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BIOTECH

»ENSURING THE QUALITY AND RELIABILITY OF CRITICAL RAW MATERIALS AND EXCIPIENTS IN BIOPHARMA«

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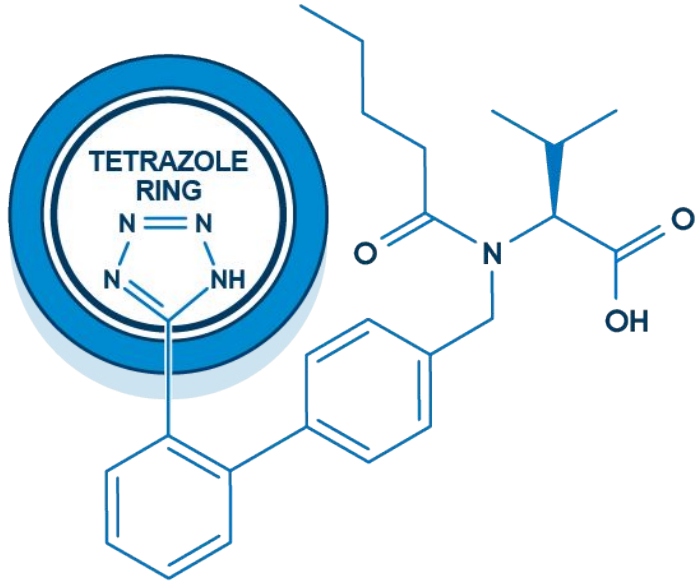
DISCLOSURE

Dr. Frank Velte

- **Head of CG Pharma and Biotech**
  CG Chemikalien GmbH & Co KG
- **Board Member of BPI**
  (Bundesverband der pharmazeutischen Industrie)
- **Advisory Committee**
  Wiesbadener Kreis der Führungskräfte in Pharma Deutschland

