

Highly Potent Parenterals... Your Place or Mine?

Featured Baxter Speakers:

Michael Borlet

Director of Mktg

Contract Manufacturing

Burkhard Wichert

VP, Mfg

Raul Soikes

Director, Project Mgmt



THE MARKET



Traditional High Containment Categories

Category	Includes
Traditional cytotoxics	Platinum, anti-metabolites, cytotoxic antibiotics, vinca alkaloids, alkylating agents
New generation small molecule cancer compounds	Compounds targeting enzyme/receptor systems expressed in cancer cells like GLEEVEC, VELCADE, SUTENT, TARCEVA, NEXAVAR
Hormones & steroids	Female sex hormones, human growth hormones, thyroids/parathyroids, SERMs, anabolic steroids
Genotoxic/mutagenic	Retinoids, cyclosporins, nucleoside analogs
Conjugated MABs	Cytotoxins and radiopharmaceuticals conjugated to MABs
Low dose	Fentanyl, interferons, prostaglandins, 5 alpha reductase inhibitors
Antibiotics	Penicillin & cephalosporin
Live virus and bacteria	Vaccines, gene therapy vectors, lytic viruses for cancer

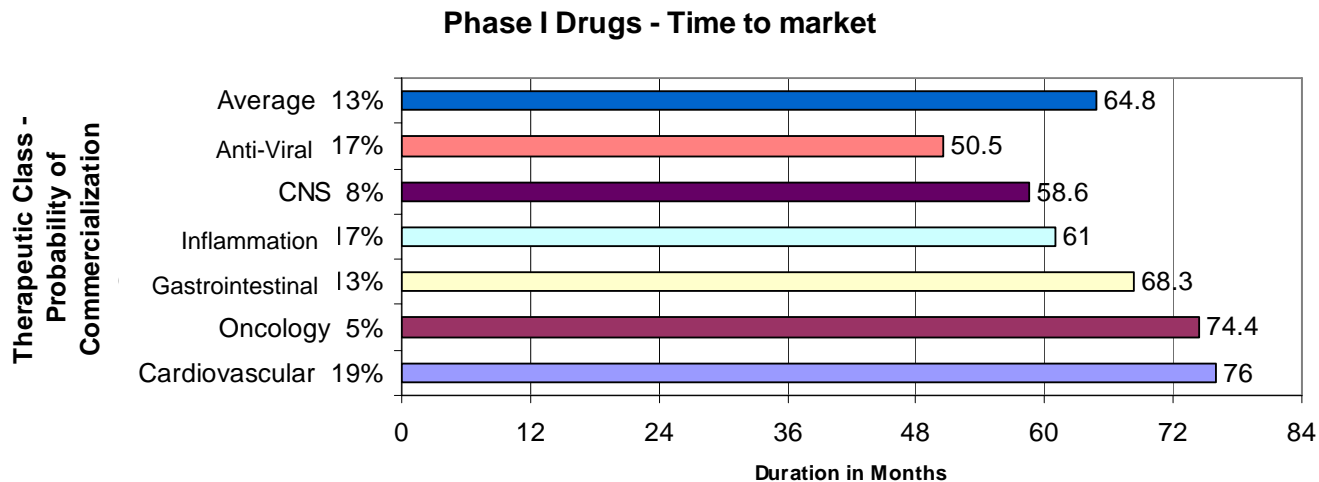


High Containment Compounds Span Pipeline

Therapeutic Area	Always	Case by case
Cancer	<ul style="list-style-type: none"> • Classic cytotoxic • Conjugated MABs • Lytic viruses 	<ul style="list-style-type: none"> • Novel small molecule cancer (e.g., Thalidomide, Gleevec)
Hormones	<ul style="list-style-type: none"> • All 	
Pain	<ul style="list-style-type: none"> • Fentanyl • Oxycodone 	<ul style="list-style-type: none"> • Other narcotic analgesics
Dermatology	<ul style="list-style-type: none"> • Retinoids 	
Antivirals	<ul style="list-style-type: none"> • Nucleoside analogues 	
Transplant	<ul style="list-style-type: none"> • Cyclosporine 	
Other	<ul style="list-style-type: none"> • Interferons • Prostaglandins 	<ul style="list-style-type: none"> • Other low dose compounds • Cell Therapy, gene therapy
Vaccines	<ul style="list-style-type: none"> • Live virus • Bacterial 	
Antibiotics	<ul style="list-style-type: none"> • Cephalosporin • Penicillin 	<ul style="list-style-type: none"> • Beta lactams • Macrolides

Investing in Cytotoxic Manufacturing Remains Risky

- Large capital investment required to manufacture cytotoxic
- Investment required prior to approval - low chance of commercial success
 - Cannot predict the "winners"
- Multiple years prior to commercial success - >6 years
- Containment requirements not confirmed until very late in development
- **Investment in proprietary facilities ill-advised until need confirmed**



Source: Parexel 2007/08 Biopharmaceutical R&D statistical source book

Most Branded Cyto Drugs Are Small Volume

Product	Active	Company	US Units 2006	EU Units 2006
DOXIL	Doxorubicin	J & J	0.2 m	-
CAMPTOSAR	Irinotecan HCL	Pfizer/ Pharmacia	1.0 m	1.2 m
GEMZAR	Gemcitabine HCL	Lilly	2.0 m	2.7 m
TAXOTERE	Docetaxel	Sanofi-Aventis	1.6 m	1.3 m
HYCAMTIN	Topotecan HCL	GSK	0.2m	0.1 m
ELOXATIN	Oxiplatin	Sanofi Aventis	0.9 m	0.9 m
VIDAZA	Azacitidine	Pharmion	0.4 m	-
ABRAXANE	Paclitaxel	Abraxis	0.2 m	-
ALIMTA	Pemetrexed	Lilly	0.2 m	0.1 m

Distribution	Volume Projection
Average expected volume	0.66 million
Minimum (25% probability)	0.25 million
Mid-low (50% probability)	0.5 million
Mid-high (15% probability)	1.0 million
Maximum (10% probability)	2.0 million

