EAHP (EU)</td>
<td>• Clinical studies</td>
<td>• Non clinical data</td>
<td>• GaBI editorial section</td>
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<td>• ESCP (EU)</td>
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<td><strong>Industry</strong></td>
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<tr>
<td>• Presentations in regulatory science conferences</td>
<td>• Reviews</td>
<td>• Clinical studies</td>
<td>• AAPS Blog</td>
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<td>• Non clinical data</td>
<td>• GaBI editorial section</td>
</tr>
<tr>
<td></td>
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<td>• Wikipedia</td>
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</table>

**Key Interaction Strategies**

- Joint symposia with FDA and EMA members
- Presentations at ASEAN Group
- ASHP (US), EAHP (EU), ESCP (EU)
- ISS slide deck
- Targeted campaign
- AAPS Blog
- GaBI editorial section
- Wikipedia
- NBCD working group meetings
- Pharmacopoeia
- BINIR research program
- Workshops and roundtables
<table>
<thead>
<tr>
<th>Conference</th>
<th>Date</th>
<th>Venue</th>
<th>Target Audience</th>
<th>Format</th>
<th>Status</th>
<th>Project lead</th>
<th>Vifor responsible</th>
<th>Vifor presence</th>
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<td>EAHP</td>
<td>16-18 Mar. 2016</td>
<td>Vienna</td>
<td>Global Pharmacists</td>
<td>Pharmacists Advisory Board</td>
<td>Done</td>
<td>SM</td>
<td>SM</td>
<td>SM BF JK</td>
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<tr>
<td>FCPF</td>
<td>7-8 May 2016</td>
<td>Beijing</td>
<td>Pharmacists</td>
<td>Lecture and roundtable</td>
<td>Done</td>
<td>Wu Yunpeng</td>
<td>BF</td>
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<tr>
<td>ASEAN PPWG</td>
<td>18 May 2016</td>
<td>Siem Reap</td>
<td>ASEAN Regulatory authorities half day workshop</td>
<td>Done</td>
<td></td>
<td>GaBI</td>
<td>BF</td>
<td>BF SM</td>
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<tr>
<td>CLINAM</td>
<td>26-29 Jun. 2016</td>
<td>Basel</td>
<td>Regulators / Nanomedicine scientific community</td>
<td>3 h session SC meeting</td>
<td>Done</td>
<td>JdV</td>
<td>BF</td>
<td>BF SM</td>
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<tr>
<td>GSRS</td>
<td>7-9 Sep. 2016</td>
<td>Rockville Maryland</td>
<td>Regulators</td>
<td>KOL interaction</td>
<td>Done</td>
<td>BF</td>
<td>BF</td>
<td>BF SM</td>
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<tr>
<td>SRAC</td>
<td>10-11 Oct. 2016</td>
<td>Budapest</td>
<td>EU regulators, industry and regulatory scientists</td>
<td>2 day standalone meeting</td>
<td>Done</td>
<td>JdV</td>
<td>SM</td>
<td>BF SM</td>
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<tr>
<td>NYAS</td>
<td>9 Nov. 2016</td>
<td>New York</td>
<td>US regulators, industry and regulatory scientists</td>
<td>1 day standalone meeting</td>
<td>Done</td>
<td>JdV</td>
<td>SM</td>
<td>BF SM</td>
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<tr>
<td>AAPS</td>
<td>16 Nov. 2016</td>
<td>Denver</td>
<td>US regulators, industry and regulatory scientists</td>
<td>3 h CME session</td>
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<td>JdV</td>
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<td>IDDST</td>
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<td>Regulatory science</td>
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<td>(working) title</td>
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<td>Target audience</td>
<td>Target journal</td>
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<td>Clinical consequences of differences between intravenous iron compounds and preparations</td>
<td>Review</td>
<td>Clinicians</td>
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<td>Jankovska et al</td>
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<td>SB</td>
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<td>Non-Biological Complex Drugs (NBCDs) and their follow on versions (generics): time for an editorial section</td>
<td>Editorial</td>
<td>Regulators</td>
<td>GaBI</td>
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<td>Editorial section with biweekly articles and 4 full text publications</td>
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<td>Regulators</td>
<td>GaBI</td>
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<td>Crommelin et al</td>
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<td>How to select a nanosimilar</td>
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<td>Hospital pharmacists</td>
<td>EJHP</td>
<td>Submitted</td>
<td>Astier A. et al</td>
<td>JK</td>
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<td>Medication practice in hospitals: are nanosimilars evaluated and substituted correctly?</td>
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<td>Flühmann b. JK et al</td>
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<td>Wikipedia article ISS</td>
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<td>AAPS Blog</td>
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<td>Conference report ASEAN PPWG</td>
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<td>Manuscript under development</td>
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<td>Review</td>
<td>Chinese</td>
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<td>Manuscript under development</td>
<td>Ariel XJJ</td>
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NBCD Strategic Framework

**Scientific Evidence**
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**Awareness**
- Not all iron are same
- Iron products are non-biological complex drugs
- Iron products require appropriate regulatory pathways

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- Ensure appropriate regulatory approval standards are applied

**Risk Management**
- Establish mechanisms to track specific IS brands post approval

- Healthcare Authorities
- Industry
- Hospital Pharmacists
- Physicians
KOL Advocacy

Map the issues
Engage in discussions
Create policy

... Patient Safety
Characterization is Complex
PK/PD
*In vivo* performance

Science based!
Global Harmonization
Interchangeability?
Substitution?
The NBCD Working Group: KOL, Societies and Authorities Interactions consists of experts from industry, academia and knowledge institutes. It is hosted at Lygature (NL), an independent public private partnership and supported by Vifor Pharma, Teva and Allergan.
NBxCD Working Group
Steering Committee Members

Prof. dr. Stefan Muhlebach (Chair)
Head Regulatory Sciences, Vifor Pharma
Univ Basel Hospital Pharmacy

Dr. Vinod Shah
Retired Research Scientist from FDA
FIP – SIG chair Regulatory Sciences

Dr. Scott McNeil
Director National Cancer Institute
Nanotechnology Characterization Lab

Prof. dr. Gerrit Borchard
University of Geneva
President of the Swiss Academy of
Pharmaceutical Sciences

Prof. dr. Daan Crommelin
Prof. Emeritus Utrecht University
Former Scientific Director TI Pharma

