Orion

Building well-being

ORION
Building well-being

Orion today — year 2017 in figures

Net sales 1 085 MEUR
Operating profit 293 MEUR

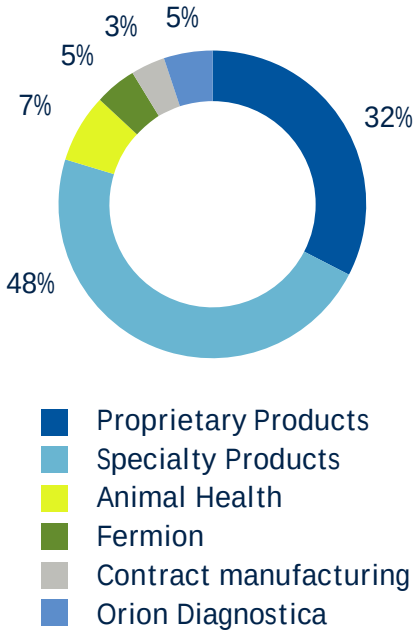
Personnell 3 500

R&D investments
105 MEUR

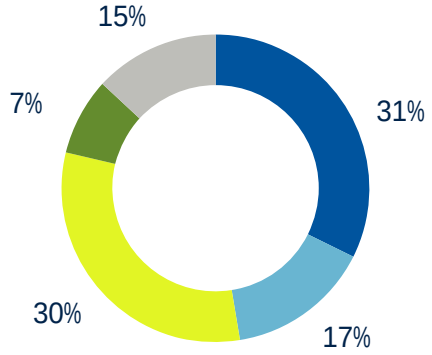
6 production sites in
Finland

Own sales unit in
26 European countries

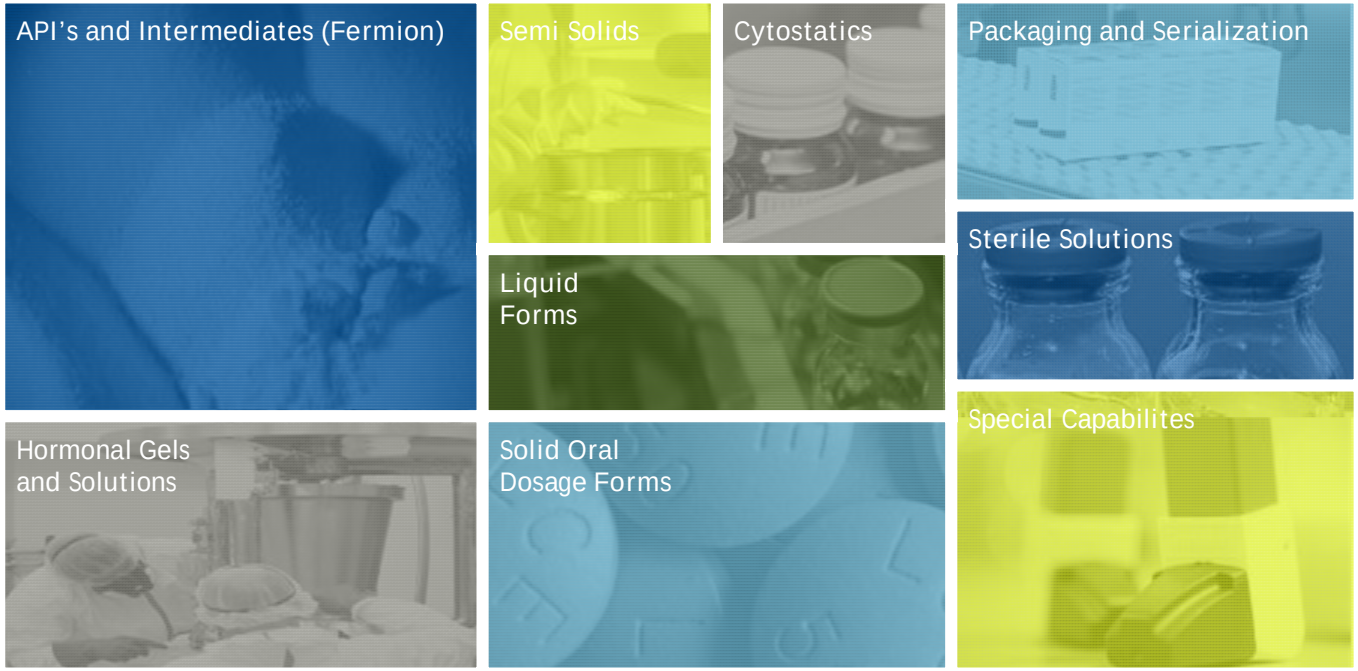
Sales split by business



Sales split by market area



Orion Contract Manufacturing



Your Partner for API Contract Development and Manufacturing Services

Fermion Oy

www.fermion.fi

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Fermion Today

Fully owned subsidiary of Orion Corporation

Develops, manufactures and sells active pharmaceutical ingredients (APIs)

- New chemical entities for Orion's existing and new proprietary products
- Custom development and manufacturing for innovators with focus on high potency APIs
- Generic APIs to pharmaceutical companies worldwide

Fermion in 2017
Net sales: EUR 82 million (62 % External, 38 % Captive)
Main markets: USA, EU and Japan, India, Brazil, ca. 100 customers
Ca. 35 products, both innovative and generic APIs
Head office, R&D, bench scale production, regulatory department in Espoo
Two commercial manufacturing sites: Hanko and Oulu
Personnel: ca. 340

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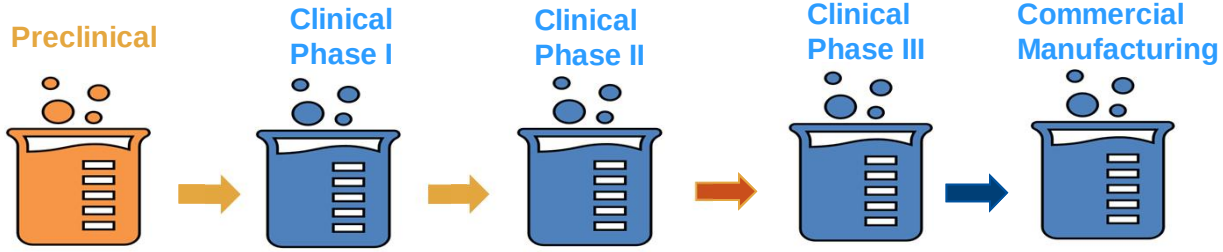
Fermion CDMO

Synthesis route development

Process development

Lifecycle management

Small molecules



In collaboration with Pharmatory Ltd

Manufacturing

Fully automated GMP production from kilo scale to commercial scale

High delivery service level

Compliance

FDA approved since 1979

EMA approved since 1971

Regulatory

DMF compilation, maintenance and consultancy (EU, USA, etc.)