Low chance of success and small commercial volumes characterize the cyto drugs



Containment Requirement is a Late-Stage Decision

- Chiral compounds have created a new class of potentially high potency compounds that are not readily identified
- Full characterization requires battery of long-term tox studies and clinical results
 - Studies not started until after proof-of-concept established (Phase IIA)
 - May be after Phase III before data available and decision made
- Active/excipient blend will have different OEL than active alone
- In early clinicals, most sponsors will assume highest level of containment in absence of data

Source: PharmSource interviews of pharma sourcing professionals and CMOs



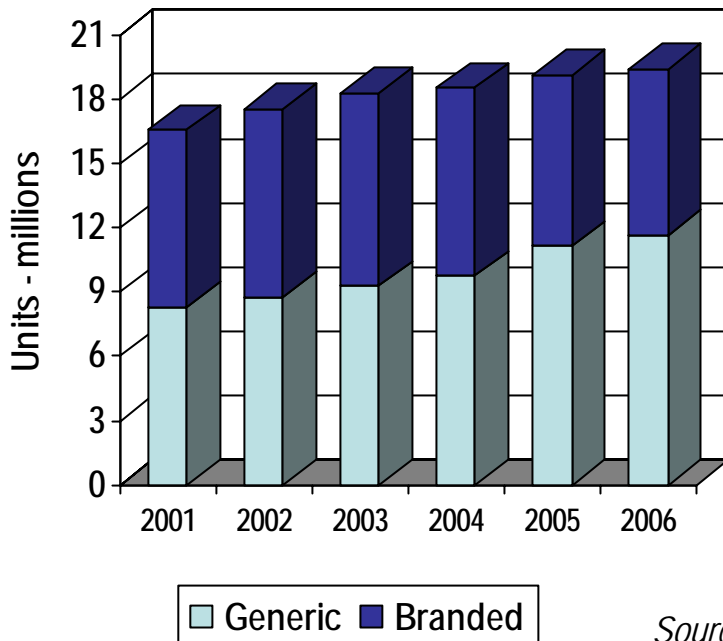
Standards Are Variable and Evolving

Safebridge	<ul style="list-style-type: none"> • More compounds should be HP based on OELs • 50 % of marketed • 80% of pipeline
FDA	<ul style="list-style-type: none"> • Does not mandate segregation for cyto and high potency • Accepts validated cleaning procedures
EU	<ul style="list-style-type: none"> • Demands dedicated operations for cytotoxic vs. high potency
OSHA	<ul style="list-style-type: none"> • Moving to higher containment standards <ul style="list-style-type: none"> • From 1000x assumed glove box safety to 25x
Big pharma	<ul style="list-style-type: none"> • Demands dedicated operations for cyto vs. high potency • Very conservative on classification, esp. in early clinical • Refining "cytotoxic" versus "cytostatic" distinction • A Class 4 cholesterol-lowering drug?
Small/mid pharma	<ul style="list-style-type: none"> • Less conservative in classification • Doesn't insist on segregation, but may require other measures like dedicated equipment



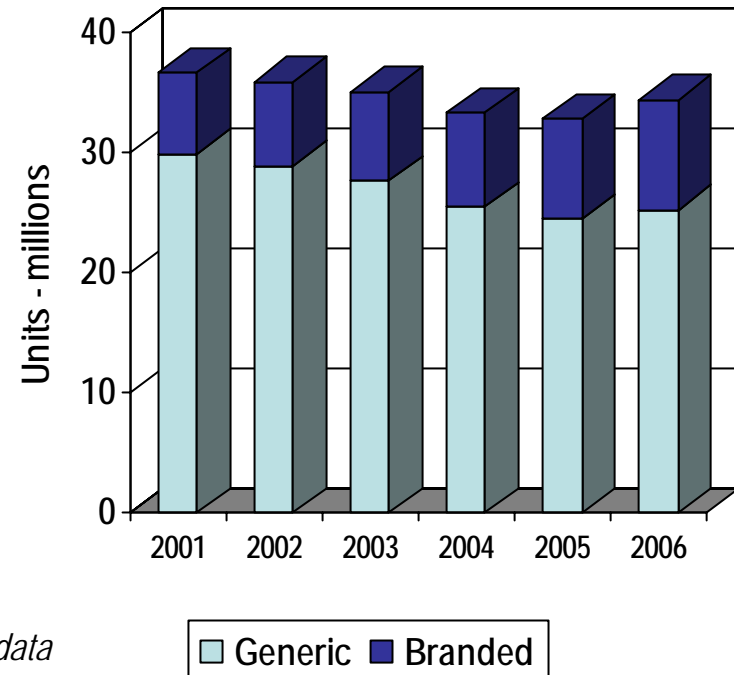
Cyto Market Experiencing Growth

Cytotoxic Injectable Unit Volume
US Market 2001-2006



Source: IMS data

Cytotoxic Injectable Unit Volume
European Market 2001-2006



Cyto remains a market with good unit growth rates



Cytotoxic - Outsourcing

- Cytotoxic products will remain a healthy market
 - 3.5% CAGR units
 - 5.5% CAGR revenue
- However, due to the very low chance of a commercial launch and low commercial volumes, most companies will outsource all cytotoxic manufacturing

	Cytotoxic
Global pharma	50%
Small and mid-size pharma, North America and Europe	100%
Rest-of-world companies	50%