Dr. Vera Weinstein
Senior Director CMC and Global R&D
TEVA Pharmaceuticals

Dr. Beat Flühmann
Director Global Lead NBCD
Vifor Fresenius Medical Care Renal Pharma

Dr. Sesha Neervannan
Senior Vice President
Pharmaceutical Development
Allergan Inc.
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Venofer® versus ISS costing model

Model objectives

This model evaluates the total anaemia drug costs associated with switching from Venofer® (iron sucrose) to iron sucrose similar (ISS). The analysis is based on a study undertaken by Rottembourg et al.¹

¹ Rottembourg J, Kadri A, Leonard E et al. Do two intravenous iron sucrose preparations have the same efficacy? Nephrol Dial Transplant 2011; 0:1-6.
Selection criteria for biosimilars were used as starting point

Additional criteria for nanosimilars in red

Pharmaceutical quality
- Chemical composition
- Identity
- Quantity
- Pharmacopeial specifications
- Particle size and size distribution
- Particle surface characteristics
- Uncaptured pharmacological active moiety fraction
- Storage stability

Efficacy/Safety
- Pharmacokinetics
  - Uptake
  - Distribution
- Clinical data
- Range of indications
- Immunogenicity
- Potential for therapeutic interchange
- Number of similar agents on formulary
- Pharmacovigilance requirements

Manufacturer considerations
- Supply reliability
- History of drug shortages
- Supply chain security
- Anti-counterfeit measures
- Patient assistance programs
- Reimbursement support
- Manufacturer services, expertise

Product considerations
- Product packaging and labeling
- Bar coding
- Compatibility with CSTDs*, robotics
- Ready-to-use preparation and administration
  - Stability for ready-to-use administration
  - Storage requirements

Hospital and patient factors
- Economic considerations
  - Hospital
  - Payer
  - Patient
- Transitions of care
- IT and medication system changes
- Educational requirements
- Pharmacovigilance requirements

Adapted from Griffith N, et al. Hospital Pharmacy 2014
<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
<th>Presenter</th>
<th>Venue</th>
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<tbody>
<tr>
<td>08:30 – 08:45</td>
<td>Day 2 Welcome</td>
<td>Beat Flühmann</td>
<td>Hotel Einstein</td>
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<tr>
<td>08:45 – 09:30</td>
<td>Are All Iron the Same? A Nano Perspective</td>
<td>Stefan Mühlebach</td>
<td>St. Gallen</td>
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<tr>
<td>09:30 – 10:00</td>
<td>Group 1 + 2: Evaluation Tool for Pharmacists</td>
<td>Beat Flühmann / Stefan Mühlebach</td>
<td>St. Gallen</td>
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<tr>
<td>10:00 – 10:20</td>
<td>Break</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>10:20 – 10:50</td>
<td>Group 1 + 2: Regulatory Update</td>
<td>Beat Flühmann / Stefan Mühlebach</td>
<td>St. Gallen</td>
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<td>10:50 – 11:00</td>
<td>China NBCD Initiative</td>
<td>Xu Jun Jing</td>
<td>St. Gallen</td>
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<tr>
<td>11:20 – 12:30</td>
<td>Implementation Workshop</td>
<td>Beat Flühmann</td>
<td>St. Gallen</td>
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<td>12:30 – 13:30</td>
<td>Lunch</td>
<td>Hans-Martin Müller</td>
<td>Hotel Einstein</td>
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<td>13:30 – 14:00</td>
<td>Introduction St. Gallen site</td>
<td>Beat Flühmann</td>
<td>Viforia</td>
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<td>14:00 – 14:20</td>
<td>Transfer Einstein - Vifor Pharma</td>
<td>Rita Touihri, Isabelle Gerber</td>
<td>Ebenalp Kronenberg</td>
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<td>14:20 – 14:30</td>
<td>Group photo shooting</td>
<td>Robert Stürmer, Isabelle Gerber</td>
<td>Viforia</td>
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<td>14:30 – 15:50</td>
<td>Group 1 + 2: Chemistry of Venofer</td>
<td>Peter Geisser, Roland Riederer,</td>
<td>Ebenalp Kronenberg</td>
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<td></td>
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<td>Dominique Schreiber, Dominic Lampert</td>
<td>Production</td>
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<td>15:50 – 17:10</td>
<td>Group 1 &amp; 2: Site tour</td>
<td>Peter Geisser, Roland Riederer,</td>
<td>Reception</td>
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<td></td>
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<td>Manuel Senn, Christian Stübi</td>
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<tr>
<td>17:10 – 17:30</td>
<td>Transfer Vifor Pharma - Einstein</td>
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</table>
Targeted iron therapy.
ARE ALL THE IRONS THE SAME? A NANO PERSPECTIVE

STEFAN MÜHLEBACH, PROF. PhD
REGULATORY SCIENCE LEAD NON BIOLOGICAL COMPLEX DRUGS
CHAIR NBCD WG C/O LYGATURE, UTRECHT NL
http://lygature.org/non-biological-complex-drugs-working-group
- Introduction and IV iron characteristics
- Consequences of the nano character
- Regulatory thinking
- Follow-on evaluation and authorization
- Conclusion
NEED FOR (IV) IRON: ERYTHROPOIESIS (EPO)

- **ERYTHROPOIESIS**: DAILY Fe NEED 25 MG
  [≈ 95% recycled from (old)]

<table>
<thead>
<tr>
<th>Iron requirements per day</th>
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</thead>
<tbody>
<tr>
<td>4 months to 1 year</td>
</tr>
<tr>
<td>2 years to 10 years</td>
</tr>
<tr>
<td>Puberty</td>
</tr>
<tr>
<td>Adult male</td>
</tr>
<tr>
<td>Menstruating woman</td>
</tr>
<tr>
<td>Pregnant woman</td>
</tr>
</tbody>
</table>

Iron deficiency (anemia):
Most prevalent disease (25-30%)

- **Decreased iron intake**
  - Vegetarian or otherwise unbalanced diet
  - Eating disorder
  - Disease-related anorexia

- **Decreased iron absorption**
  - Celiac disease
  - Malabsorption
  - Chronic inflammatory or malignant diseases
  - Concomitant intake of drugs

