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Challenges of the first sterile i.v. reference Formulation

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Forecast Therapeutic Class Growth 2010-2012

Major therapeutic classes driving brand growth between 2010 and 2020 are expected to be:

- Oncology plus 5-8% annually
- Diabetes plus 4-7% annually and
- Immune Diseases less than 6%

- Emerging Market revenues forecast is to grow average of 14% between 2010 and 2020.

- That means investments in the future will be mostly in Emerging Markets and have to be fast!!

SKAN AG Business Development
Paul Ruffieux

- **New Developments in Medical Care**

We can see actual a strong trend to personalized medication for different medical treatments. One of them is today cancer treatments. Each patient can have today more and more his treatment, that means, the best medication for him.

The consequences are small batches, perhaps only a few hundred vials, bags etc. This trend is triggered very often by a low stability of the product.

The products have to be all sterile and are very often high toxic!!

Needs Protection of the Product and the Operators

Drug Development / Right First Time Workflow for Sterile Injections

Influencing an optimal Right First Time Workflow?

- Characteristic of API (Solubility, Sensitivities e.g. O2)
- Characteristic of the solution
- Characteristic of containers
- Environmental influences
- Reduce risks
- Reasons for freeze drying
- Influence of filtration
- **Objective:** An optimal solution in an optimal container produced under optimal conditions gives an optimal stability and bioavailability

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- **Critical Path Initiative (FDA)**

  Industrialization of a new sterile Product:

What is important to know for Production:

- **Characterization of the Product:**
- **Critical Parameters like solubility, toxicity, oxidation sensitivity, solvents (ex-proof),**
- **Characteristic of the containers: Glass, other materials like COC etc.**
- **Possible Production Capacities**

Critical parameters of the product

- Solubility, forming of special molecules (dimer forms of proteins)
- Toxicity of the product
- Oxygen sensitivity, risk of residual H2O2,
  - Inertisation with N2
- Temperature sensitivity (cold filling, cold storage)
- Influence of filtration 0,2 micron

Influence of the containers

- Glass:
  - Can trigger dimer structures or crystallization over strong surface potentials of the silicate structure.
- Plastic:
  - COC is a relative inert material, optimal surface, very low water permeability, needs no washing and sterilization

GMP Rules for production of sterile Injections

- Manufacturing processes are clearly defined and controlled. All critical processes are validated to ensure consistency and compliance with specifications.
- Manufacturing processes are controlled, and any changes to the process are evaluated. Changes that have an impact on the quality of the drug are validated as necessary

Production of new Products has to fulfill GMP-Guidelines

- All installations used to produce a sterile product for humans has to be qualified and validated.
- Isolated systems can be validated, especially the H2O2 decontamination with bio indicators.
- Integrity and pressures (Neg. and positive) of isolated systems can permanently be checked.
- Physical data like Temperature, Humidity, Air Speed, Particle counting etc. is recorded permanently