Source: PharmSource 2008

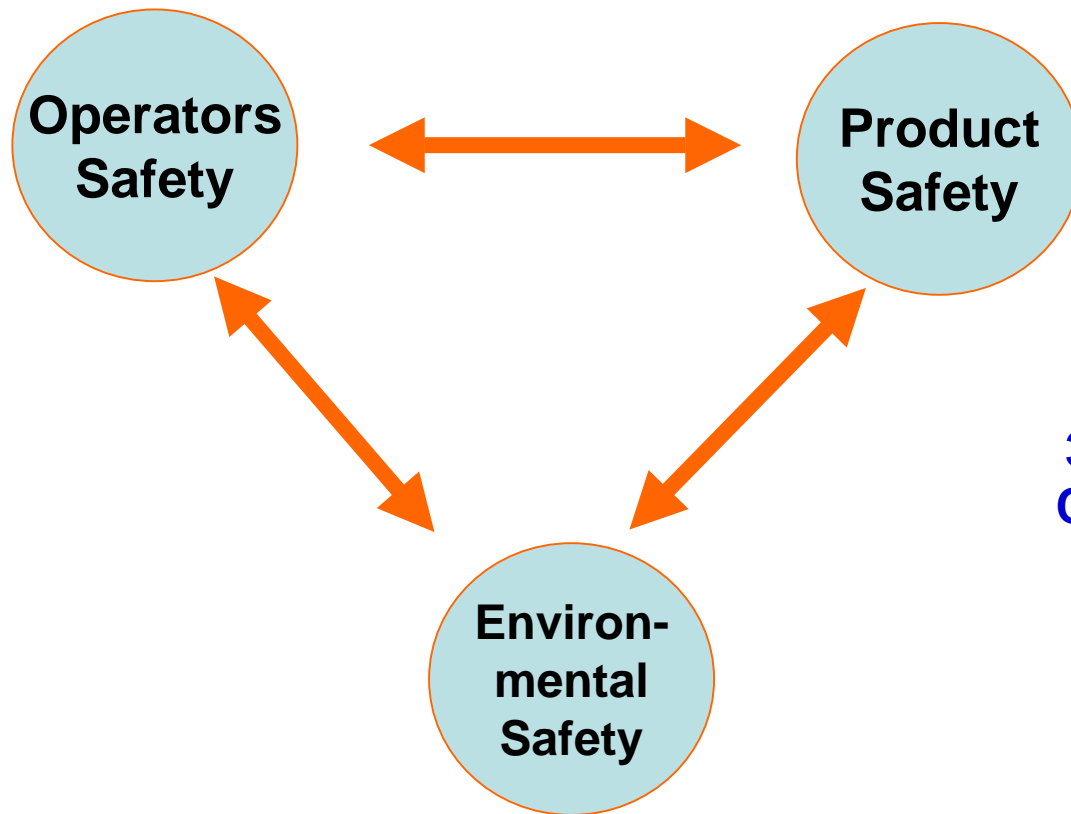
Cyto clearly is a market for outsourcing



INFRASTRUCTURE



Highly Potent Products Add an Additional Layer of Complexity to Aseptic Manufacturing



**3 Main Topics with
Conflicting Impacts
on Design**





Routes of Occupational Exposure & Control

Routes of Occupational Exposure =RISKS

- Inhalation
- Dermal Absorption
- Ingestion
- Inadvertent Contact with Skin & Mucous Membranes

Exposure Control =POTENTIAL ANSWERS

- Engineering controls (“hardware”)
- Administrative controls (“software”)
- Personal Protective Equipment

Separation and Containment: General Requirements for Manufacturing Cytotoxics

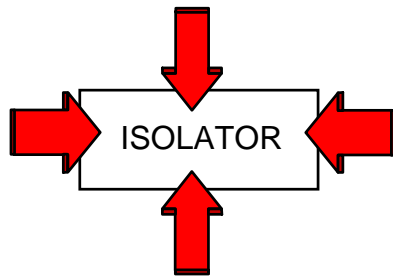
- Dedicated building or “house in house” concept for manufacturing
- Dedicated machines and dedicated qualified personnel
- Documented risk analysis for **all** processes with focus on GMP and EHS
- Dedicated HVAC with HEPA filtered air entering and leaving the production building for all production suites
- Definition of minimum required containment for each manufacturing step
- 100% waste collection
- Local waste water treatment



Risk & Process Analysis Defines Isolator Design

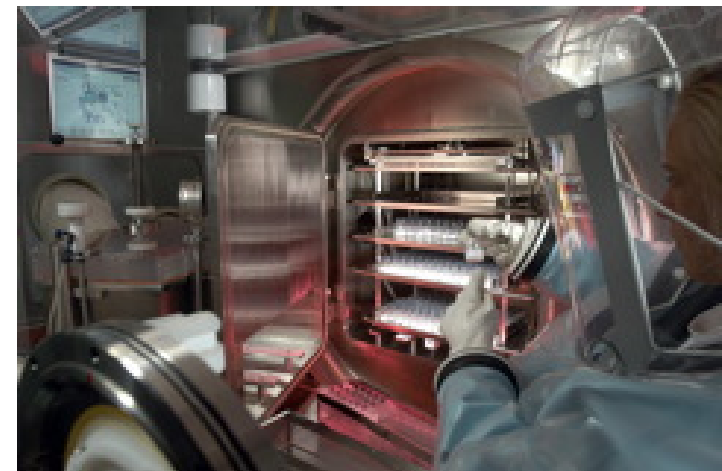
Isolators for compounding & handling of toxic powder

Negative pressure isolators
(-50 Pa to -150 Pa)



Isolator for manual operations

=> "Closed Isolator"

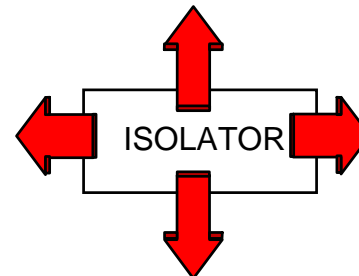


Risk & Process Analysis Defines Isolator Design



Sterilizable isolators for aseptic processing

Positive pressure isolators
(25 Pa to 100 Pa)



Isolators on automatic filling machines

=> "Open Isolators"

Separation and containment depend on the process

Decontamination, Air and Waste Handling

“Protection of the Environment and Operators”

Engineering controls

- Protection of HVAC System by double HEPA filtration
- Bag in / Bag out system for exhaust filters
- Dynamic gasket with pressure monitoring
- PLC controlled cleaning processes
- Negative Pressure Mode for barrier system in case of an emergency

Administrative controls

- Training
- Standardized processes
- Tightness Tests for the barrier system and gloves
- Monitoring Concept (Industrial Hygiene)

Cleaning and maintenance are high risk operations!