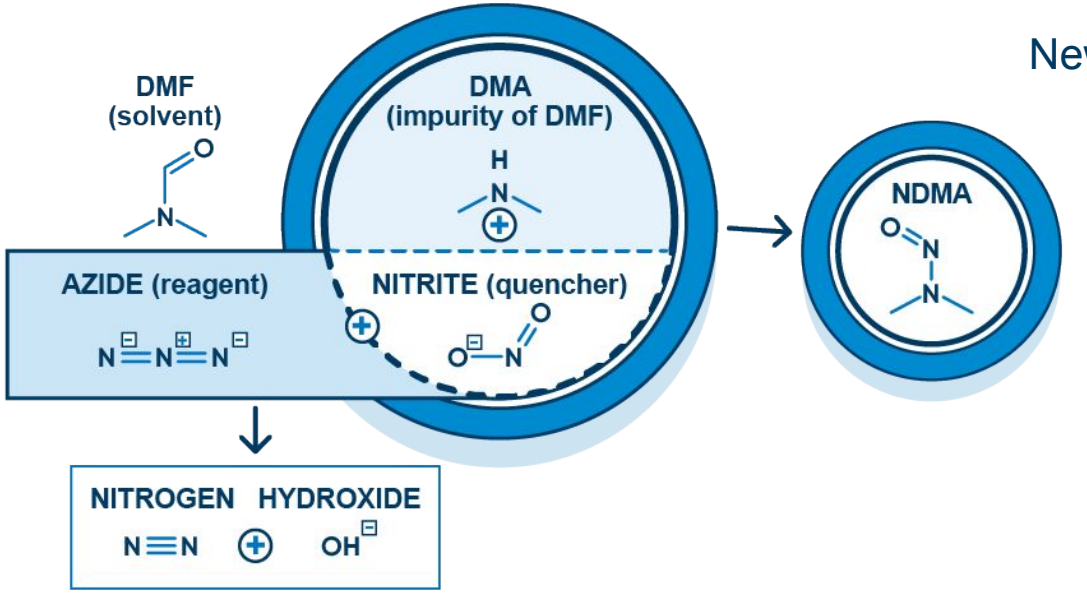
THE FIRST NITROSAMINE CASE

2018 – Zhejiang Huahai



Valsartan

New Process



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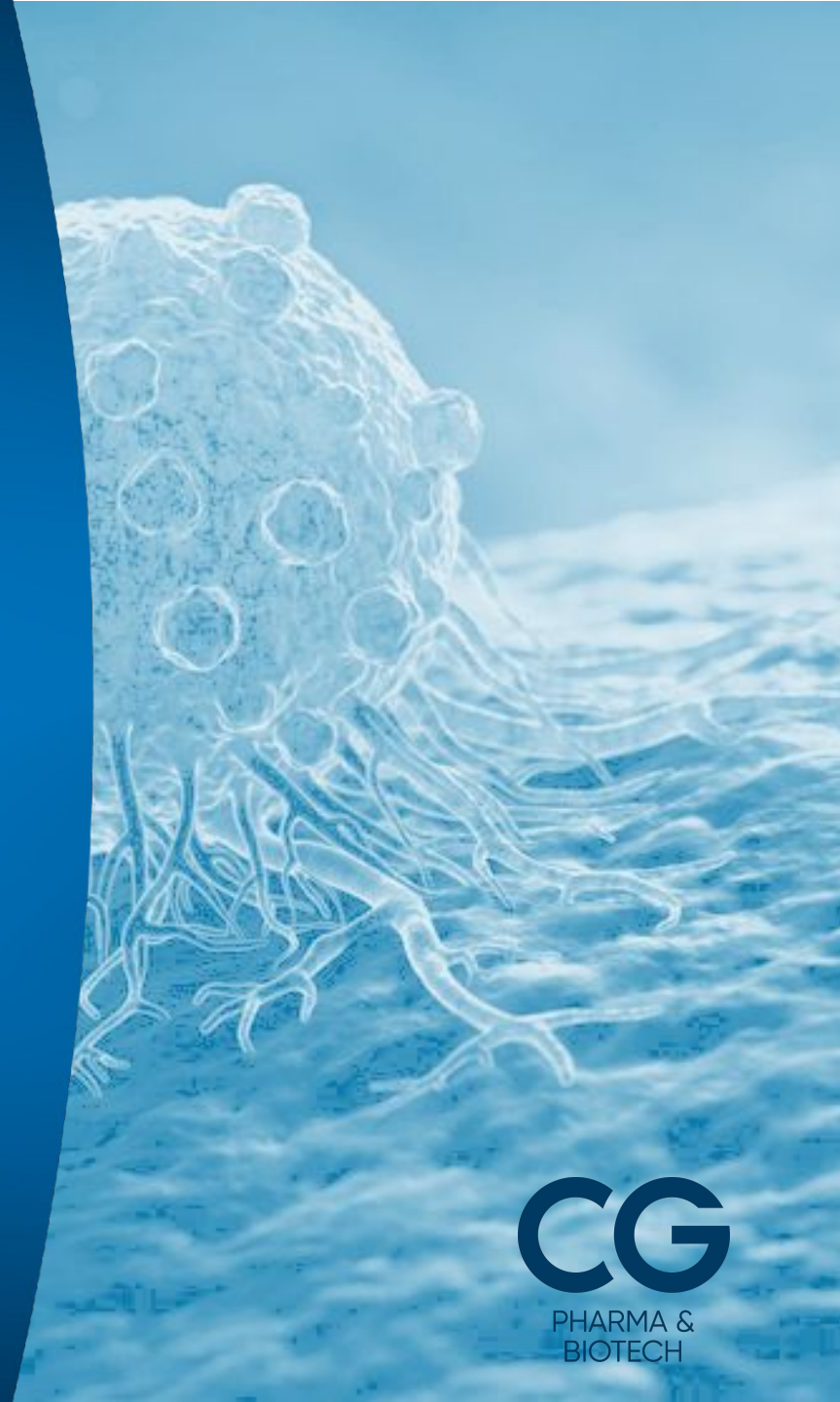
INTRODUCTION

Nitrosysimethylamine

Since 2018 we observe partially nitrosamine contaminations in pharmaceutical industry

- N - Nitrosodimethylamine (NDMA)
- N - Nitrosodiethylamine (NDEA)

- Carcinogenic chemicals
- Found in widley used medications
  e.g. blood pressure lowering drugs, Ranitidine, …
- Leading to recalls and regulatory scrutiny