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Fermion references

Innovative APIs

- 10 NCEs developed and manufactured by Fermion for commercial use
- Several NCEs currently under development in different clinical phases
- Developed for Orion corporation and for external customers

Generics

- 25 generic products
- Main markets USA, EU, Japan and India

Hospira SHIONOGI INC. G1 THERAPEUTICS NOVARTIS ORION

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Fermion services

Contract Development

- Synthesis development and process engineering
- Analytical development and testing
- Particle engineering
- Scale-up
- Validation
- Lifecycle management

Contract manufacturing

- Production from laboratory scale to commercial scale
- 3 manufacturing sites in Finland
- Total volume of reactors 320 m^3
- GMP reactor sizes vary from 10 l to 6300 l
- Annual API capacity >400 metric tons
- High-potency APIs (OEB5) (cytotoxic and non-cytotoxic) from grams to tens of metric tons
- Orion Corporation: Contract manufacturing of finished dosage forms

Regulatory and Compliance

- DMF compilation, maintenance and consultancy services
- Experience in regulatory filings in e.g. USA, Canada, EU DMF/CEP, Japan, Taiwan, China, Brazil, Australia
- FDA approved since 1979 and EMA approved since 1971

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Latest inspection history

- FDA inspected and approved since 1979
- In addition several customer audits and internal audits yearly

	Espoo	Hanko	Oulu
FDA	2003 2011	2011 2014 2016 2018	2010 2013 2016 2017
FIMEA (Finland)	2010 2013 2017	2011 2014 2017	2011 2014 2017
PMDA (Japan)		2006*	
MOH (Mexico)			2010
KFDA (South Korea)			2010
ANVISA (Brazil)			2011 2016

* Remote inspections since 2006

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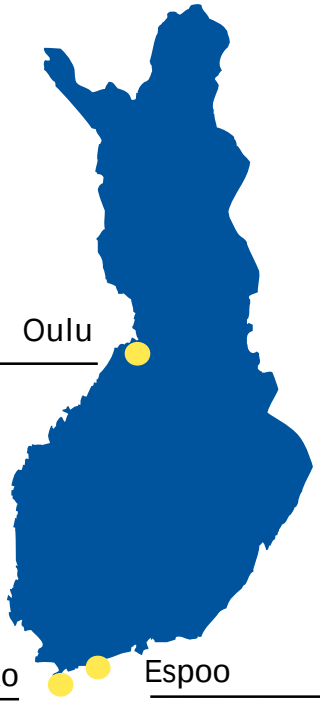
Fermion capabilities per location



- Commercial HPAPIs and standard APIs (fully automated)
- Containment 0,1 µg/m^3
- QA, QC

Oulu

- Commercial large scale API production (fully automated)
- Containment 0,1 µg/m3
- QA, QC

Hanko

Espoo

- R&D
- GMP kilo production, also HPAPI
- Containment 0,1 µg/m^3
- Analytical development, QA, QC and regulatory affairs

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Batch sizes and containment levels

Facility	Batch size	Containment level µg/m³ 10 -	1 - 10	0,1 - 1
Espoo Laboratory	1 – 100s g	x	x	x
Espoo Kilo	0,2 - 5 kg	x	x	x
Oulu Pilot	2 - 20 kg	x	x	x
Oulu small scale	20 - 100 kg	x	x	
Oulu large scale	20 - 500 kg	x		
Hanko large scale	100 – 1000 kg	x	x	x
Micronization	0,5 – 60 kg	x	x	x
	30 – 1000 kg	x	x	x

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Automation

Advantages	Overall benefits	Measurable benefits
Less manual labor	Reduced costs	50% reduction in operator labor in the fully automated unit. Company-wide 15-20%.
Consistent quality, increased productivity and yields	Reduced costs, shorter timelines	30% less reprocessing
Fewer emissions, reduced energy consumption, less waste	Regulatory criteria exceeded, positive brand image, minimal impact on the environment	8% reduction in energy consumption in 2014
Access to electronic recipes, batch records and process data	Process optimization leading to decreased costs	Up to 50% decrease in COGS with process optimisation
Increased worker safety		Invaluable

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Health and Safety

Safety of our staff and patients

Minimise cross-contamination potential	Minimise overall regulatory and patient risk

High occupational health and safety standards

Corporate level strategic targets

Safety observations
Lost Time due to Injury

Big pharma EHS audits approved

Pfizer

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Emission control

Emissions into air

- Exhaust air passed through on-site incinerators or catalytic converters
- Cryogenic condensation plant in 2016 to Oulu
- International Responsible Care Program and the national Energy Efficiency Program

Waste and waste water treatment

- All solids, also hazardous waste, recycled or incinerated
- Waste decreased by 5% in 2015
- Biological pretreatment of waste waters (Hanko)
- 2017 system to collect and incinerate API and chemical waste waters

Materials and energy efficiency

- Plant heating with energy derived from VOC combustion (Hanko)
- Energy consumption decreased by 5% in 2015
- Solvent recovery (regenerated solvents 44% of total use in 2015)
- Environmentally friendly raw material and solvent options are used when possible