- **Blood loss**
  - Heavy or prolonged menstrual bleeding
  - Delivery
  - Gastrointestinal bleeding
  - Surgery
  - Blood donation

- **Increased iron demand**
  - Pregnancy and lactation
  - Infancy
  - Adolescence
  - Endurance sport

Anaemia assessment: Haematocrit [Hct]

Hb content
RBC assessment (blood count)

Size: Hct/RBC:
Mean Corpuscular Volume
MCV [fl] 80-100

Content: Hb/RBC Mean Corpuscular Hemoglobin MCH [pg] 27-32
FERRITIN: INTRACELLULAR IRON STORE (450 kDa; ≤ 4500 Fe$^{3+}$)

- Most important for iron body store in a non-toxic form and its disposition
- Prevents free toxic iron presence (ROS formation like hydroxyl radicals)
  
  \[
  \text{Fe}^{2+} + \text{O}_2 \rightarrow \text{Fe}^{3+} + \text{O}_2^{-} [\text{H}_2\text{O}_2]
  \]
  \[
  \text{Fe}^{2+} + \text{H}_2\text{O}_2 \rightarrow \text{Fe}^{3+} + \text{OH}^{-} + \text{OH}^{-}
  \]
  \[
  \text{Fe}^{3+} + \text{H}_2\text{O}_2 \rightarrow \text{Fe}^{IV+}=\text{O} + \text{H}_2\text{O}
  \]

  * Fenton reaction labile radical
- Allows release of required iron (RES)

about 8 nm in diameter
Fe\(^{3+}\) (also called “free” iron) cannot exist under physiological conditions.

\[
pK_a(H_2O) = 14
\]

\[
pH = 7
\]

\[
-pH^+ \quad \text{polynuclear iron(III)-oxohydroxide core carbohydrate ligands}
\]

\[
-pn-Fe(OH)_3 \text{ can be combined with carbohydrates with different molecular weight distributions to a very large number of different iron carbohydrate complexes}
\]

\[
\text{polynuclear iron(III)-oxohydroxide core carbohydrate ligands}
\]
(NANO-)COLLOIDAL IV IRON MEDICINAL PRODUCTS
Fe(III)-PRODRUGS (IRON SUCROSE)

- The pn-iron-oxyhydroxy core is stabilized by sucrose.
- Differences in core size, carbohydrate chemistry, and particle characteristics (nanoparticles) determine drug profile in vivo (PK, PD safety, immunogenicity).
- The stability of the iron complex influences efficacy and tolerance of the IV iron preparation: (iron dissociation, formation of reactive species).

Venofer®
MW = 34-60 kDa;
Particle size ~ 7nm (DLS in vitro)
pH 11

From Mühlbach S et al, Nanomedicine 2015;10(4), 659–674
NON-BIOLOGICAL COMPLEX DRUGS (NBCDs)

- Synthetic, not biological medicinal products
- Not homo-molecular, closely related, often nanoparticular, polymeric structures
- Can’t be fully characterized by physicochemical analytical means
- Unknown structural elements that might impact the therapeutic performance (clinically meaningful differences in copies?)
- The properties of the product dependent on the manufacturing process influencing composition, quality and in vivo performance

From Crommelin et al. AAPS J 2014;16-14 (Terminology)
THERAPEUTIC EQUIVALENCE: FROM MANUFACTURING TO EFFICACY AND SAFETY

Manufacturing

- Complex, proprietary process
- In-process controls

Evaluation of:

Pharmaceutical equivalence

- Not fully characterisable:
  - Structure, surface, morphology of particles
  - Stability, Reactivity
  - Quality

Specific nano-particle formulation

Pharmaco-kinetics

- Tissue targeting
- Uptake into physiological metabolism
- Biodisposition

Pharmacodynamics

- Efficacy
- Efficiency
- Tolerability
- Toxicity

In vivo performance

Adapted from GabiJ 2013;2(4):204-7

GLOBAL VENOFER MEETING 2016, ST.GALLEN
NANOMEDICINES (DRUG TARGETING)

- **Nanomedicines** are Medicinal Products [MP] using nanomaterials and nanotechnology during their development and manufacturing (**size-specific design** and **manufacturing** at an atomic or molecular level not to be accomplished at larger scales)

- Potential to revolutionize medicine but also safety concerns

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# CHARACTERISTICS OF AUTHORIZED IV IRON DRUG PRODUCTS

<table>
<thead>
<tr>
<th></th>
<th>Iron gluconate</th>
<th>Iron sucrose</th>
<th>HMWID</th>
<th>LMWID</th>
<th>Ferric carboxymaltose</th>
<th>Iron isomaltoside 1000</th>
<th>Ferumoxytol</th>
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<tbody>
<tr>
<td><strong>Brand name</strong></td>
<td>Ferrlecit®</td>
<td>Venofer®</td>
<td>Dexferrum®</td>
<td>Cosmofer®</td>
<td>Ferinject®, Injectafer®</td>
<td>Monofer®</td>
<td>FeraHeme®</td>
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<tr>
<td><strong>Manufacturer</strong></td>
<td>Sanofi-Aventis</td>
<td>Vifor</td>
<td>Watson</td>
<td>PharmaCosmos</td>
<td>Vifor</td>
<td>PharmaCosmos</td>
<td>AMAG Pharmaceuticals</td>
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<tr>
<td><strong>Carbohydrate shell</strong></td>
<td>Gluconate (monosaccharide)</td>
<td>Sucrose (disaccharide)</td>
<td>Dextran (branched polysaccharide)</td>
<td>Dextran (branched poly-saccharide)</td>
<td>Carboxymaltose (branched poly-saccharide)</td>
<td>Isomaltoside (linear oligo-saccharide)</td>
<td>Polyglucose sorbitol (branched poly-saccharide)</td>
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<tr>
<td><strong>Molecular weight (kDa)</strong></td>
<td>289-440</td>
<td>340</td>
<td>265</td>
<td>165</td>
<td>150</td>
<td>150</td>
<td>750</td>
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<td><strong>Plasma half-life (h)</strong></td>
<td>1</td>
<td>6</td>
<td>60</td>
<td>30</td>
<td>16</td>
<td>20</td>
<td>15</td>
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<tr>
<td><strong>Iron content (mg/mL)</strong></td>
<td>12.5</td>
<td>20</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>100</td>
<td>30</td>
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<td><strong>Maximal single dose (mg)</strong></td>
<td>125</td>
<td>300</td>
<td>20 mg/kg BW</td>
<td>20 mg/kg BW</td>
<td>20 mg/kg BW (max. 1000 mg)</td>
<td>20 mg/kg BW</td>
<td>510</td>
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</tbody>
</table>