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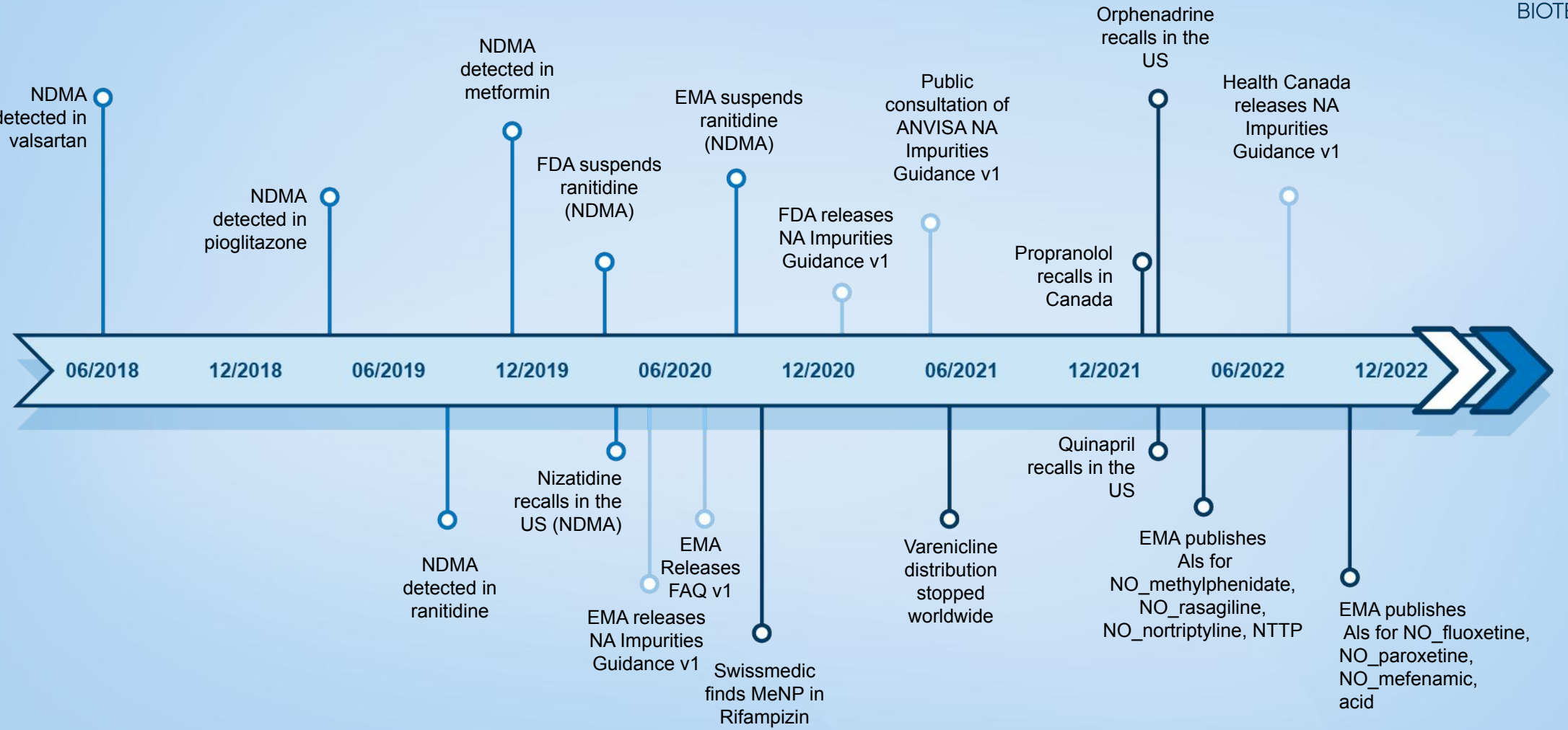
IMPORTANT NITROSAMINE EVENTS

2018 – 2022

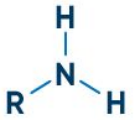
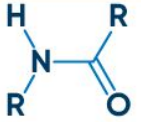