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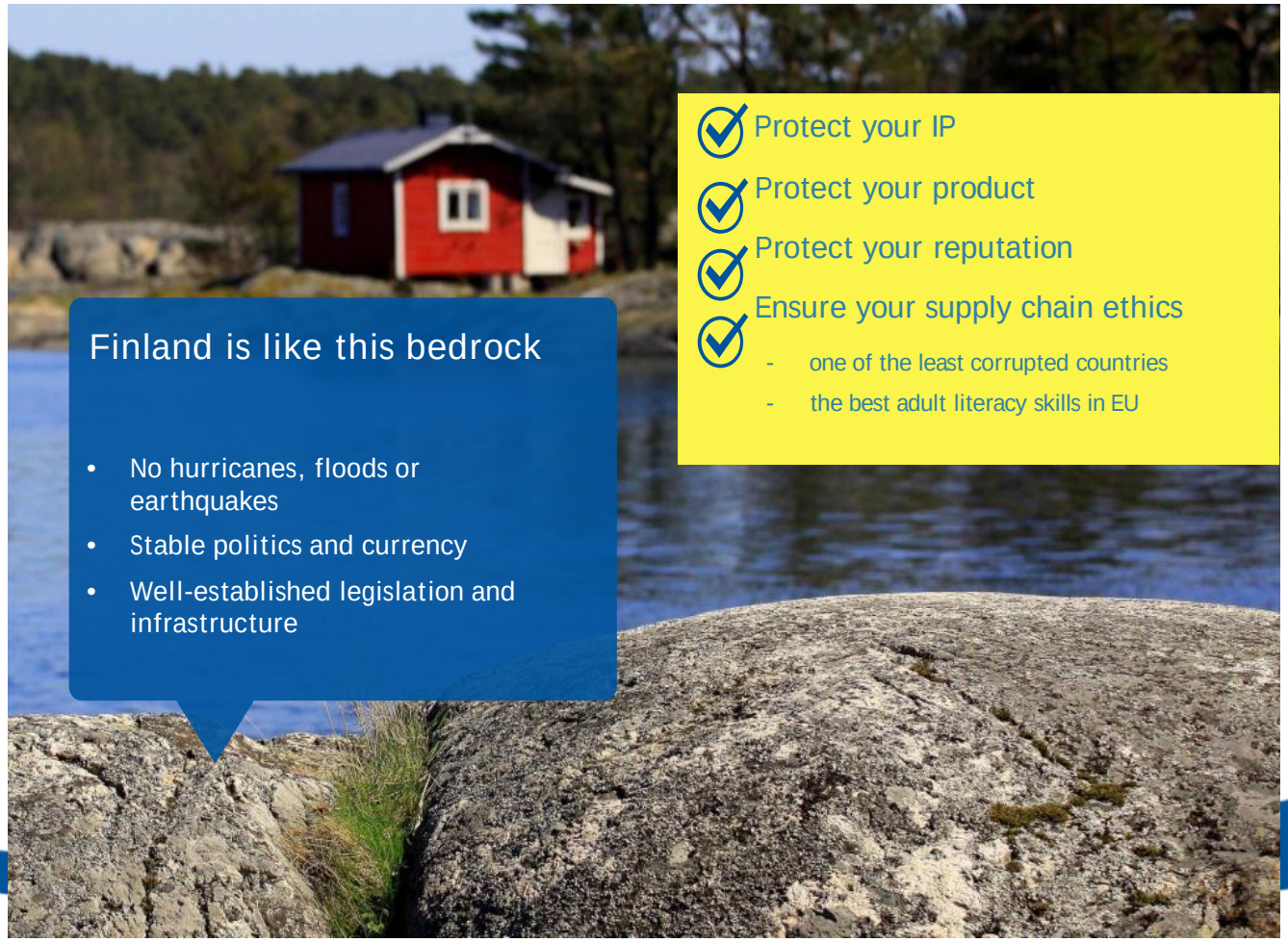
Finland is like this bedrock
• No hurricanes, floods or earthquakes
• Stable politics and currency
• Well-established legislation and infrastructure
Protect your IP
Protect your product
Protect your reputation
Ensure your supply chain ethics
- one of the least corrupted countries
- the best adult literacy skills in EU

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Do it once, do it right

R&D facilities and capabilities

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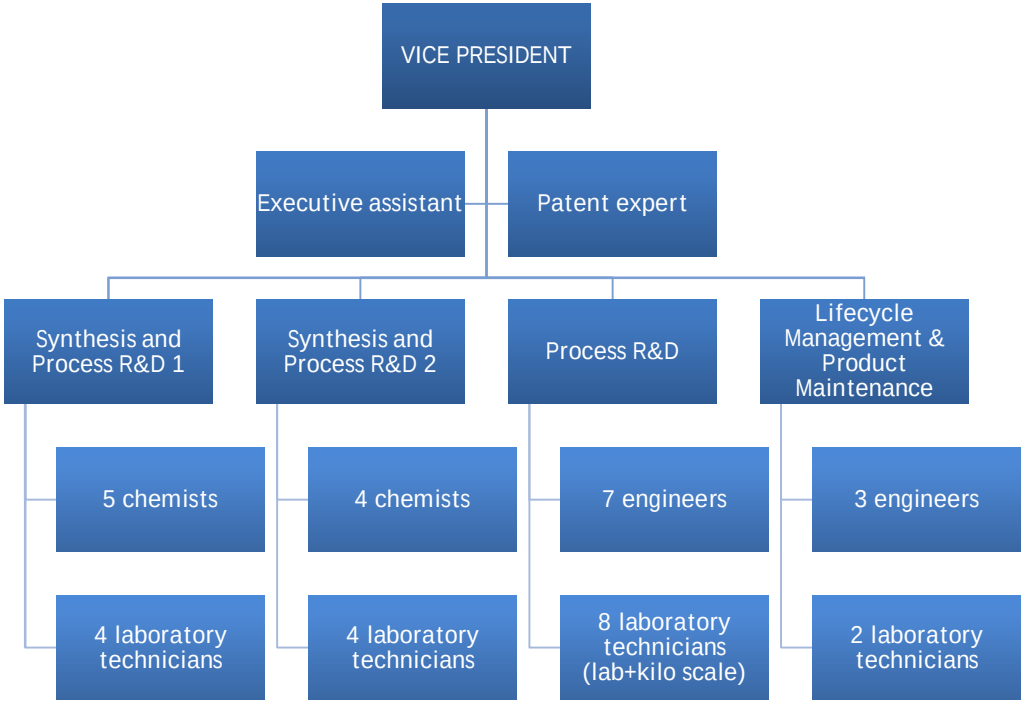
R&D organisation



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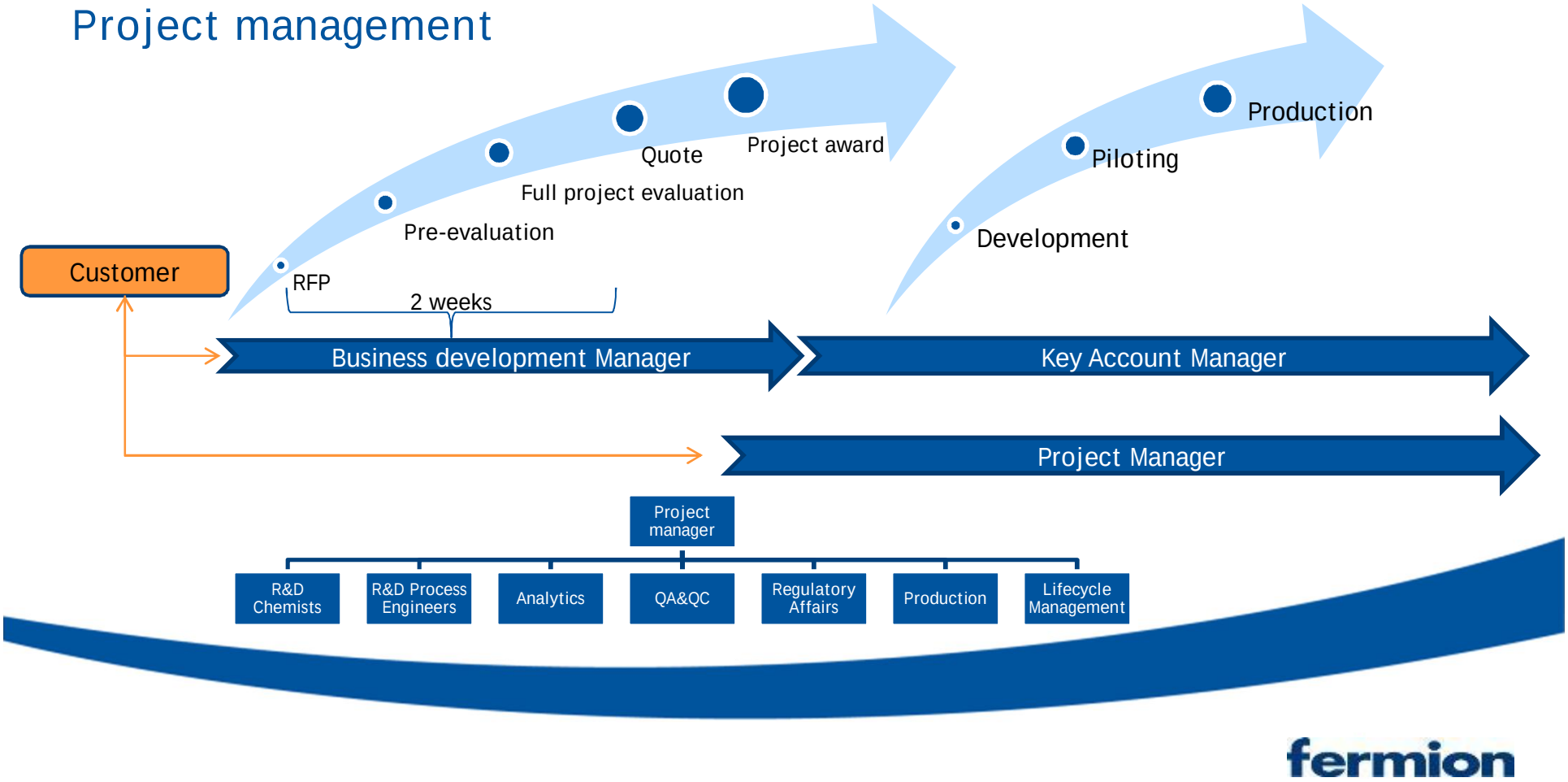
Project management