Waste Water Treatment

- Highly potent products:
 - are often not sufficiently biodegradable
(exceedance of limit for chemical oxygen demand)
 - are high active pharmaceutical ingredients (carcinogen, mutagenic)
(exceedance of biological test-limits)
 - are organic halogen compounds
(exceedance of limit for adsorbable organic halogen compounds)
- Separate sewage system for effluents with highly potent molecules
- 100% collection of potentially contaminated water

Industrial Hygiene Exposure Evaluation Monitoring of Air in Rooms



Mobile sampler affixed to operators gown to check for cytotoxics in air

Stationary sampler at critical locations
to check for cytotoxics in air



Industrial Hygiene Exposure Evaluation Monitoring of Personnel

Monitoring of air and surfaces in working environment for HAPI`s

- Stationary and mobile samplers
- Wipe tests of surfaces

=> Improvement of cleanliness and risk evaluation

Biomonitoring

- Check for HAPI in urine or blood
- Check for degradation products in urine or blood
- Check for biological indicators in blood

=> overall system check and evaluate operators behavior

Medical checks

- Annual medical checks of all employees

=> Health status

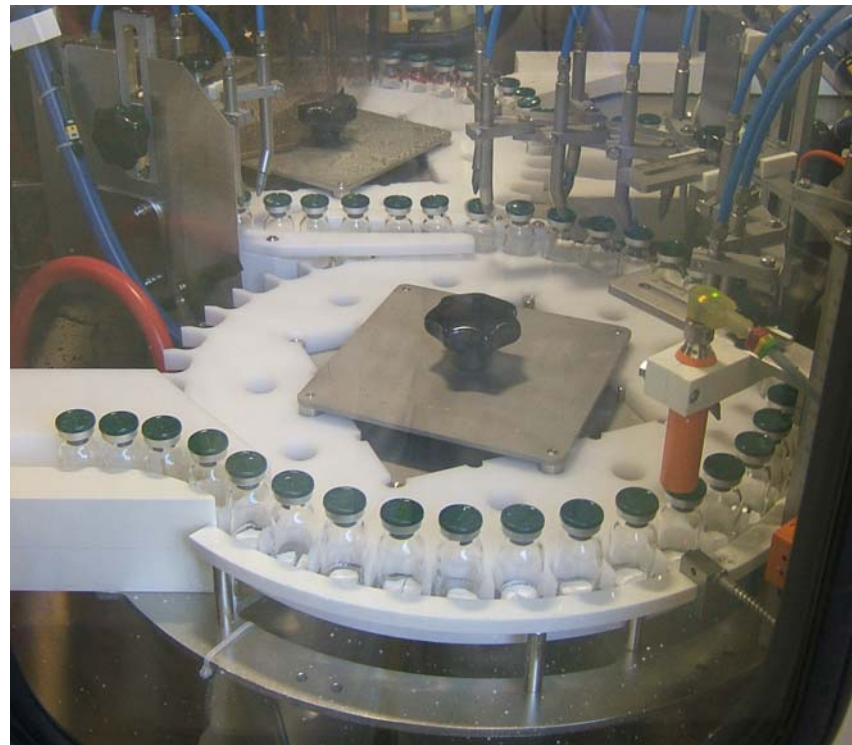


Decontamination and Avoidance of Cross Contamination

- Risk with product residues high for highly potent compounds
- Determine “worst case” API based on toxicological data (LD 50, daily dose and solubility)
- Challenge “worst case” positions with “worst case” API
- Verification by sampling (rinse and swab i.e. 100 cm², limit determination based on OELs)

Safety of Health Care Providers: Confirmation of Cleaning Process in Routine

100 % outer washing of filled vials



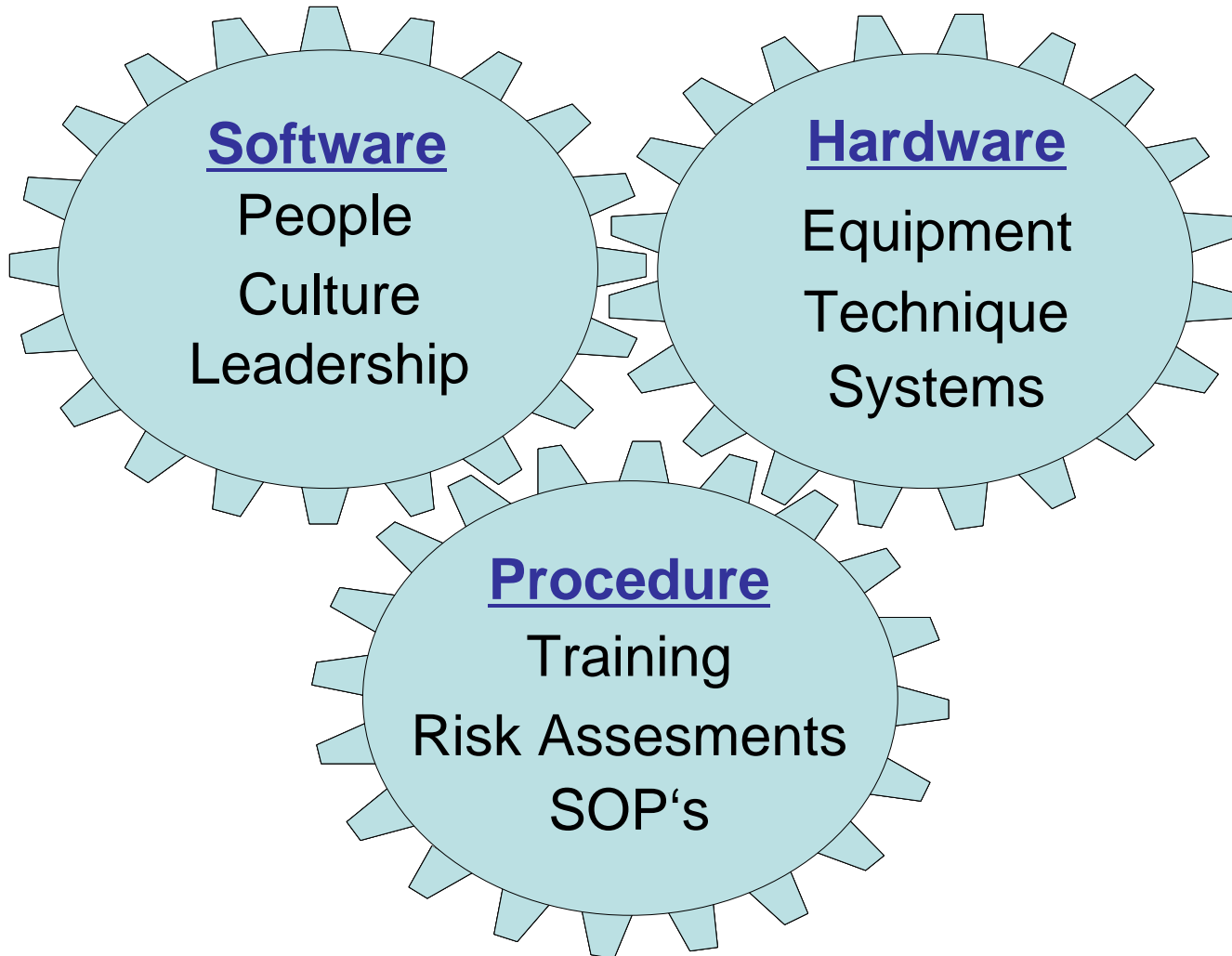


Training

- cGMP`s and handling of highly potents
- Openess
- Understanding, prudence and trust build the foundation of training
- No fear in handling highly potent molecules
- Potential risks including risks to the unborn need to be openly addressed (on a biannual basis for women of child bearing age)
- Transparent training level through all hierarchical levels creates trust and robust processes