GUIDANCE NDSRI SMALL DIALKYL NITROSAMINE

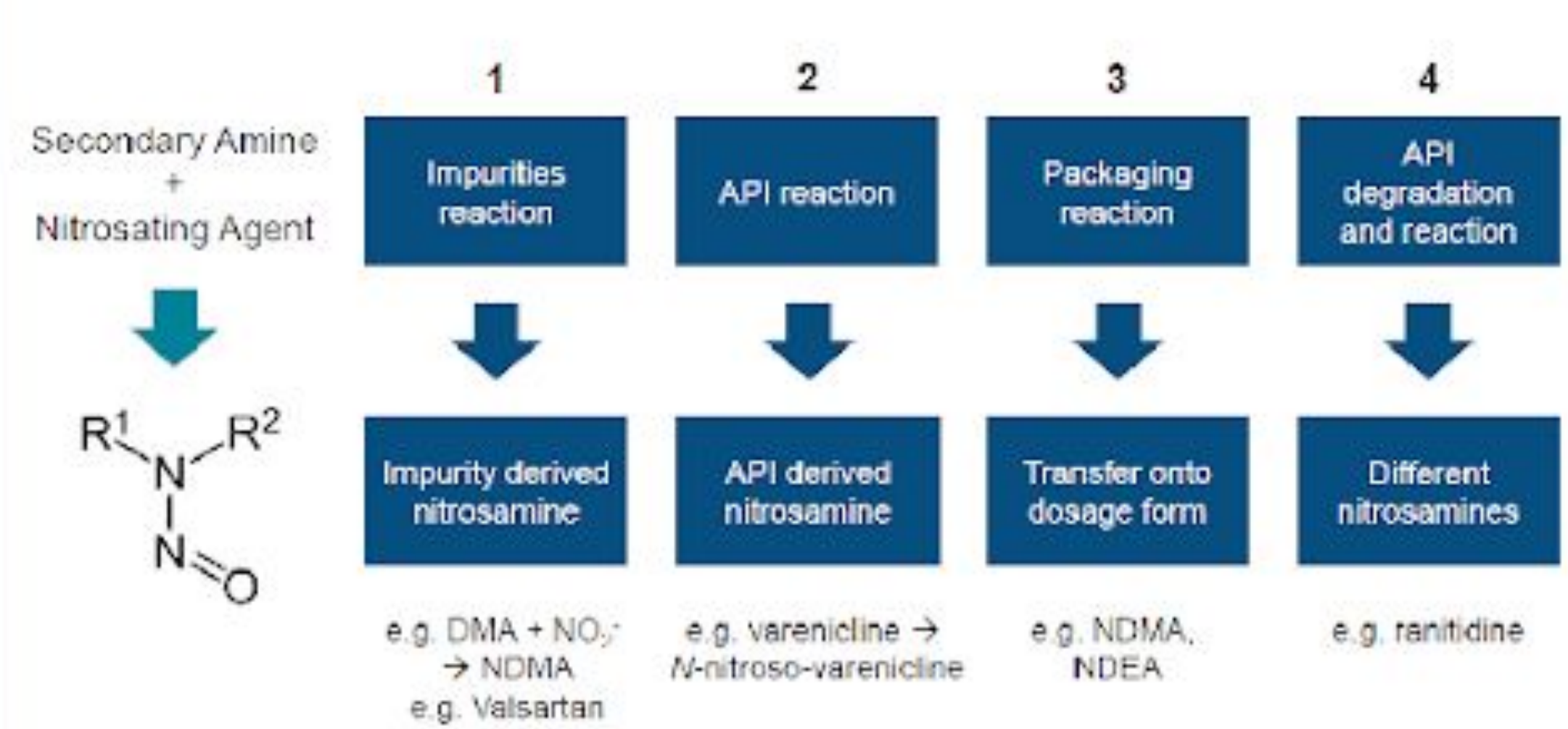
NITROSAMINE PRECURSORS

Secondary amines | tertiary amines

- **Secondary amines are the most relevant nitrosamine precursor**
- Tertiary amines only under specific conditions

MOLECULE CLASS	STRUCTURE	NITROSAMINE PRECURSOR?
Primary amine		NO
Secondary amine		YES
Tertiary amine		YES – but requires nitrosative dealkylation, which is normally slow
Quaternary ammonium		NO – but could contain secondary or tertiary amine impurities
Secondary amide		NO