HMWID high molecular weight iron dextran, LMWID low molecular weight iron dextran, BW body weight


GLOBAL VENOFER MEETING 2016, ST.GALLEN
NANOSIMILARS (ISS): SIMILARITY AND THERAPEUTIC EQUIVALENCE

- Critical Attributes
  - Complex, proprietary process
  - Starting Materials
  - In Process Controls

- Pharmaceutical Equivalence
  - Not to be fully characterized:
    - Structure, Surface, Morphology of Particles
    - Stability
    - Quality

- Bio-Equivalence
  - Tissue targeting
  - Uptake into physiological Iron Metabolism (functional iron)
  - Biodisposition

- Manufacturing
  - Specific nano-particle formulation

- PK

- PD

- Efficacy
- Efficiency
- Safety
- AE
- Toxicity
PHYSICAL STABILITY OF NANOPARTICLES

Environment
Temperature / light / package material

Particle surface characteristics

Physical stability

Size distribution

Uncaptured pharmacological active moiety

Nanoparticle aggregation

Nanoparticle solution (colloidal)

Nanoparticle decomposition

Captured active moiety

Uncaptured active moiety
IS_{ORIG} vs ISS IN NON-ANEMIC RATS (40MG/KG/W)
PRUSSIAN BLUE (Fe^{3+}), FERRITIN IMMUNOSTAINING

IN VIVO PROFILE OF NANOMEDICINES: ASPECTS TO CONSIDER (Efficacy, Safety)

- Physical stability
- Protein interactions
- Interaction with immune system

Clinical outcome
BIOEQUIVALENCE OF IV Fe(III) : IMPORTANCE OF THE INNATE IMMUNE SYSTEM

Uptake of IV iron complexes (Fe(III) core with CH shell)

modifiziert nach Brock JH et al., (eds), Iron Metabolism in Health and Disease. Saunders (WB) Co. Ltd, 1994
SWITCHING ISS TO IS\textsubscript{ORIGINATOR} IN HD PATIENTS REDUCES IV IRON AND EPO DOSING

- A prospective, observational multi-centric study comparing two subsequent treatment periods of 13 months each, including 342 HD patients.

- Hb levels were stable over two treatment periods of 13 month each
  
  After switch to IS\textsubscript{ORIGINATOR}:
  
  TSAT went up from 28.6±7.2% to 30.7±7.6% (p<0.001)

  Ferritin increased from 507ng/ml to 579 ng/ml (p<0.001)

34.3% less IV iron dosing with IS\textsubscript{ORIGINATOR} (p<0.001)

12.5% less ESA consumption after switching to IS\textsubscript{ORIGINATOR} (p<0.001)

CURRENT REGULATORY THINKING ON IV IRON CARBOHYDRATE NANOCOLLOIDS

EMA (similarity) (2011-2015)

FDA (sameness, substitutable) (2011-2013)
EMA RP 2015 “IV Fe NANOCOLLOIDS” COMPARABILITY OF FOLLOW-ON VERSIONS

- Highly similar Pharmaceutical Quality (MP and stability)
  - Structure, composition (CH)
  - Iron core (size, labile iron, polymorphism, morphology)
  - Particle sizing, surface, charge
  - Degradation, in-use stability

Weight of evidence approach for similarity (justifications!)
[Reflection paper to assist to generate relevant data (quality, non-clinical and clinical) also for control of the manufacturing]
### AUTHORIZATION OF FOLLOW-ON VERSIONS

<table>
<thead>
<tr>
<th>SMALL MOLECULE DRUGS</th>
<th>BIOLOGICS</th>
<th>NON BIOLOGICAL COMPLEX DRUGS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Molecular weight</strong></td>
<td>Low (&lt;500)</td>
<td>High (range 5-5000 kDa)</td>
</tr>
<tr>
<td><strong>Structure</strong></td>
<td>Simple, well-defined</td>
<td>Complex, heterogeneous defined by manufacturing process</td>
</tr>
<tr>
<td><strong>Modifications</strong></td>
<td>Well-defined</td>
<td>Many options</td>
</tr>
<tr>
<td><strong>Manufacturing</strong></td>
<td>Chemical synthesis</td>
<td>Produced in living cells or organisms</td>
</tr>
<tr>
<td><strong>Characterization</strong></td>
<td>Complete characterization</td>
<td>Synthetic technologies (including nanoparticles)</td>
</tr>
<tr>
<td><strong>Stability</strong></td>
<td>Stable</td>
<td>Generally unstable, sensitive to external conditions</td>
</tr>
<tr>
<td><strong>Immunogenicity</strong></td>
<td>Mostly non-immunogenic</td>
<td>Mostly immunogenic</td>
</tr>
<tr>
<td><strong>Copy characteristics</strong></td>
<td>Identical copies can be made</td>
<td>Immunogenicity varies</td>
</tr>
</tbody>
</table>

#### NBCDs (incl. nanoparticles*)

- Impossible to ensure identical copies versions

---

**Critical attributes**

**Clinically meaningful differences**

---

**GLOBAL VENOFER MEETING 2016, ST.GALLEN**

**VENOFER® IRON SUCROSCE**
IV IRON DRUG PRODUCTS

- IV iron Drug products are complex Prodrugs
- They are
  - NBCDs: Non homomolecular macromolecular Mixtures
  - Nanocolloids: Drug Targeting, Biodistribution
  - Follow on versions are Similars
- The manufacturing defines the drug product: in vitro und in vivo Profil (manufacturing «intellectual property»)
  Analytical (physicochemical) full Characterization is not possible
- Among chemically different iron carbohydrate drug products but also among similars compared to their reference products clinically relevant differences can occur. Therefore, comparative clinical data are necessary to define the necessary extent of similarity:

Substitution and Interchange are challenges (efficacy, safety)
Venofer®: iron sucrose originator

Targeted iron therapy.