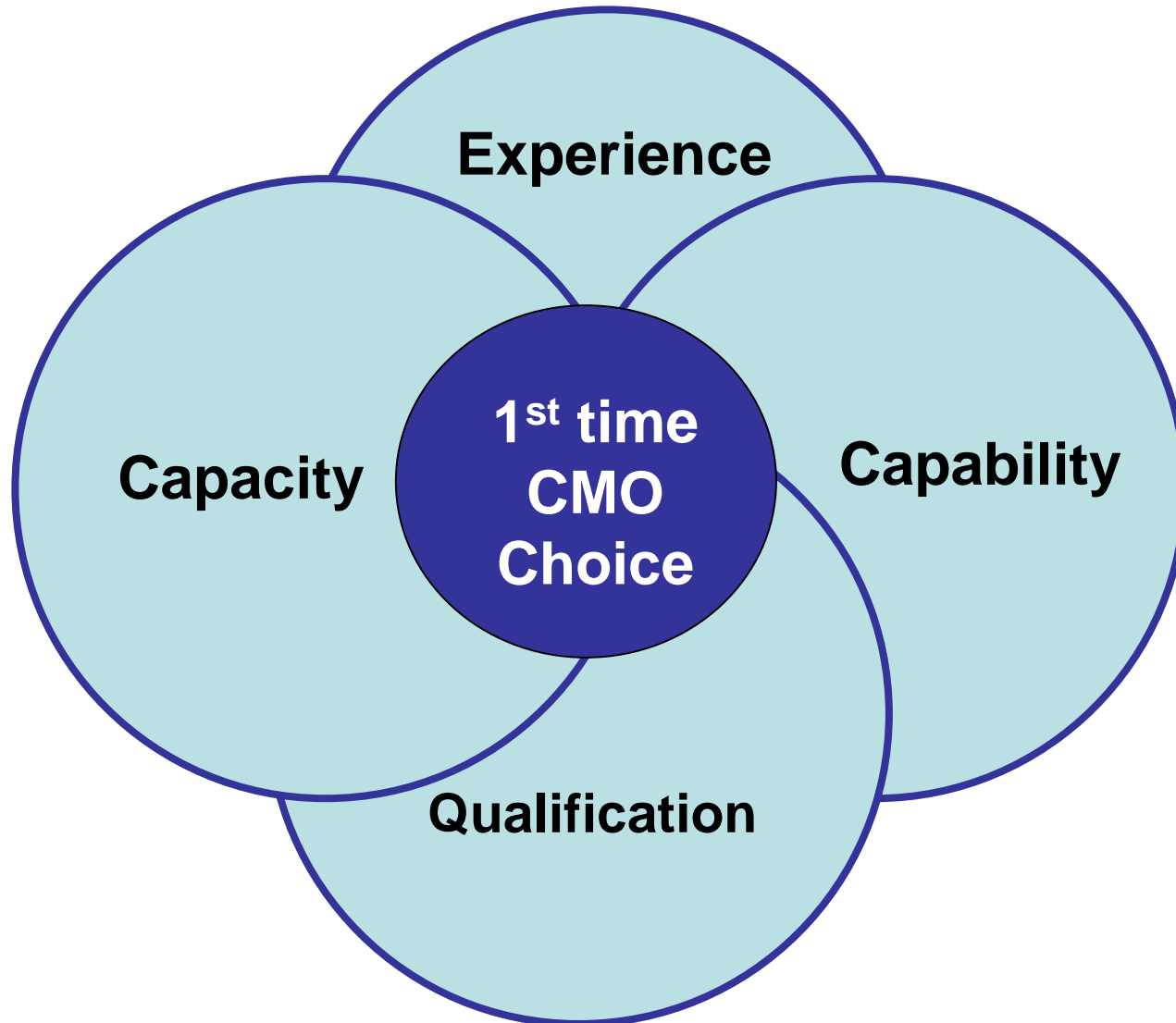
Success Factors in Safe Handling of Highly Potent Compounds