PATHWAYS TO NITROSAMINES IN DRUG PRODUCTS



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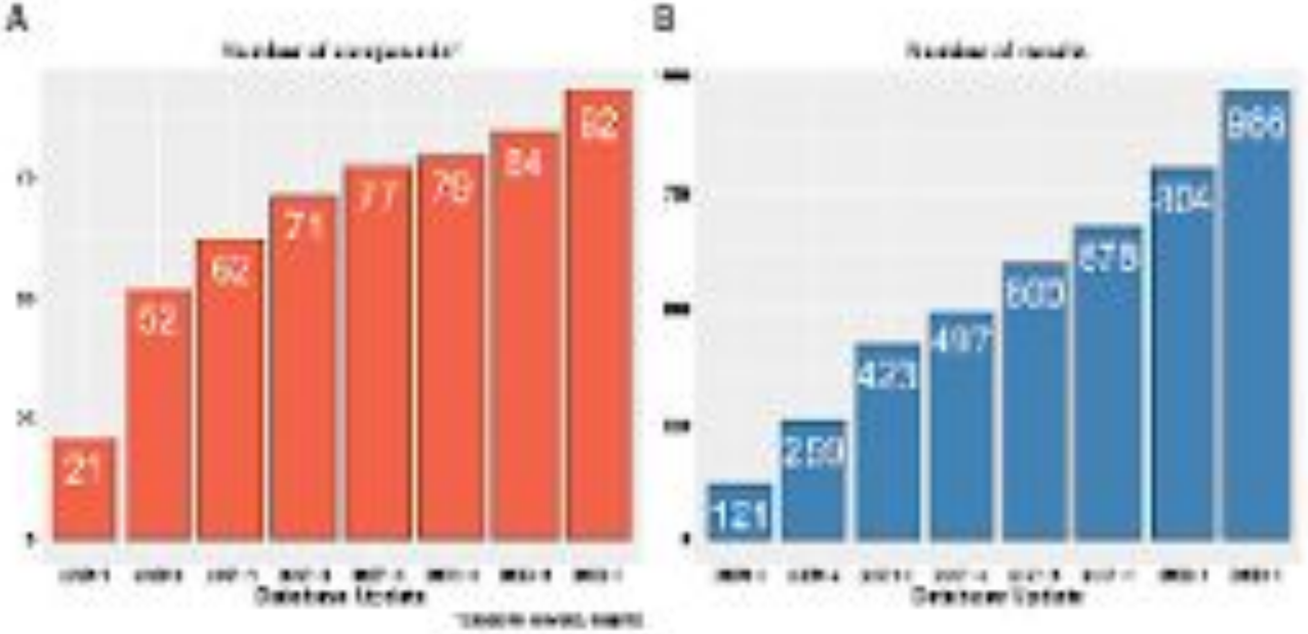
NITRITES IN EXCIPIENTS

Table 5

Name	Number of formulations	Number of results
Magnesium stearate	52	44
Microcrystalline cellulose	41	23
Colloidal silicon dioxide	33	6
Hypromellose (HPMC)	25	40
Lactose monohydrate	25	34
Croscarmellose sodium	23	14
Povidone	21	32
Mannitol	22	6
Talc	15	2
Crospovidone	14	13
Sodium lauryl sulfate	13	2
Polyvinyl alcohol	11	1
Sodium starch glycolate	[illegible]	5
Hydroxypropyl cellulose	7	7
[illegible]	5	3
[illegible]	4	2
Sodium chloride	4	4
Sucrose	2	3
Modified starch	1	–
Stearic acid	1	–



EXCIPIENTS

Important Components of Medicines

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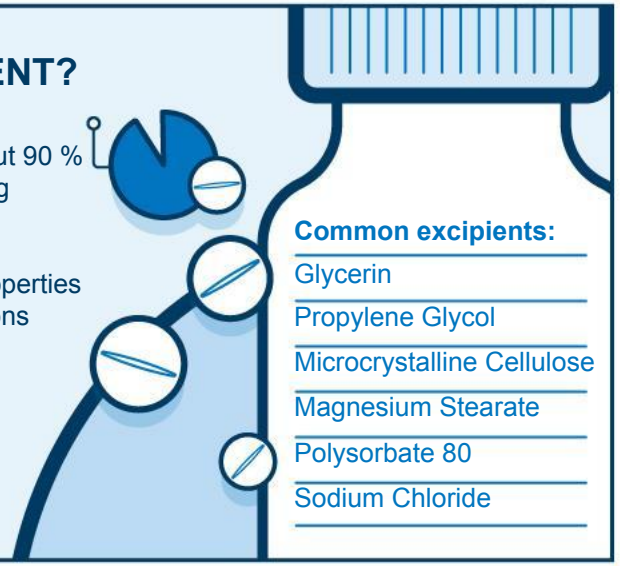
WHAT IS AN EXCIPIENT?