The nanocolloidal character explains uniqueness
Targeted iron therapy.
Rational Approach to the Selection and Clinical use of Nanomedicines and Nanosimilars

Targeted iron therapy.
Nanomedicines an Upcoming Challenge for HCPs

- Iron sucrose (Venofer®)
- PEGylated liposomal doxorubicin (Doxil® / Cealyx®)
- Glatiramer acetate (Copaxone®)
- Paliperidone palmitate (Invega Sustenna® / Xeplion®)

- Nanosimilars

- Nanoparticles: 9
- Liposomes: 10
- Nanocrystals: 2
- Polymers: 2

+ 52 in clinical development
Observed Clinical Differences → Iron Sucrose Similars

- Efficacy
- Safety

Draft Guidance on Iron Sucrose

Reflection paper on the data requirements for intravenous iron-based nano-colloidal products developed with reference to an innovator medicinal product

Liposome Drug Products

Guidance for Industry

Reflection paper on the data requirements for intravenous liposomal products developed with reference to an innovator liposomal product

Joint MHLW/EMA reflection paper on the development of block copolymer micelle medicinal products

Pharmacists Are Not Aware of Differences Between Iron Sucrose Brands

The newly-introduced alternative iron sucrose are just as effective as the original drug

<table>
<thead>
<tr>
<th>Country</th>
<th>Disagree</th>
<th>Neutral</th>
<th>Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>1%</td>
<td>59%</td>
<td>41%</td>
</tr>
<tr>
<td>Spain</td>
<td>1%</td>
<td>54%</td>
<td>46%</td>
</tr>
</tbody>
</table>

The newly-introduced alternative iron sucrose are just as safe as the original drug

<table>
<thead>
<tr>
<th>Country</th>
<th>Disagree</th>
<th>Neutral</th>
<th>Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>1%</td>
<td>56%</td>
<td>43%</td>
</tr>
<tr>
<td>Spain</td>
<td>1%</td>
<td>57%</td>
<td>41%</td>
</tr>
</tbody>
</table>

**Percentage of responding hospital pharmacists**

Pharmacists’ perception of differences between available branded i.v. iron products (A) and between IS and ISS (B) in 2013. A 7-point scale was used, where 1 stands for “completely disagree” and 7 stands for “completely agree”.
Pharmacists Substitute Iron Sucrose

Dispensing ISS is decision of physician or in agreement with a physician

Dispensing ISS is decision of the pharmacist

Dispensing ISS is a requirement

Iron sucrose dispensing behavior

<table>
<thead>
<tr>
<th>Percentage of hospital pharmacists</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
</tr>
<tr>
<td>-----------------------------------</td>
</tr>
<tr>
<td>4%</td>
</tr>
<tr>
<td>n = 70</td>
</tr>
</tbody>
</table>

- No, I cannot dispense alternative iron sucrose drugs instead of the branded product — what the physician prescribes is dispensed
- Yes, I can dispense alternative iron sucrose drugs instead of the branded product — but, I must first obtain agreement from the physician
- Yes, I can dispense alternative iron sucrose drugs instead of the branded product — but, I inform the physician as a courtesy
- Yes, I can dispense alternative iron sucrose drugs instead of the branded product — without informing the physician
- Yes, I can dispense alternative iron sucrose drugs instead of the branded product — in fact, I am required to do so in our institution, if the alternative is cheaper
- I typically do not need to dispense alternative iron sucrose drugs instead of the branded product — in our institution, the physicians are required to write their prescriptions for the alternative, if one is available
- I typically do not need to dispense alternative iron sucrose drugs instead of the branded product — in our institution, the physicians are required to write only the molecule name on their prescriptions (not the branded name) and I dispense an alternative
Pharmacists’ Substituting Behavior

ISS dispensing in hospital wards

<table>
<thead>
<tr>
<th>Ward</th>
<th>Dispensing an ISS instead of IS</th>
<th>2013 (n=52)</th>
<th>2012 (n=55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardio ward</td>
<td></td>
<td>30%</td>
<td>49%</td>
</tr>
<tr>
<td>Onco ward</td>
<td></td>
<td>43%</td>
<td>47%</td>
</tr>
<tr>
<td>Gastro ward</td>
<td></td>
<td>45%</td>
<td>49%</td>
</tr>
<tr>
<td>Neph ward</td>
<td></td>
<td>44%</td>
<td>49%</td>
</tr>
<tr>
<td>Gyn ward</td>
<td></td>
<td>44%</td>
<td>51%</td>
</tr>
<tr>
<td>Surgery ward</td>
<td></td>
<td>47%</td>
<td>52%</td>
</tr>
</tbody>
</table>

Dispensing an ISS instead of IS

- 2013 (n=52)
- 2012 (n=55)
**Need for Guidance: Expert Round Table Vienna March 17th 2016**

<table>
<thead>
<tr>
<th>Evaluation criteria of nanosimilars for formulary inclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pharmaceutical quality</strong></td>
</tr>
<tr>
<td><strong>Chemical composition</strong></td>
</tr>
<tr>
<td>Chemical components in the formulation of the nanosimilar</td>
</tr>
<tr>
<td><strong>Identity</strong></td>
</tr>
<tr>
<td>Is the chemical structure of the active ingredients similar?</td>
</tr>
<tr>
<td>- Pharmacological active moiety</td>
</tr>
<tr>
<td>- Nanoparticulate structure</td>
</tr>
<tr>
<td><strong>Quantity</strong></td>
</tr>
<tr>
<td>Are there differences in quantity of the pharmaceutical complex in the formulations of the nanosimilar under consideration compared to the reference product?</td>
</tr>
<tr>
<td><strong>Pharmacopoeia specifications</strong></td>
</tr>
<tr>
<td>Are there any differences between the properties of the nanosimilar under consideration and the pharmacopoeia of the reference product?</td>
</tr>
<tr>
<td><strong>Particle size and size distribution</strong></td>
</tr>
<tr>
<td>Does the average size of the nanosimilar differ from the reference product?</td>
</tr>
<tr>
<td>Is there a similar size distribution between the nanosimilar under consideration and the reference product?</td>
</tr>
<tr>
<td><strong>Particle surface characteristics</strong></td>
</tr>
<tr>
<td>Do particle morphology/surface and charge/zeta potential differ from the reference product?</td>
</tr>
<tr>
<td><strong>Uncaptured pharmacological active moiety</strong></td>
</tr>
<tr>
<td>Is the fraction of free active moiety released at time of administration similar compared to the reference product, showed in vitro and in vivo studies?</td>
</tr>
<tr>
<td>(ratio captured/uncaptured active moiety)</td>
</tr>
<tr>
<td><strong>Storage stability</strong></td>
</tr>
<tr>
<td>Are there differences in shelf life between the nanosimilar under consideration and reference product?</td>
</tr>
<tr>
<td>Is the ratio captured/uncaptured active moiety included for the determination of the shelf-life of the nanomedicine?</td>
</tr>
<tr>
<td>Is the degree of aggregation of the nanoparticles included for the determination of the shelf-life of the nanomedicine?</td>
</tr>
<tr>
<td><strong>Efficacy/safety</strong></td>
</tr>
<tr>
<td><strong>Pharmacokinetics</strong></td>
</tr>
<tr>
<td>Are there non-clinical and/or clinical studies available showing the (comparative) uptake of the active pharmaceutical ingredient?</td>
</tr>
<tr>
<td>- Are there major differences between the nanosimilar under consideration and the reference product regarding uptake by the innate immune system or plasma clearance?</td>
</tr>
<tr>
<td>Are there differences in biodistribution profiles between the nanosimilar under consideration and the reference product?</td>
</tr>
<tr>
<td>- What is the effect of these differences on the efficacy and safety and use compared to the reference product?</td>
</tr>
</tbody>
</table>
Distinct Physical Properties of Nanomedicines Need to be Considered