CUSTOMER NEEDS

Corporate Culture and Service



Corporate Culture and Service

Regulatory

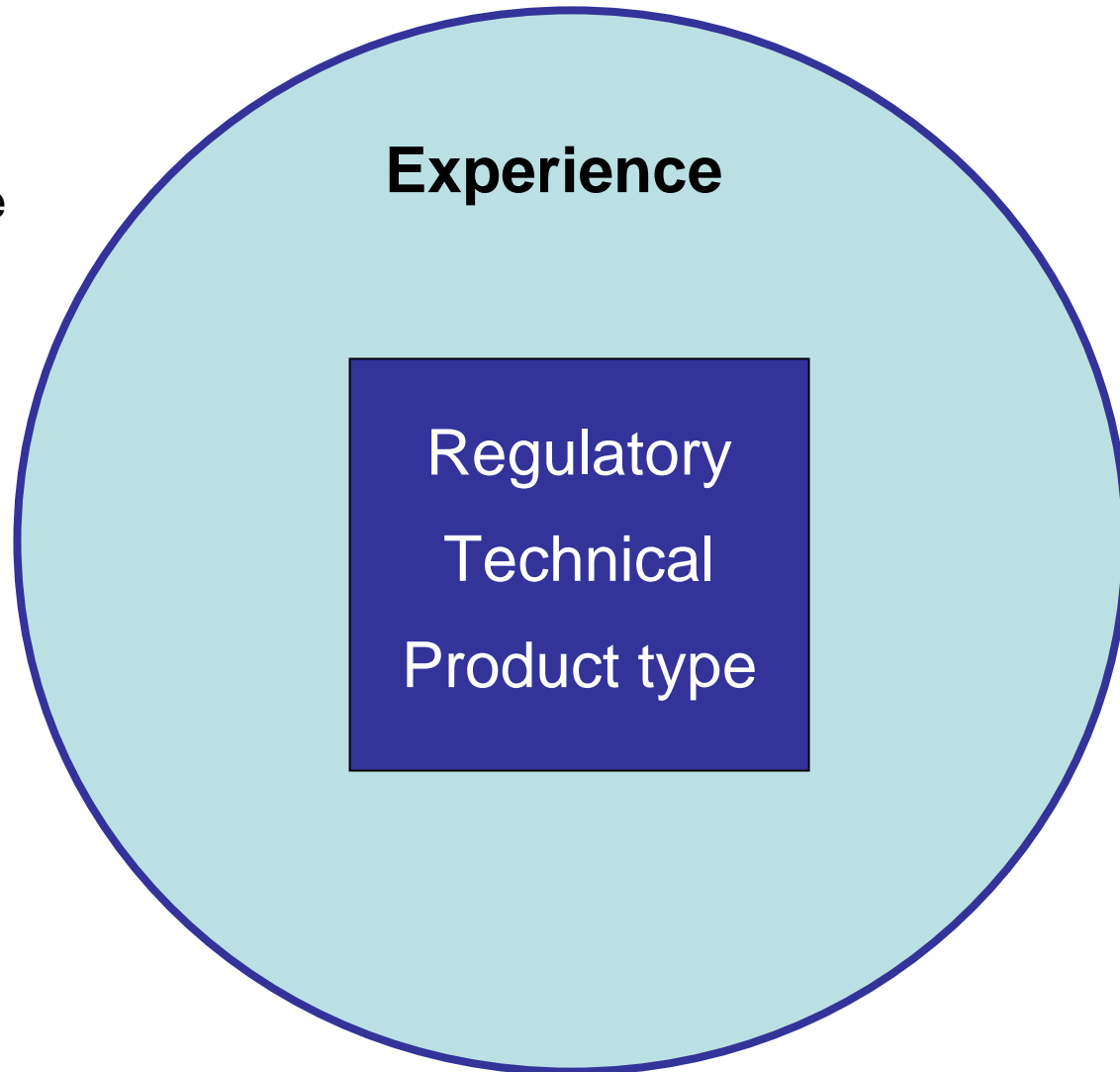
- Global and local compliance
- Audit history
- Regulatory review and approval process

Technical

- Product Safety
- Operator Safety
- Environmental Safety

Product Type

- Highly potent products
- Cytotoxics





Corporate Culture and Service

Resources

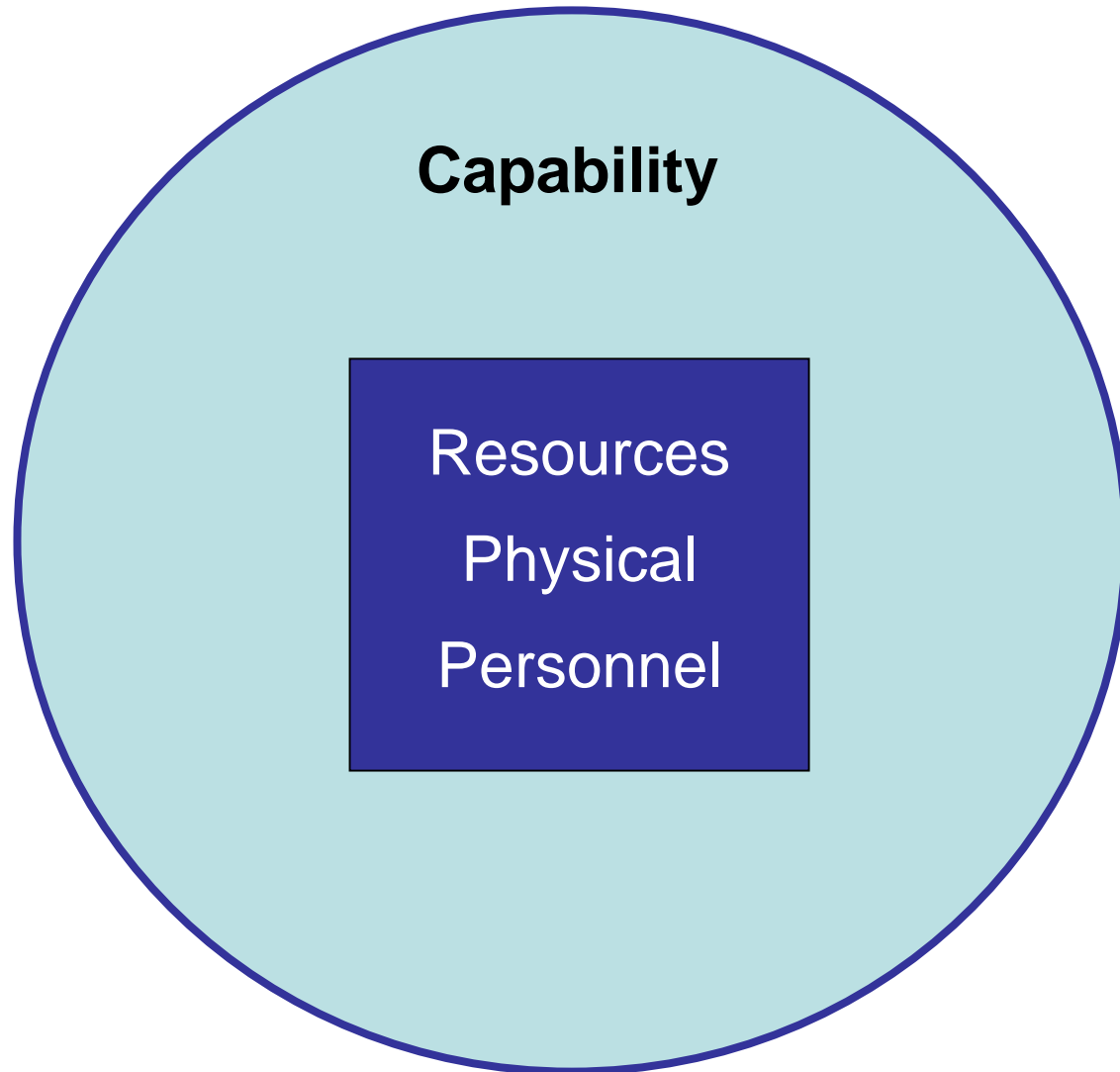
- Part of global company
- Redundancy
- Multidisciplinary