Excipients can make up to about 90 % of the total mass/volume of drug products and are required for

- Enhancing therapeutic properties
- Bulking up solid formulations
- Modifying viscosity
- Enhancig solubility
- Long-term stabilisation
- Drug delivery
- Drug release



Common excipients:

- Glycerin
- Propylene Glycol
- Microcrystalline Cellulose
- Magnesium Stearate
- Polysorbate 80
- Sodium Chloride

RISK FACTORS AFFECTING EXCIPIENT QUALITY

WHY EXCIPIENT QUALITY MATTERS

Fatal consequences linked to high-risk excipients

Pharmaceutical facility closure due to excipient quality/GMP violations

Product recalls and corporate reputational damage

Increased regulatory scrutiny surrounding excipient quality

HOW TO ENSURE THE QUALTY OF EXCIPIENTS

Supplier qualification

Evaluations are needed to assess a supplier´s facilities, personnel, documentations and quality control procedere

General Chapters:

<1078> GMP for Bulk Pharmaceutical Excipients

<1195> Significant Change for Bulk Pharmaceutical Excipients

<1197> GMP for Bulk Pharmaceutical Excipients

<1080> Bulk Pharmaceutical Excipients - Certificate of Analyses

<1083> Supplier Qualification

Excipient standards and solutions

Excipient Monographs
Excipient Reference Standards
Ingredient Verification Program
Good Manufacturing Practices
Ingredient testing
GMP Facility Audit

SOURCE OF CONTAMINATION
(creating conditions for NDMA and NDEA formation)

Traced back to **Excipients**
Improperly sourced
Inadequately tested

IMPACT

Caused regulatory challenges
Financial losses
Draw down of public trust

KEY LESSON

- Excipients play a critical role in drug quality and patient safety
- Contamination can have severe consequencens
- In Biologics, stability and purity are paramount

»Excipient-related risks must be carefully managed«

WHAT ARE EXCIPIENTS IN BIOPHARMACEUTICAL MANUFACTURING?

Definition
- Inactive ingredients, that aid formulation, stability and delivery of API`s
- Maintain the structural integrity of proteins, mAB`s and complex molecules

Function
- Stabilizer (Sucrose, Trehalose)
- Buffer (Tris, PBS, Hepes, EDTA)
- Preservative (Mannitol, Benzyl Alcohol)
- Antioxidants (Ascorbic Acid)
- Specific in Biologics: preventing degradation, aggregation, immunogenic responses

BIOLOGIC DRUGS
=
» high sensitivity to environmental factors like temperature, pH value and light «

EXCIPIENTS IN BIOPHARMACEUTICALS

Specific Roles and Considerations

STABILIZATION OF ACTIVE INGREDIENTS

- Sensitivity of proteins to changes in temperature, pH and ionic strength
- Excipients (Trehalose, Sucrose) prevent the proteins from unfolding or aggregating (loss of biological activity)
- Lyophilized biologis: Mannitol preserve drug`s structure during freeze-drying/reconstitution

BUFFERING CAPACITY

- Biologics urgent need = pH stability (Histidine etc.)
- Improper buffering: protein instability, aggregation, denaturation, defolding

PRESERVATIVES AND ANTIOXIDANTS

- Protection of biologics from oxygen, light…
- Polysorbat
- Ascorbic acid

 No precise selection or overdosing can lead to
  - Affect the biologics activity
  - Increase in immunogenicity

IMPURITIES AND CONTAMINANTS

Risks of Excipients

Types of Contaminants

- Microbial: Bacteria, viruses, fungi, especially water, polyols, glycerin
- Chemical: solvents and chemicals in exipient synthesis
- Particulate: Foreign particles, dust, metallic residues
- Endotoxins: eq. From Gram-negative bacteria; fever, inflammation, sepsis