- Size & size distribution
- Particle surface characteristics
- Uncaptured pharmaceutical active moiety
- Storage stability

Effect of particle size on spleen uptake of poloxamer-407-coated polystyrene particles on in rats

Uptake of pharmacological active moiety with and without gold nanoparticles as carriers

2Doane T & Burda C, Chemical Society Reviews 2012
Distinct Physical Properties of Nanomedicines Need to be Considered

- Size & size distribution
- Particle surface characteristics
- Uncaptured pharmaceutical active moiety
- Storage stability
Product Handling

![Bar chart showing the number of patients experiencing different side effects from Iron Sucrose (original) and Iron Sucrose Similar (in 100 ml saline) and Iron Sucrose Similar (in 200 ml saline). The side effects include headache, nausea, injection site reaction, and phlebitis. The percentages for each side effect are as follows: Headache - 2 (0.7%), Nausea - 2 (0.7%), Injection Site Reaction - 23 (8.2%), Phlebitis - 10 (4.8%), and 13 (4.7%).]
Clinical pharmacokinetics: Uptake & Biodistribution

No linear correlation between:

- physicochemical properties
- biological reaction
- pharmacokinetics

COMPARATIVE CLINICAL PHARMACOKINETIC DATA REQUIRED
Manufacturing Defines the Product

Manufacturing process

Physical Characteristics

- Size distribution
- Uncaptured pharmacologic al active moiety
- Particle morphology

Storage and handling: Temperature / light / package material

Physical stability

PK/ Clinical outcome
Selection criteria for biosimilars were used as starting point

Additional criterias for nanosimilars in red

<table>
<thead>
<tr>
<th>Pharmaceutical quality</th>
<th>Efficacy/Safety</th>
<th>Manufacturer considerations</th>
<th>Product considerations</th>
<th>Hospital and patient factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical composition</td>
<td>Pharmacokinetics</td>
<td>Supply reliability</td>
<td>Product packaging and labeling</td>
<td>Economic considerations</td>
</tr>
<tr>
<td>Identity</td>
<td>• Uptake</td>
<td>History of drug shortages</td>
<td>• Bar coding</td>
<td>• Hospital</td>
</tr>
<tr>
<td>Quantity</td>
<td>• Distribution</td>
<td>Supply chain security</td>
<td>• Compatibility with CSTDs*, robotics</td>
<td>• Payer</td>
</tr>
<tr>
<td>Pharmacopoeial specifications</td>
<td>• Clinical data</td>
<td>Anti-counterfeit measures</td>
<td>• Ready-to-use preparation and administration</td>
<td>• Patient</td>
</tr>
<tr>
<td>Particle size and size distribution</td>
<td>• Range of indications</td>
<td>Patient assistance programs</td>
<td>• Stability for ready-to-use administration</td>
<td>• Transitions of care</td>
</tr>
<tr>
<td>Particle surface characteristics</td>
<td>• Immunogenicity</td>
<td></td>
<td>• Storage requirements</td>
<td>• IT and medication system changes</td>
</tr>
<tr>
<td>Uncaptured pharmacological active moiety fraction</td>
<td>• Potential for therapeutic interchange</td>
<td></td>
<td></td>
<td>• Educational requirements</td>
</tr>
<tr>
<td>Storage stability</td>
<td>• Number of similar agents on formulary</td>
<td></td>
<td></td>
<td>• Pharmacovigilance requirements</td>
</tr>
<tr>
<td></td>
<td>• Pharmacovigilance requirements</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Griffith N, et al. Hospital Pharmacy 2014
Selection criteria for biosimilars were used as starting point

Important focus points:
- Manufacturing defines the product
- The physical stability and physicochemical reactivity of particles during shelf-life and ready-to-use drug preparation
- The particle interaction with the innate immune system, which influences the pharmacokinetic and pharmacodynamic profile of the drug.

“Evaluation Criteria” submitted for publication
Targeted iron therapy.
Same Same, but DIFFERENT

From brand differentiation and beyond.
Why is it important to talk about a new category called “NBCT”

It will never be easy to create a new category of drugs and get support. But it has to be done.