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R&D facilities 600 m2
Espoo, Finland
1 HPAPI lab
6 fume hoods
GMP kilo
scale unit
10-30 l reactors
2 equipment labs +
hydrogenation
8 fume hoods
R&D lab
41 fume hoods

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Kilo GMP facility details

- Unit 1, OEB3 (10-100 µg/m^3)
  - 2 x 30 l reactors
  - 1 x 10 l
  - Suitable for small scale GMP manufacturing

- Unit 2, OEB3 (10-100 µg/m^3)
  - 2 x 10 l reactors for crystallizations
  - Final API separated by air locks
  - Jet mill for micronizations
  - Frewitt for sievings
  - Pin mill

- Unit 3, OEB5 (0,1 – 1 µg/m^3)
  - Designed like a plant; efficient and reliable scale-up work utilizing a production-type Honeywell data acquisition system
  - Isolator for raw material and API dispensing
  - Filtration isolator
    - Pressure filtrations by cartridges, bags and Nutsche
  - Isolator with integrated tray dryer, conical mill and mixer
  - 3 x glass-lined 30 l reactors with split valve charging
  - 1 x hastelloy 30 l pressure reactor for e.g. hydrogenations (30 bar)

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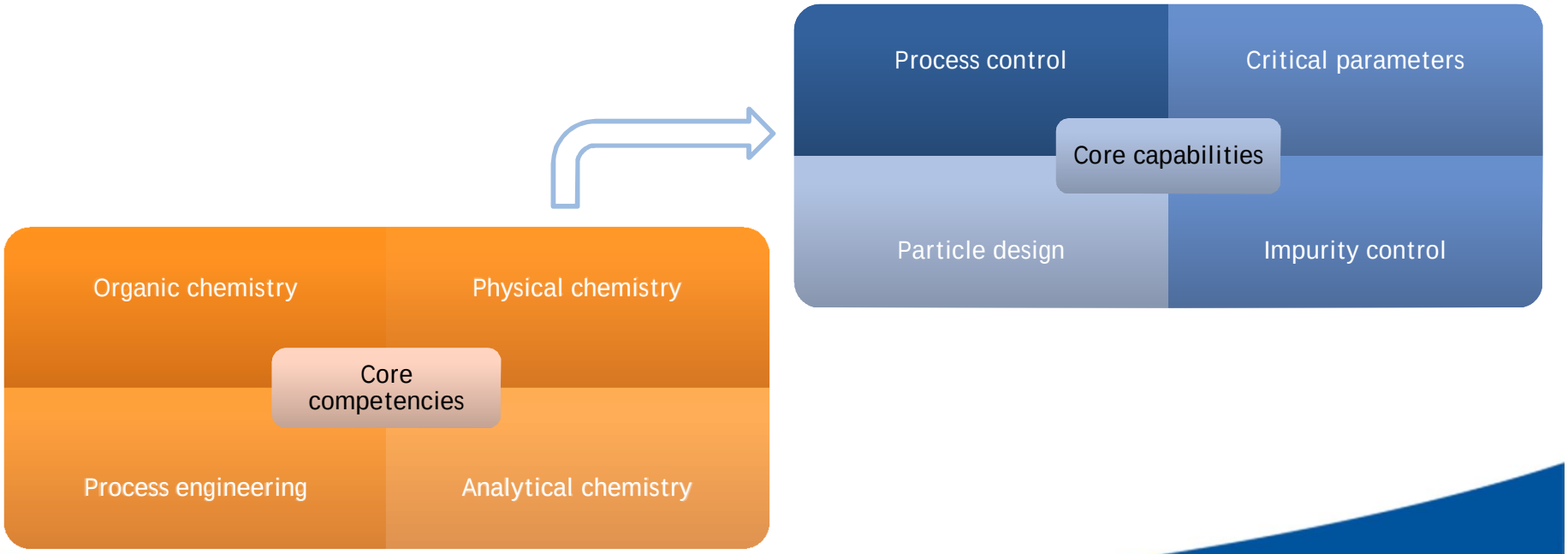
R&D core capabilities



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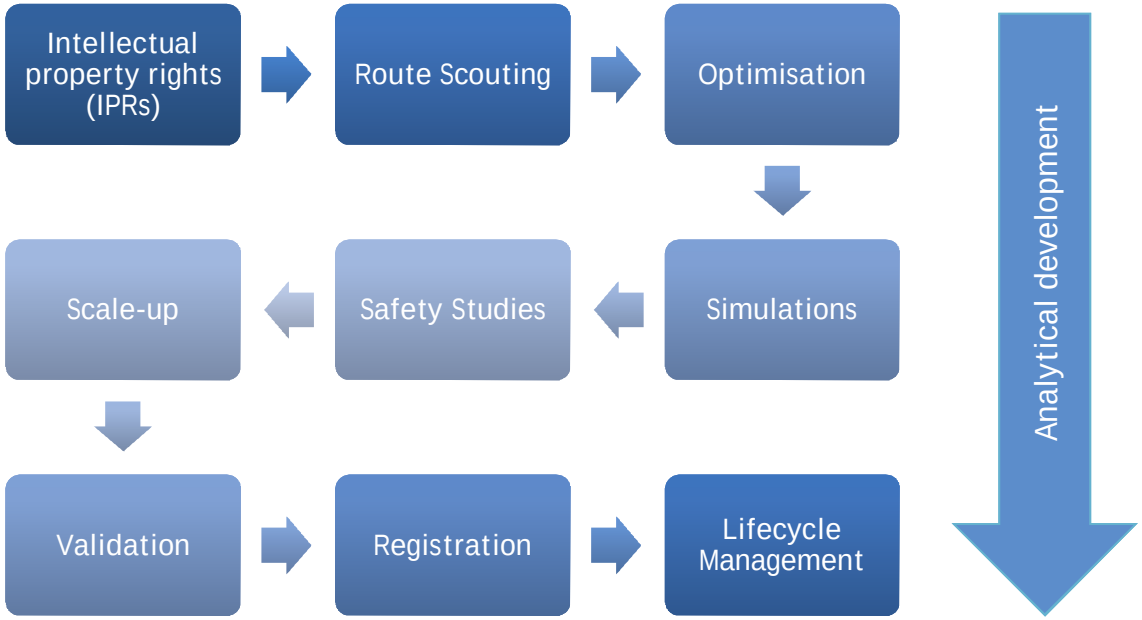
Fully Integrated, Pick What You Need