Implications of contaminated Excipients in Biologics

- Lost of Efficacy: Affecting confirmation or activity of API in Biologics
- Immunogenic Reactions: Immune responses, allergic reactions, anaphylaxis, formation of neutralizing antibodies
- Toxicity: Can cause systemic toxicity and organ damage (Attention: pediatric patients)
- Regulatory Risks:
  - product recalls
  - regulatory scrutiny
  - Loss of market approval
  - Delay of development timelines
  - Harm of clinical trials
  - Prevent the new drug from reaching the market

EXAMPLES:

- Nitrosamine in different drug formulations
- Endotoxin contamination in mAB

 PYROGENIC RESPONSE

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Supplier requirements

- Excipient availability overall
- Supplier capability to comply with the requriements of user specification
- Excipient data package
- Existing agreements
- Level of Relationship
- Pricing

- Excipient supplier relationship characteristics
  - Audit availability (initial and routine)
  - Production experience

CRITERIA FOR MANUFACTURER

choosing an Excipient supplier

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» GMP ENSURES EXCIPIENTS ARE MANUFACTURED TO THE HIGHEST STANDARDS AND MINIMIZING THE RISK OF CONTAMINATION «

REGULATORY CONSIDERATIONS AND COMPLIANCE FOR BIOLOGIC EXCIPIENTS

Global Regulatory Guidelines

- FDA, EMA and ICH enforce strict guidelines for Excipient safety in Biologics
- Good manufacturing practice (GMP), minimizing the risk of contamination
- USP/NF Standards: Standards outlined in the USP or EP
  □ ensure purity, safety and quality
- IPEC Europe develops and publishes guidelines to promote the best use of excipients

Safety Testing

- Endotoxins, critical for Biologics adminstered parenterally (IV, subQ)
- Microbial contaminants, bacterial andotoxins, fungal spores and mycoplasma (Attention: injectable biologics)
- Heavy metals (e.g. lead, mercury)
- Residual solvents

EXCIPIENTS

The challeng of audits

According to GMP standards Excipients supplier audits are essential.

Excipient user perspective

How many excipient suppliers?

- How many audits needed?
- Frequence of audits?

 Decisions based on risk

Excipient suppliers perspective

- How many audits?

 Decisions based on commercial reasons

EXIPACT STANDARD

 3rd party GMP certification

EXCIPIENTS

EXIPACT – how it works.

PRODUCTION IN EXCIPIENT MANUFACTURING

Development | Scale Up versus Routine Production

Development | Scale up
Flexibility and Innovation
Experiments and Process Adoption
Smaller and flexible facilities
Faster Adoption
Lower regulatory levels

Routine Production
Stability and Standardization.
Efficient and secure Production
Large scale production facilities
Validated repeatable processes
Strict GMP Compliance

»Split the two tasks in two teams -
may be an advantage in Exipient manufacturing for biologics.«

MAKE OR BUY.

Streamline your supply chain by outsourcing activities

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MAKE

Advantage

- Control over exipient quality, sourcing and purity

Risks

- Higher capital investment
- Operational complexity
- Increased regulatory burden
- Increased number of high trained staff

BUY

Advantages

- Access to expert suppliers

CONCLUSION & SUMMARY

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KEY TAKEAWAYS

- Right excipients are crucial for biologic drug efficacy and stability
- Contamination in exipients poses significant risks
  - Immunogenicity
  - Toxicity
  - Regulatory non-compliance
- Supplier selection is paramount to minimize contamination risks and ensure high-quality excipients
- The make or buy decision impacts contamination control, cost and regulatory compliance in biologics
- Rigorous testing. Proper supplier audits and adherence to regulatory standards are necessary to mitigate contamination risks in biologic exipients

» EXCIPIENTS ARE VITAL FOR THE STABILITY, BIOAVAILABILITY AND SAFETY OF BIOLOGIC DRUGS.«

Presence of impurities or contaminants in exipients can lead to severe risks

- Product instability
- Immunogenic reactions
- Regulatory failure

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» GMP COMPLIANT MANUFACTURER «