For now
- Emphasis product quality standard
- Provide solid evidence in Competitive advantage

For future
- Increase product standard
- Increase competitor access barriers
2015. Sep

- **Master class**
- **Topic:**
  - NBCD and regulatory aspects
- **Audience:**
  - 50 KOLs

- **Stand alone meeting**
- **Topic:**
  - NBCD with Venofer as example
- **Audience:**
  - 200 onsite clinicians from nephro, ob&GYN, surgery
  - 800 live broadcast
2016. Jan

- Internal workshop
- Topic
  - Understanding of NBCD
- Audience:
  - Marketing access, medical, alliance, marketing, regulatory, marketing, sales management
2016. May

China NBCD working group

2016. May 8, establishment of China PBM working group

Educational sessions

• Beijing Forbidden city Forum

Authority meeting

• Meeting with China pharmacopeia
2016. Sep

• Stand alone meeting
• Topic:
  • NBCD
  • PBM in OB&GYN
• Audience:
  • 200 clinicians from OB&GYN,
2016.11.10

- Hospital level bidding meeting
- Topic:
  - NBCD concept introduction from pharmacists perspective
  - Iron metabolism
  - Difference from Rottermburg
- Audience:
  - 15 from Hematology, Pharmacist, ob&GYN and nephrologist
Leverage NBCD to differentiate Venofer vs ISS activities in 2016

Target customer vs vs vs vs

Activity type

Core influencers

Mass education

China NBCD working group

CME education

Publication

Establishment of China PBM working group

Beijing Forbidden city Forum UCB stand alone meeting Reached 7000 audience

2016.May8

2016.May 9

2016.Sep

2016.Dex

12 issues of advertisement on NBCD /year

Review publication (3 Chinese Version to come) First expected in Dec

Target customer

Top pharmacists

Selective clinicians

Mass pharmacists

Mass clinicians

2016.May 8

2016.May 9

2016.Sep

2016.Dex

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Leverage NBCD to differentiate Venofer vs ISS activities in 2017

<table>
<thead>
<tr>
<th>Target customer</th>
<th>Activity type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Core influencers</td>
<td>Train the trainer</td>
</tr>
<tr>
<td>Top pharmacists</td>
<td>Train NBCD KOLs in China</td>
</tr>
<tr>
<td>- International speakers</td>
<td></td>
</tr>
<tr>
<td>- Top Pharmacist from each region</td>
<td></td>
</tr>
<tr>
<td>- Selective clinicians</td>
<td></td>
</tr>
<tr>
<td>Selective clinicians</td>
<td></td>
</tr>
<tr>
<td>Mass education</td>
<td></td>
</tr>
<tr>
<td>Mass pharmacists</td>
<td>Regional NBCD meeting</td>
</tr>
<tr>
<td>Mass clinicians</td>
<td>Publication</td>
</tr>
<tr>
<td>Meeting structure</td>
<td></td>
</tr>
<tr>
<td>Speakers :</td>
<td></td>
</tr>
<tr>
<td>- Pharmacists as trainers</td>
<td></td>
</tr>
<tr>
<td>- Nephrologists</td>
<td></td>
</tr>
<tr>
<td>- Hematologists</td>
<td></td>
</tr>
<tr>
<td>- OB&amp;GYN</td>
<td></td>
</tr>
<tr>
<td>Content</td>
<td></td>
</tr>
<tr>
<td>- NBCD introduction</td>
<td></td>
</tr>
<tr>
<td>- Clinical evidence from Rottermburg</td>
<td></td>
</tr>
<tr>
<td>- Clinical evidence of safety</td>
<td></td>
</tr>
<tr>
<td>- Iron metabolism and treatment</td>
<td></td>
</tr>
<tr>
<td>- NBCD advertisement in magazine</td>
<td></td>
</tr>
<tr>
<td>- Rest of 2 publications on NBCD</td>
<td></td>
</tr>
</tbody>
</table>
Targeted iron therapy.
Iron Sucrose is a Nano Medicine

- Venofer® is a nano medicine and therefore an NBCD
- Other iv iron brands and ISS might have different clinical efficacy and safety profiles

NBCD HQ team focusing on key activities:

- Awareness creation by scientific publications, presence at scientific conferences, interaction with regulators and regulatory KOL
- Data Generation
- Support of NBCD brands
- Support of key countries

NBCD HQ team focusing on key target groups:

- Regulators
- Pharmacists KOLs
- Regulatory science community
Targeted iron therapy.
VIFOR PHARMA
A leader in iron therapy
St. Gallen Site

Dr. Hans-Martin Müller, Site Manager, 7 December, 2016
All products of Vifor Pharma for treatment of iron deficiency were researched, developed and manufactured in St. Gallen.
St. Gallen site – overview

1952
Formation of Hausmann Laboratories

Now
Vifor Pharma, St. Gallen Site
Area 71,180 m²
Building volume 111,361 m³
Employees in St. Gallen

Development 2007 to 1st November 2016

Number of employees

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of Employees</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>195</td>
</tr>
<tr>
<td>2008</td>
<td>200</td>
</tr>
<tr>
<td>2009</td>
<td>218</td>
</tr>
<tr>
<td>2010</td>
<td>229</td>
</tr>
<tr>
<td>2011</td>
<td>248</td>
</tr>
<tr>
<td>2012</td>
<td>259</td>
</tr>
<tr>
<td>2013</td>
<td>251</td>
</tr>
<tr>
<td>2014</td>
<td>258</td>
</tr>
<tr>
<td>2015</td>
<td>245</td>
</tr>
<tr>
<td>01.11.2016</td>
<td>271</td>
</tr>
</tbody>
</table>

Shares of employees

- R&D incl. Site of Schlieren: 16%
- Quality Control: 15%
- Quality Assurance: 10%
- Active Ingredient Production: 14%
- Technical Department: 6%
- Supply Chain: 14%
- Technical Department: 10%
- Rest: 2%
- Warehouse: 2%

As at 31 December 2015

- Share of educational qualification at “tertiary level” (University, University of Applied Sciences & higher vocational education): 43%
- Employees from 16 nations
- 11 apprentices
- Share of women: 37%
Important historic dates

1872
Hecht pharmacy…
Everything began in St.Gallen…

1952
Formation of Laboratorien Hausmann by Caspar Friedrich Hausmann

1955
Moving into the Site at Rechenstrasse in St. Gallen

1983
Galenica takes over Laboratorien Hausmann AG, which specialises in solutions for infusion and sterile solutions, and in iron products.

1991
Sale of the Hospital Supply Division to B. Braun Medical AG, including land and buildings.

The activities of Laboratorien Hausmann in the field of pharma-ceutical specialities lead to the formation of Vifor (International) AG

1999
Vifor (International) AG buys the land and buildings except the warehouse from B. Braun Medical

2008
- Formation of Vifor Pharma with its Headquarters in Zurich, Switzerland
- Integration of Aspreva Pharmaceuticals.