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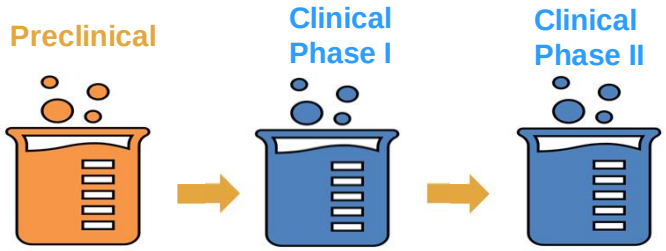
Early phases in collaboration with Pharmatory Ltd



In collaboration with Pharmatory Ltd

Collaboration experience				
FTE Lab Research	Route Scouting mg – 100 g	100 g – 1 kg	1 kg – 10 kg	>10 kg
6 years continuous agreement	~ 10 projects	~ 20 projects	~ 20 projects	~ 10 projects

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R&D process

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Synthesis route

- Drawing board
- Reaction sequence
- Non-continuous parameters (e.g. choice of solvent or base) considering environmental factors and safety
- Parallel experimentation
  - more data in less time
  - more reliable data
  - find the unexpected

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Process development

- Optimise the yield and purity
- Design of experiments (DoE)
  - systematic approach
  - less experiments for same information
- Safety studies and environmental assessment of the process
- Scale-up and scale-down
  - Deeper understanding of the process for transfer to production

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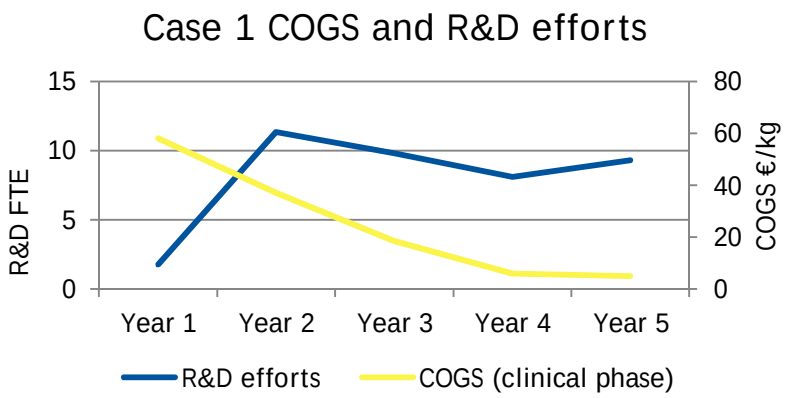
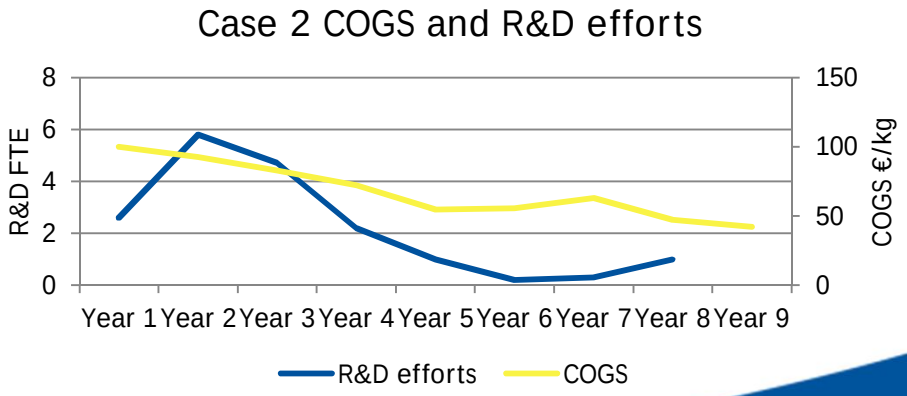
Lifecycle management

Constantly evaluating how to improve process cost-efficiency, EHS aspects and the quality of the product and implementing relevant actions





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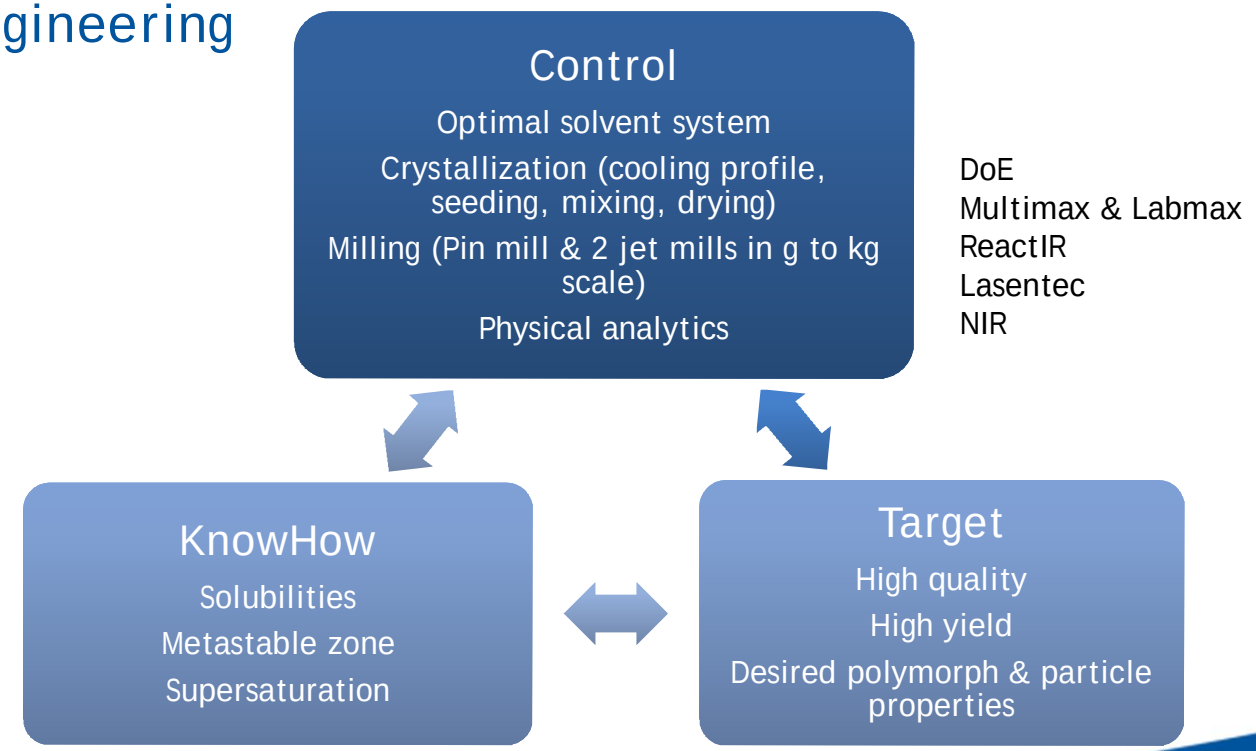
Particle engineering