CLEANING IN PLACE SOLUTIONS
PROCESS SOLUTIONS
BUFFER SOLUTIONS
PHARMACOPOEIA TESTED RAW MATERIALS & EXCIPIENTS

For use in the production of drug substance and drug products

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In an nutshell

HIGHLIGHTS

- Qualified partner of global pharma and biopharma companies
- GMP-compliant manufacturing of liquid and solid components for use as ingredients, starting materials or excipients
- GMP-certified production facility with cleanroom class C&D
- Management of pharmacopoeia-compliant raw materials (e.g. EP, BP, USP, JP, ChP)
- In-house GDP logistics
- “Made in Germany”
- One vendor for multiple chemicals

KEY COMPETENCES

- Manufacturing of customised, sterile-filtered (bio)pharmaceutical process solutions and excipients for upstream and downstream applications
- Standard catalogue products for several pharma-ceutical applications
- Scalable from small scale to commercial production
- Ready-to-use sterile filtered solutions in single-use bags
- GMP cleaning solutions for CIP and SIP applications
- Processing of hazardous substances in the cleanrooms (corrosive and flammable)
- In-house production of WfI and AP

CERTIFICATION

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- Manufacturing authorisation to the German Medicinal Products Act
- GMP

HEALTH & NUTRITION

- FSSC 22000 (HACCP)
- Kosher
- Halal

QUALITY & SUSTAINABILITY

- ISO 9001
- ISO 50001
- ISO 14001
- SQAS/ESAD
- Responsible care
- EcoVadis
- GDP

THE CG PHARMA & BIOTECH CONCEPT

Services & Products

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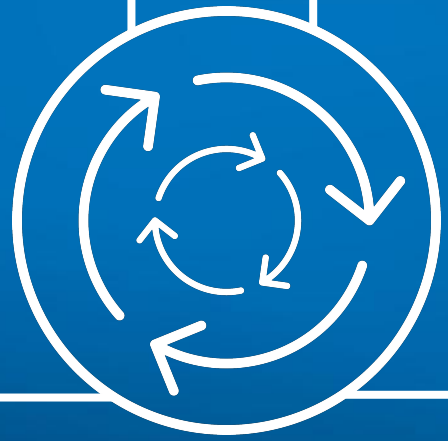
C-MADE

Manufacturing and development of
CUSTOMISED FORMULATIONS
for the biopharma
production process - upstream,
downstream and
final formulation steps.

Liquids
Customised Formulations

Solid
Customised formulations simple
and highly complex mixtures



PharmProve®

Manufacturing of
MULTI-COMPENDIAL
PRODUCTION CHEMICALS
for use as ingredient, starting material
or excipient.

Liquids
Single Components

Solid
Single Components

CUSTOMERS | APPLICATIONS & PRODUCTS

Extract

Biological medicinal products

- Plasma derived medical products (PDMP)
- Enzymes
- Heparines

Classic pharma (chemical/synthetic drugs, API)

- Oral solid, liquid and semi-solid formulations
- Inhalation formulations
- Ophthalmic formulations
- Dialysis formulations

Biotechnologic based drug substances and drug products

- Vaccines (mRNA, recombinant DNA, cell culture based and vector based)
- ATMP's (advanced therapy medical products) cell and gene therapy
- Cell culture media
- Monoclonal antibodies (mAbs)
- Biosimilars

TAILORD SOLUTIONS

- Development and production of customised formulations
- In-house R&D department, from laboratory scale to commercial production
- Agile project management, consulting and planning
- Pharma Logistic Concepts

CUSTOMER APPLICATIONS & PRODUCTS

- biotechnologically produced active ingredients and drugs
- e.g. vaccines, ATMPs, cell culture media and biosimilars
- biological drugs
  e.g. plasma-derived medical products, enzymes and heparins.

PROFESSIONAL ANALYTICS

- In-house chemical/physical analytical laboratory
- Testing of starting materials according to pharmacopoeia (e.g. EP, BP, USP, JP, ChP)
- Finished product testing
  (e.g. appearance, pH, conductivity, density, refractive index, osmolality, assay)
- Microbiological testing
  (e.g. sterility, endotoxins, RNAse, bioburden)
- Stability testing

OUTSTANDING QUALITY

- EU GMP certified facility
- Cleanroom production ISO 7/8
- GDP storage and transport
- Quality assurance agreements with customers and suppliers
- Batch release by authorised person
- Change control management
- Supply chain information
- Process validation & equipment qualification
- Quality-related customer questionnaires

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GOOD REASONS

Highlights | Solutions
Applications
Services
Quality


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