- **Humans can not be validated**

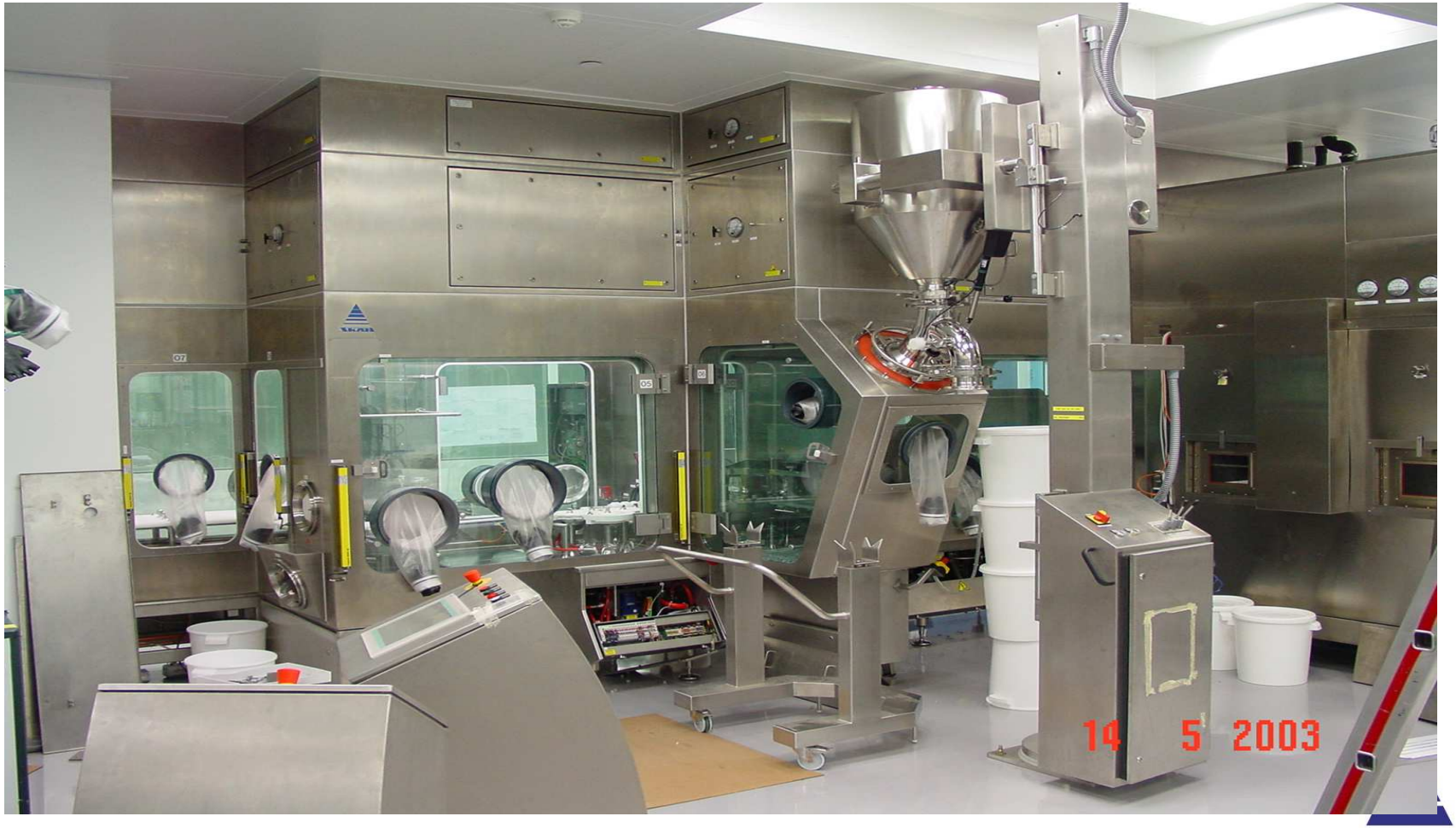
Development of Sterile/toxic Injection

State of the Art production today:

- Protection of microbiological contamination
- Protection of the operators

- **Production is under full isolation**
- The total system can be decontaminated with H2O2

Inside View of the New Sterile Plant



Inside View, Sterile Loading and Unloading of Freeze Dryers

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About Isolator Technology

Rick Friedman, Director, Division of Manufacturing & Product Quality, FDA,

- *„Isolator technology is an advanced technology, to meet 21st century objectives for process consistency, well established, providing significantly increased sterility assurance" (ISPE 2006)*

International Guidelines

- *Isolator technology is today described in all main standards like the FDA, USP, PIC/S, Ph. Eur., ISO, VDI and supported by all major pharmaceutical societies like the ISPE, PDA, APV.*

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Founded in 1968, SKAN AG hold today a leading position in the field of isolator technology for the pharmaceutical Industry

- innovative products
- customer specific solutions
- professional support
- scientific basis

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Milestones in Isolator Technology

From pioneer to market leader in isolator technology through permanent customer focus and own research and development work

- 1978 first isolator system for patient treatment in hospitals
- 1994 first isolator system for aseptic filling
- 1997 development of integrated H_2O_2 decontamination system
- 1998 first isolator system for Japan
- 2004 first isolator system for North America

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Position in Market Segment Today

SKAN AG is today partner of virtual all developing and producing pharma- and biotech- companies world wide

- with equipment for research- and quality control laboratories
- in pharmaceutical research-, formulation and production
- especially in isolator technology
- international with a high proportion of own products

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Core Competence

Core competence of Skan AG today is the application specific conversion of problems of the cleanroom technology into functional concepts and machines which finally can be validated

- integration of customer- and authority- requirements
- customer support concept design to performance qualification
- customer specific development of pharmaceutical processes
- Skan AG defines today the industrial standard (FDA Guidelines) of H_2O_2 decontamination and micro biological qualification

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Focus on Isolator Technology

Isolator technology is the uncompromising separation of a critical zone against human and/or the surrounding environment

- operator safety against potent substances (viruses, cytotoxic)
- product safety against contamination by human (parenterals)
- combinations of operator- and product safety (biotech products)

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Swiss News 2009 *(Blick, 04th May 2009)*

Swiss Centre for Virology:
At this Reference Laboratory in Geneva are now mouth and nose swapping of potential Swine Flue cases A/H1N1analyzed (Keystone)

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spinal cord transplantation 1978

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MSD
ALLERGAN
MERZ
Genentech
IN BUSINESS FOR LIFE
klee
inova
mapack
Bosch
VALEANT
Pharmaceuticals International
sanofi aventis
L'essentiel c'est la santé.
HEUMANN
gsk
GlaxoSmithKline
Nestlé
Pfizer
LINAC
SYSTEMS
GEA
BAYER
Bayer
JANSSEN-CILAG AG
On the way to you.
CHUGAI PHARMACEUTICAL CO., LTD.
A member of the Roche group
IMA
ZLB
PHARMACIA
GBF
groninger
IDT
HOF
Vakuum- und Kältetechnik
Sonderanlagenbau
Pierre Fabre
Abbott Laboratories
Roche
MONSANTO
imagine
Apotex
NOVARTIS
PharmaTech
Behring
A CSL Company
VETTER
Lilly
alza
DAIICHI
Schering-Plough
Boehringer
Ingelheim
Johnson&Johnson
ALTANA
BIOMIMETIC
THERAPEUTICS
BD
Bristol-Myers Squibb Company
Lilly
APP
BOC EDWARDS
Wyeth
novo nordisk
Baxter
genzyme
inspired by patients
25
YEARS
lek

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Experience in Isolator Technology

Skan AG partnering in projects of different complexity levels successfully with all reputable technology leaders

- integration of all transfer-, monitoring-, SCADA & AHU systems
- well experienced in cooperation with engineering companies
- based on a flexible und reliable Network of professional supplier

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Innovation

Flaschen Füller im PSI-M als Balkonmaschine ausgeführt

- Füllmaschine montiert

Small filling line with Robotic

Bild: Aseptic Technologies

Development of Sterile Product
Conclusion

- The technical installations for «right first time» are today available
- Qualification and validation must be possible
- All characteristics of the solution and possible interactions with containers, surrounding etc. should be known.
- Full aseptic production of low and higher numbers of product possible.

Let's do it «right first time»

Thank you for listening!

Questions?

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