DoE
Multimax & Labmax
ReactIR
Lasentec
NIR

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Chemistry in a pharmaceutical environment

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Fermion Oulu plant

GMP HPAPIs and APIs in medium scale

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Oulu plant structure and capabilities

Modules 1-5

- OEB III (10 - 100 µg/m³)
- Non-cytotoxic products
- Reactor sizes ranging from 250 l to 6300 l (70 m³ reactor space 63m3)

Modules 6 and 7

- Mod 6 OEB IV (1- 10 µg/m³)
- Mod 7 OEB III (10 - 100 µg/m³)
- Cytotoxic products
- Reactor sizes: 2 x 63 l (Module 7) and 6 x 1600 l (Module 6) (10 m³ reactor space)

Module 8

- OEB V (0,1 - 1 µg/m³)
- Non-cytotoxic products
- 2 x 250 l reactors (0,5 m³ reactor space)

Module 9

- OEB V
- Cytotoxic products
- 1 x 250 l and 2 x 400 l reactors (1,05 m³ reactor space)
- Opened in 2013

Module 10

- OEB V
- Non-cytotoxic products
- 1 x 250 l and 2 x 400 l reactors (1,05 m³ reactor space)
- Opened in 2015

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Oulu Module 9 and 10 reactor charging

- Module 9
  - High potency cytotoxic products
  - 3 reactors
  - Dispensing & reactor charging isolator
- Module 10
  - High potency non-cytotoxic products
  - 3 reactors without the reactor charging isolator

Module 9 (3rd floor) top-down material flow

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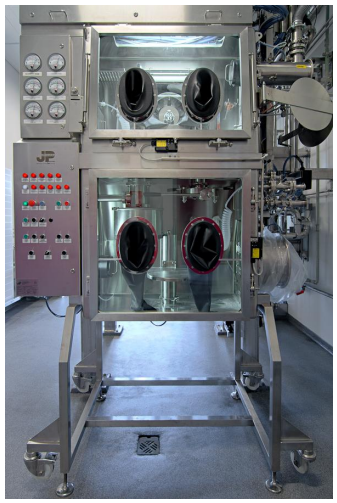
Module 9 and 10 filter dryer isolators

	Module 9 (cytotoxic)	Module 10 (non-cytotoxic)
Maximum volume	300 l	55 l
Filtering area	0,3 m^2	0,13 m^2
Multilayer filter plates	5 µm or 20 µm	5 µm or 20 µm
Milling	Inline, conical screen mill	Inline, conical screen mill



Module 9 (2nd floor)
Filter dryer isolator

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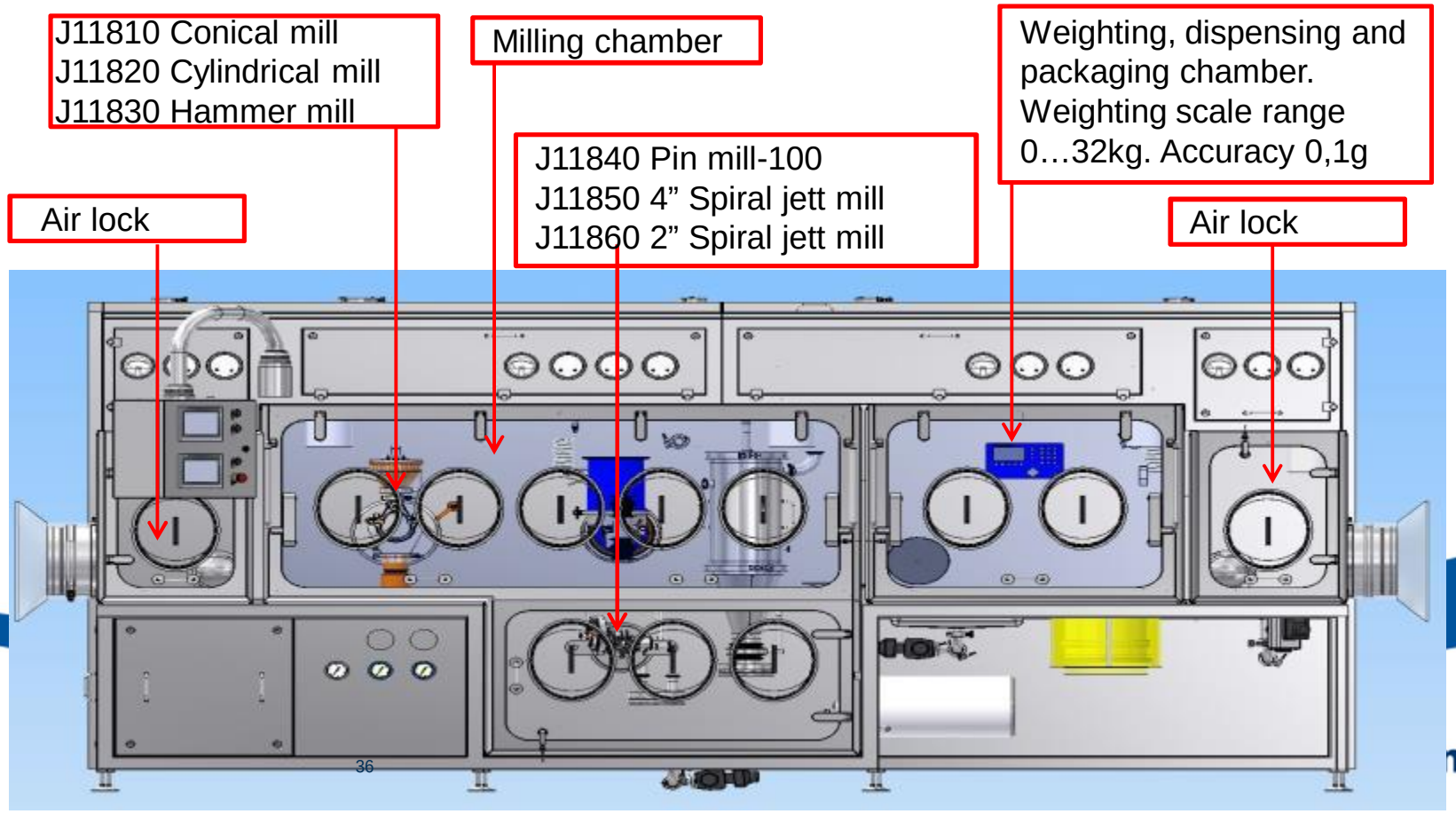
Oulu OEB5 milling/micronization module (OEL above 0,1 mcg/m3)