2008
- Formation of Vifor Pharma with its Headquarters in Zurich, Switzerland

2010/2011
Galenica and Fresenius Medical Care form a new company in the field of nephrology:

2015
28.05.2015: Galenica and Roche enter into exclusive license agreement for the commercialisation of Mircera in the US
11.08.2015: VFMCRP and Relypsa enter into partnership to commercialize Patiromer FOS (US brand name: Valtessa®)

2016
09.05.2016: VFMCRP and OPKO Health enter into Agreement for Rayaldee®
10.05.2016: Vifor Pharma licenses rights to commercialize ChemoCentryx’s CCX168
24.05.2015: Vifor Pharma expands portfolio with rights to commercialize Pfizer’s Retacrit™
21.07.2016: Galenica and Relypsa announce agreement for Galenica to acquire Relypsa.
02.09.2016: Galenica completes acquisition of Relypsa, strengthening Vifor Pharma’s position in cardio-renal therapies
Iron products – from active ingredients (API) to finished products (FP)
Production – active ingredients (APIs) only

Illustration of molecular weight distributions of selected iron API's
## History of our products

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>1949</td>
<td>Authorisation CH</td>
<td>Laboratory level</td>
</tr>
<tr>
<td>1955</td>
<td>Production level</td>
<td></td>
</tr>
<tr>
<td>since 2002</td>
<td></td>
<td>Number 1 worldwide</td>
</tr>
<tr>
<td>1959</td>
<td>Authorisation CH</td>
<td></td>
</tr>
<tr>
<td>1971</td>
<td>Production as today</td>
<td></td>
</tr>
<tr>
<td>1963/1964</td>
<td>Authorisation Peru</td>
<td></td>
</tr>
<tr>
<td>1977</td>
<td>Production as today</td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>Authorisation EU</td>
<td></td>
</tr>
<tr>
<td>2013</td>
<td>Authorisation USA / Injectafer</td>
<td></td>
</tr>
<tr>
<td>2016</td>
<td>The ESC 2016 heart failure guidelines strongly recommend Ferinject® for the treatment of iron deficiency in patients with systolic heart failure</td>
<td></td>
</tr>
</tbody>
</table>
History of our products – the latest one

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012/2013</td>
<td>Average daily dose to control hyperphosphatemia was 3.3 pills per day (i.e. ca. 8.3 g API/d)</td>
</tr>
<tr>
<td>2013</td>
<td>Authorisation USA Production level Velphoro® (PA21) is granted the US authorisation by the FDA for the treatment of hyper-phos-phataemia in dialysis patients with chronic renal insufficiency.</td>
</tr>
<tr>
<td>2014</td>
<td>Authorisation EU</td>
</tr>
<tr>
<td>2015</td>
<td>Authorisation CH &amp; Japan (P-TOL®)</td>
</tr>
</tbody>
</table>
Total API production in tons per year

<table>
<thead>
<tr>
<th>Year</th>
<th>Tons API production</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Per year</td>
<td>Per day</td>
<td>Per year &amp; employee</td>
</tr>
<tr>
<td>2015</td>
<td>486</td>
<td>2.1</td>
<td>19.4</td>
</tr>
<tr>
<td>2016</td>
<td>691</td>
<td>3.0</td>
<td>22.8</td>
</tr>
<tr>
<td><strong>Forecast 2017</strong></td>
<td>965</td>
<td>4.1</td>
<td>26.6</td>
</tr>
</tbody>
</table>

Venofer and other API's production over the years.
Contract manufacturers for finished products

- Germany
  - i.v. products
- Germany
  - i.v. products
- Germany & Austria
  - i.v. products
- Portugal
- Turkey

VELPHORD® suroferric oxyhydroxide
Maltofer®
Secondary packaging

Automatic packaging line

- Increases flexibility and short delivery times
- Focus on medium orders of approx. 5’000 to 20’000 packagings (> 50%)
- Parenteral products: Ferinject & Venofer

Ampoules & vials are still being bottled by contract manufacturers.

Automatic packaging line

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- Focus on medium orders of approx. 5’000 to 20’000 packagings (> 50%)
- Parenteral products: Ferinject & Venofer

Automatic packaging line

- Increases flexibility and short delivery times
- Focus on medium orders of approx. 5’000 to 20’000 packagings (> 50%)
- Parenteral products: Ferinject & Venofer
Iron is «Vifor's electricity from the grid»

ICH Q3D-Guideline «Elemental Impurities» valid since Q4 2014

Decision to build a company-owned plant

in order to be in full control of the supply chain

Source: Iron ore (Magnetite) Fe₃O₄

Iron powder
Future situation with own manufacturing

Ore/Iron → Ore/Iron dissolution → Oxidation → Iron (III) Chlorid
Audits since 1995 to date

- 1995: Dexfer Human USA
- 1996
- 1997
- 1998
- 1999
- 2000: Venofer
- 2001
- 2002
- 2003
- 2004
- 2005
- 2006
- 2007: Injectafer / without 483
- 2008
- 2009
- 2010: Injectafer, Venofer, Dexfer Human / without 483
- 2011
- 2012: Injectafer / without 483
- 2013
- 2014
- 2015
- 2016: All products, with focus on Injectafer & Velphoro / without 483
### Investments since 2000 (CHF)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Various (GMP, safety, kapacity)</td>
<td>27.0 Mio.</td>
</tr>
<tr>
<td></td>
<td>PA21</td>
<td>34.0 Mio.</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>87.0 Mio.</strong></td>
</tr>
<tr>
<td>Laboratories</td>
<td>Area: 1999 = 100% / 2011 = 250%</td>
<td>7.0 Mio.</td>
</tr>
<tr>
<td>Administration</td>
<td>Area: 1999 = 100% / 2011 = 180%</td>
<td>5.0 Mio.</td>
</tr>
<tr>
<td>High-bay warehouse</td>
<td></td>
<td><strong>10.0 Mio.</strong></td>
</tr>
<tr>
<td>Small investments in all areas</td>
<td></td>
<td><strong>47.0 Mio.</strong></td>
</tr>
<tr>
<td><strong>Total Investments since 2000</strong></td>
<td></td>
<td><strong>156.0 Mio.</strong></td>
</tr>
</tbody>
</table>

| Current projects | 2016 - 2018: Current investment projects, including an additional Venofer line, approx. | **23.0 Mio.** |
Thank you for your attention