Physical

- Facility
- Isolators
- Decontamination

Personnel

- Education
- Training
- Experience



Corporate Culture and Service

Good Manufacturing Practices

- Compliance
- Documentation
- Training
- Audit

Company Policies

- Business
- Quality
- Regulatory
- Manufacturing

Registration

- National entities
- Regulatory Agencies



Corporate Culture and Service

Equipment

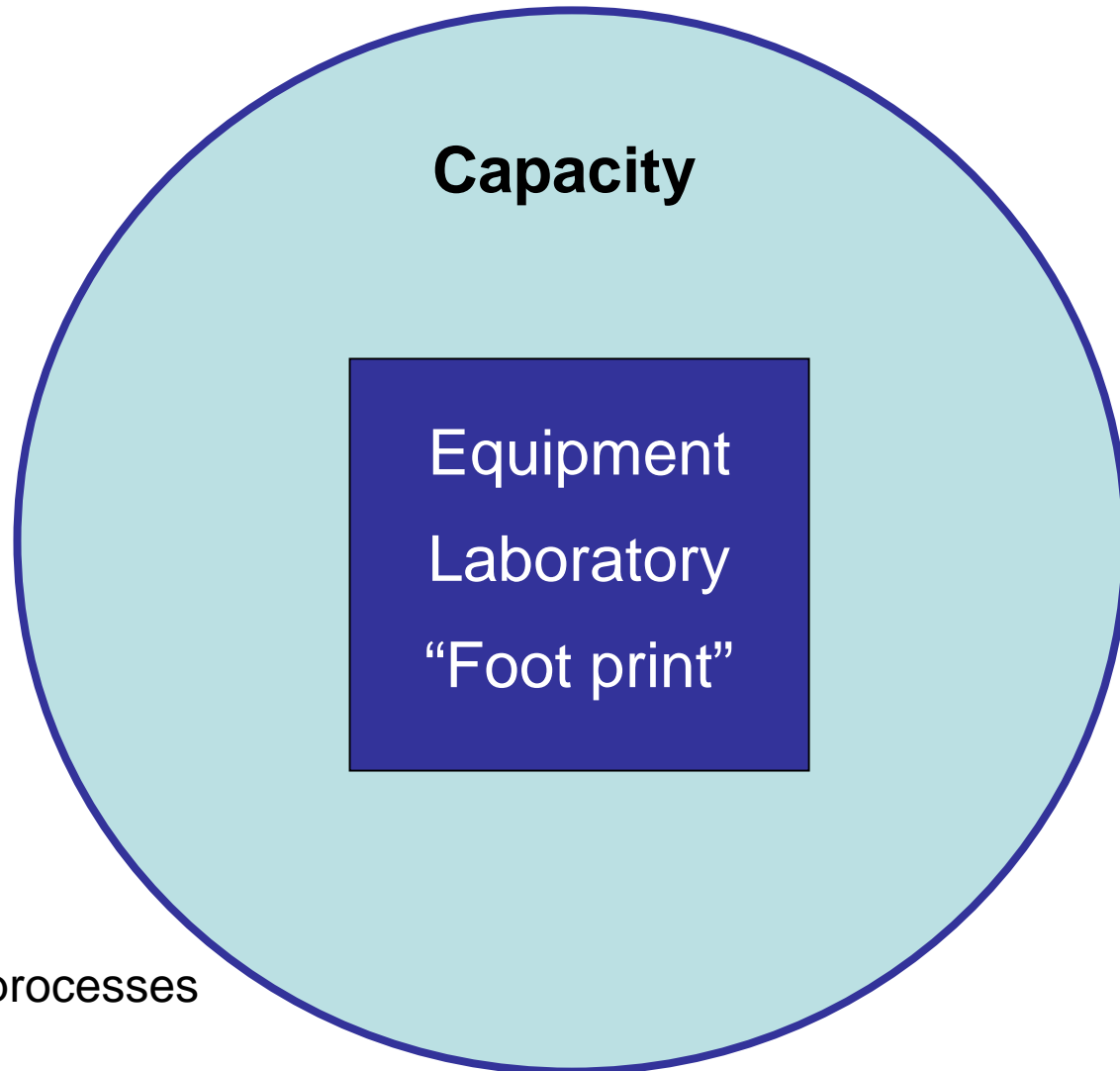
- Preparation
- Formulation/Fill
- Lyophilizer
- Capping
- Packaging