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Hanko plant

- 300 metric tons / year
- Fully automated 2-operator API production
- 0,1 -10 µg/m^3 containment
- Separate micronization areas (4 micronizers, jet mills)
- On-site incineration and waste water treatment and distillery to recover solvents
- Immuno-suppressants and controlled substances such as class IV-narcotics
- Buss loop 500 l / 80 bar

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Hanko plant structure and capabilities

Unit 1	•Manufacturing of intermediates •20 x 1000 – 6300 l reactors (70 m^3 reactor space) •Several vacuum dryers
Unit 2	•Manufacturing of intermediates •24 x 2500 – 6300 l reactors (110 m^3 reactor space) •Several vacuum dryers
Unit 3	•Highly automated •Manufacturing of final APIs •10 x 6300 l reactors (63 m^3 reactor space) •Several vacuum dryers •Several mills, e.g. air jet mill
Unit 4	•Highly automated •Manufacturing of crude/final APIs •12 x 6300 l reactors (76 m^3 reactor space) •Several Centrifuges/Vacuum Dryers/Filter Dryers

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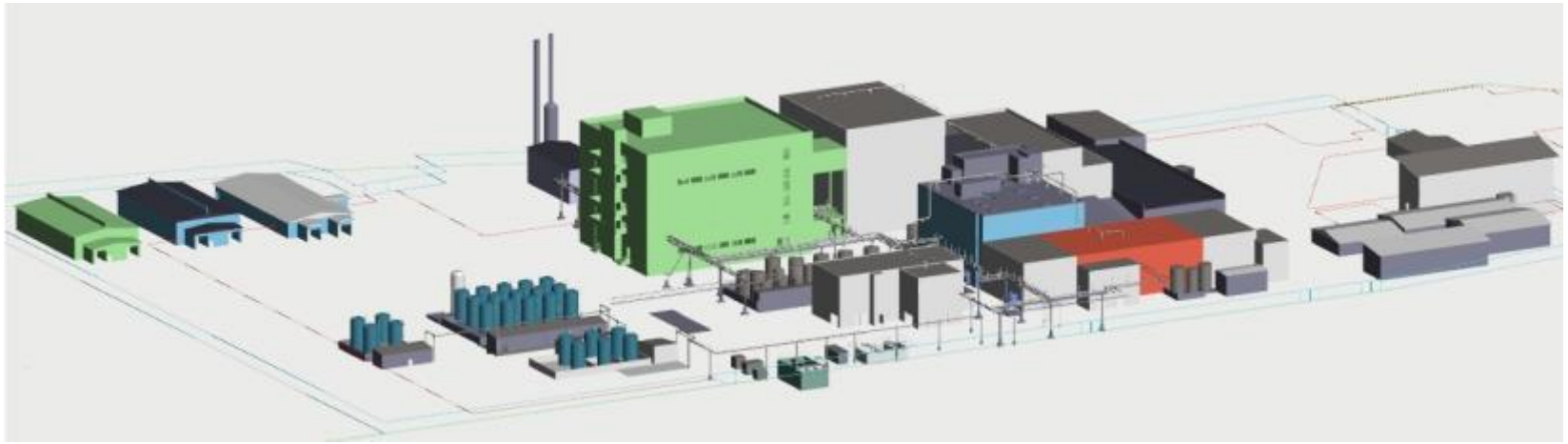
Hanko plant expansion



2018

100 m^3 reactor space (built 76 $\mathbf{m^3}$)
6000 m^2 surface area
OEB5 containment level, 25 $\mathbf{m^3}$
In use 2018

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Hanko Unit 4 has been taken into use 2018

Total of 100,8 m3 reactor capacity

Main department: total 50,4 m3 reactor capacity, OEB4 class

- Reactors 8*6.3 m3, 2 hastelloy C22 + 2 enamel + 2 stainless steel Aisi 316L
- Centrifuges 3 , 1 hastelloy c22 + 2 stainless steel Aisi 316L
- Vacuumdryers, 1600 l , hastelloy c22 + stainless steel Aisi 316L
- Filter dryer 1300 l, hastelloy c22
- High containment systems charching liquids (1) and solid materials (2) (OEB 4 and 5)

Two special synthesises modules: total 25,2 m3 reactor capacity, OEB5 class

- Capacity of one module is 12.6 m3, two reactors 6.3 m3, 1 stainless steel Aisi 316 L , 1 enamel
- Filter dryer 1300 l, stainless steel Aisi 316 L
- High containment systems charching liquids (1) and solid materials (1) (OEB 5)

Two special synthesises modules left empty for future extension:

- Total 25,2 m3 reactor capacity

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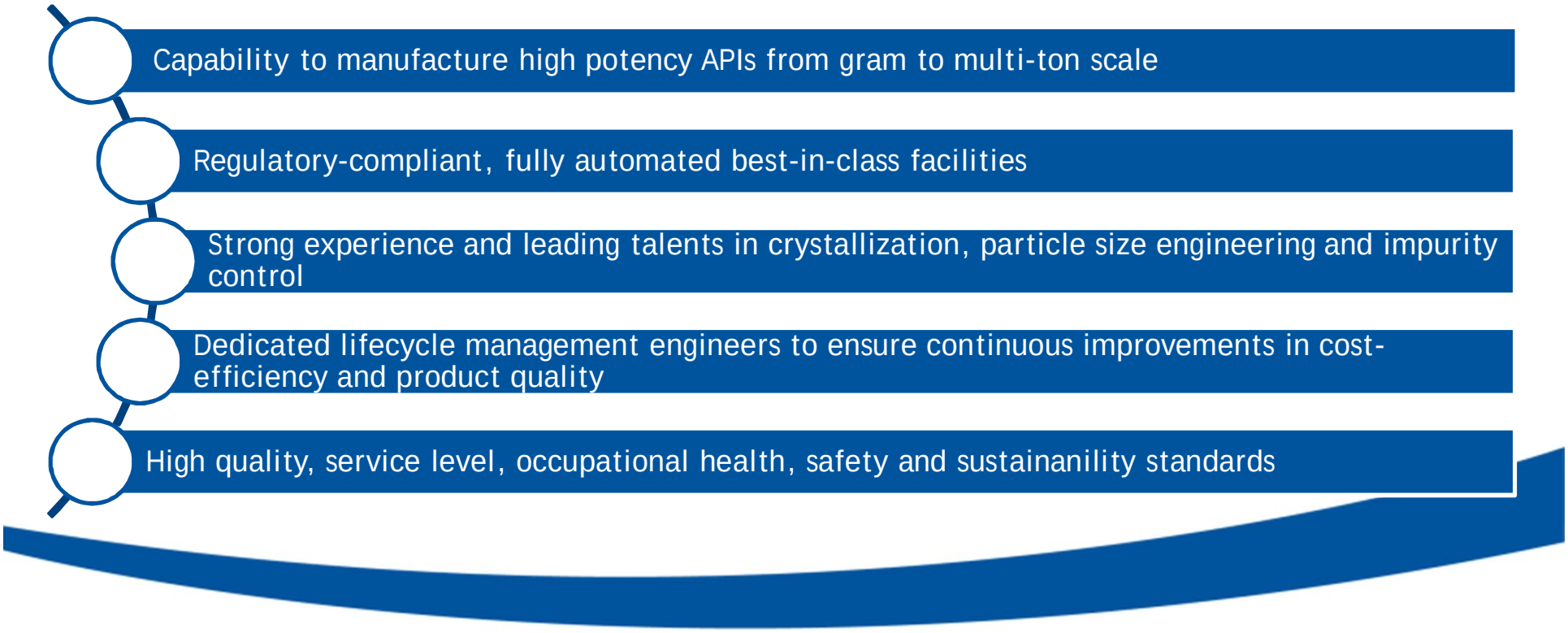
Fermion Key differentiators



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Fermion is a smart choice

Tap into the **capabilities**	•API and HPAPI development and manufacturing at all stages and scales •Fully automated API production •High EHS standards •Particle engineering
Leverage the **benefits**	•One-stop shop shortening time to market •Security of supply •Your brand image stays spotless •Peace of mind
Enjoy the **experience**	•Extension of your R&D, thinking like you •Innovative spirit •Problem-solving attitude •Transparent communication •Agile responses to your needs

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Working with Fermion

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Contact us

Contract Manufacturing Services
Teemu Korhonen, Business Development Manager

www.fermion.fi

Follow us

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Jyrki Lämsä, Manager, Marketing and Sales (Japan), jyrki.lamsa@fermion.fi

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Additional information on R&D

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Chemical reactions and technologies 1/2

- Reagents/equipment
  - Dimethyl sulfate
  - Epichlorohydrin
  - Grignard
  - LiAlH4
  - Triphosgene
  - H2-Buss loop reactor
  - Hexamethylenetetramine
  - Phosphorus pentasulfide
  - POCl3, SOCl2
- Technologies
  - Acetylenic chemistry
  - Aldol condensation
  - Alkylations (C, N, O and S)
  - Amidation/amination
  - Arylation
  - Carbonylation/carboxylation
  - Carbamoylation/thiocarbamoylation
  - Claisen condensation
  - Darzens reaction
  - Dehalogenations
  - Diazotitation
  - Dihydroxylation
  - Deprotection
  - Friedel-Crafts
  - Friedländer condensation
  - Epoxidation
  - Esterification
  - Formylation
  - Gabriel/Delépine
  - Hydrogenation
  - Hydrogenolysis
  - Hydrolysis
  - Mannich
  - McMurry
  - Mitsunobu reaction
  - Nitration
  - Organometallic reactions (Gringard, Li, etc)
  - Oxidation
  - Phase-Transfer Catalysis
  - Protection
  - Polymer coupling
  - Reduction
  - Reduction by hydride
  - Silylation
  - Sulfur containing compound (sulfide, sulfoxide etc.)
  - Thionation (C=O → C=S)
  - Wittig

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Chemical reactions and technologies 2/2

- Heterocycles
  - 1,4-benzodiazepine
  - 1,5-benzothiazepine
  - Benzothiophene
  - Cromolyn
  - Imidazole
  - Indole
  - Piperazine
  - Pteridine
  - Quinoline/one
  - Purines
  - Camptothecin derivatives
  - SERMS/SARMS
  - Triazoles
- Cross-coupling (Catalytic coupling reaction (Suzuki, Heck, Negishi etc.)
  - Suzuki
  - Sonogashira
  - Heck
  - Negishi
  - C-N/O/S
  - Ullman
  - steriolective C-C bond formation
  - steriolective C-N bond formation
- Chiral chemistry
  - Diastereomeric salt crystallization
  - Asymmetric synthesis
  - Chiral catalysis
  - Enzymatic resolution

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Reaction types and technologies not available

- Fermentation
- Azidation
- Cyanation
- Elemental bromine or chlorine
- Fluorination
- Ozonolysis

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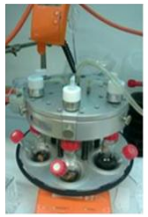
R&D equipment

Analysis and Identification
GC
HPLC (15)
UPLC (2)
GC-MS
LC-MS
NMR



Parallel synthesis
3 x Carousel 6 and 1 x Carousel 12
Multimax®
Labmax
Endeavor
Crystal 16
Easymax

Cromatography
CombiFlash
Preparative HPLC (CombiFlash EZ Prep)

Pressure reactors
Four different types
From 50 ml to 3 L
Up to 100 bar
Argonaut for small scale screening

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Safety studies

DSC, Differential Scanning Calorimeter

Measuring the enthalpies of starting materials, intermediates, products and reaction mixtures

SYSTAG, Reaction Calorimeter

Measuring the amount of energy released (exothermic) or absorbed (endothermic) by a chemical reaction

ARC, Accelerating Rate Calorimeter (by contract)
Determining the thermal runaway potential of substances and reaction mixtures

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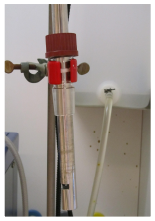
Online monitoring of reactions



NIR, FT Near infrared Analyzer

In situ determination of chemical composition and purity of in-process materials and products

React-IR, *In situ* Infrared Spectroscopy

In situ monitoring of chemical reactions

Provides specific information about reaction initiation, conversion, intermediates and endpoint

Lasentec, Inline particle size analysis

Tracking changes of particle size distribution, shape and count in real time. Optimizing particle size.

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Physical properties

TGA Thermal Gravimetric Analysis	•Weight change of the sample measured by function of temperature •Determining if a compound is a hydrate or a solvate or if it contains surface water
SSA Specific Surface Area	•Total surface area of a material per mass
DVS Dynamic Vapor Sorption	•Measurement of gravimetric moisture and organic vapor uptake of solid material.
XRPD X-ray Powder Diffraction	•Investigation of crystal properties; polymorphism, degree of crystallinity, crystalline purity
PSD Particle Size Distribution	•Particle size of a material
SEM Scanning Electron Microscopy	•Particle size, shape and surface information

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