Laboratory

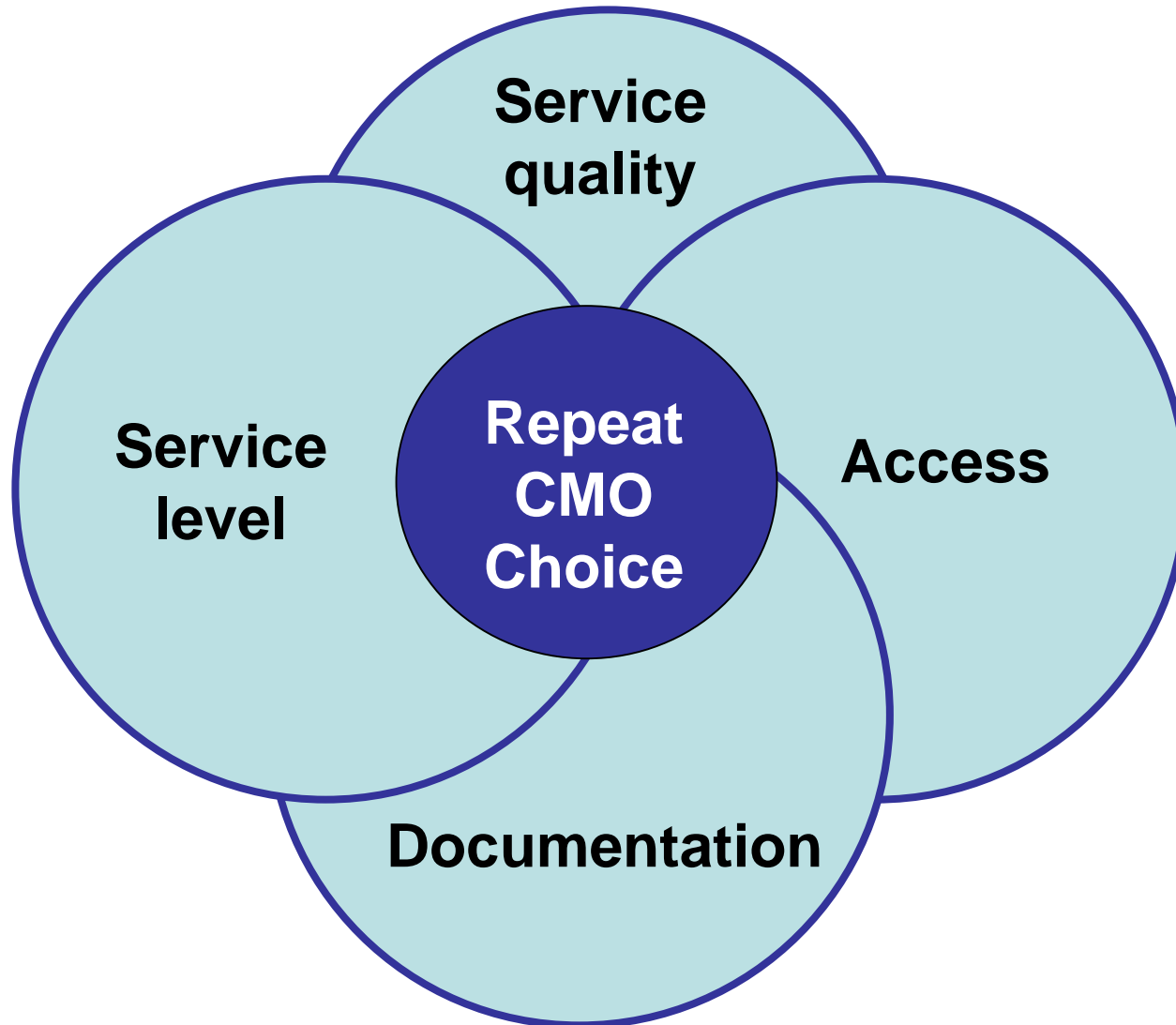
- Environmental monitor
- Product specific test
- Compendial testing

“Foot Print”

- Lyophilization area
- Waste treatment
- Supporting equipment and processes



Corporate Culture and Service





Service Quality

Through formulation, fill and finishing phases

Key contact point

Decision maker

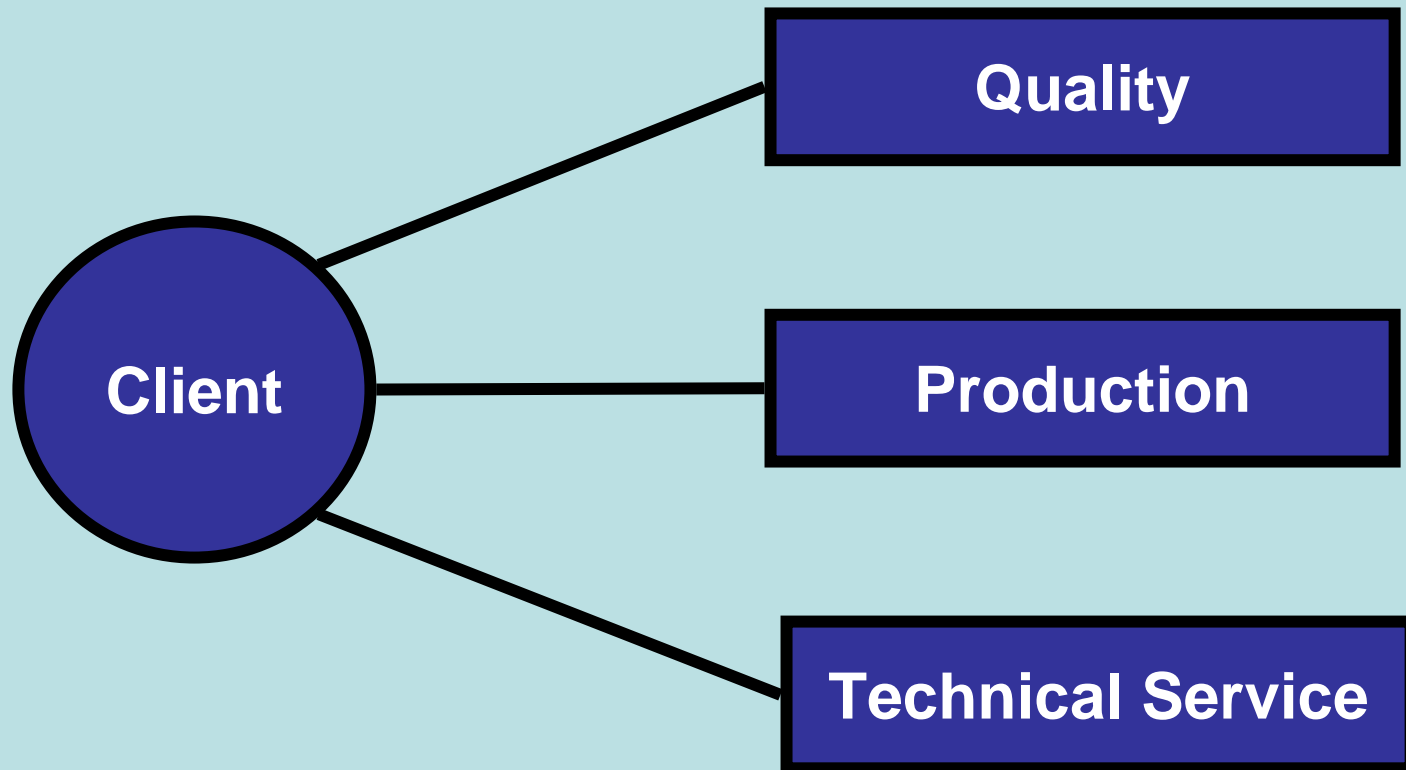
Client

Internal process

Escalation plan

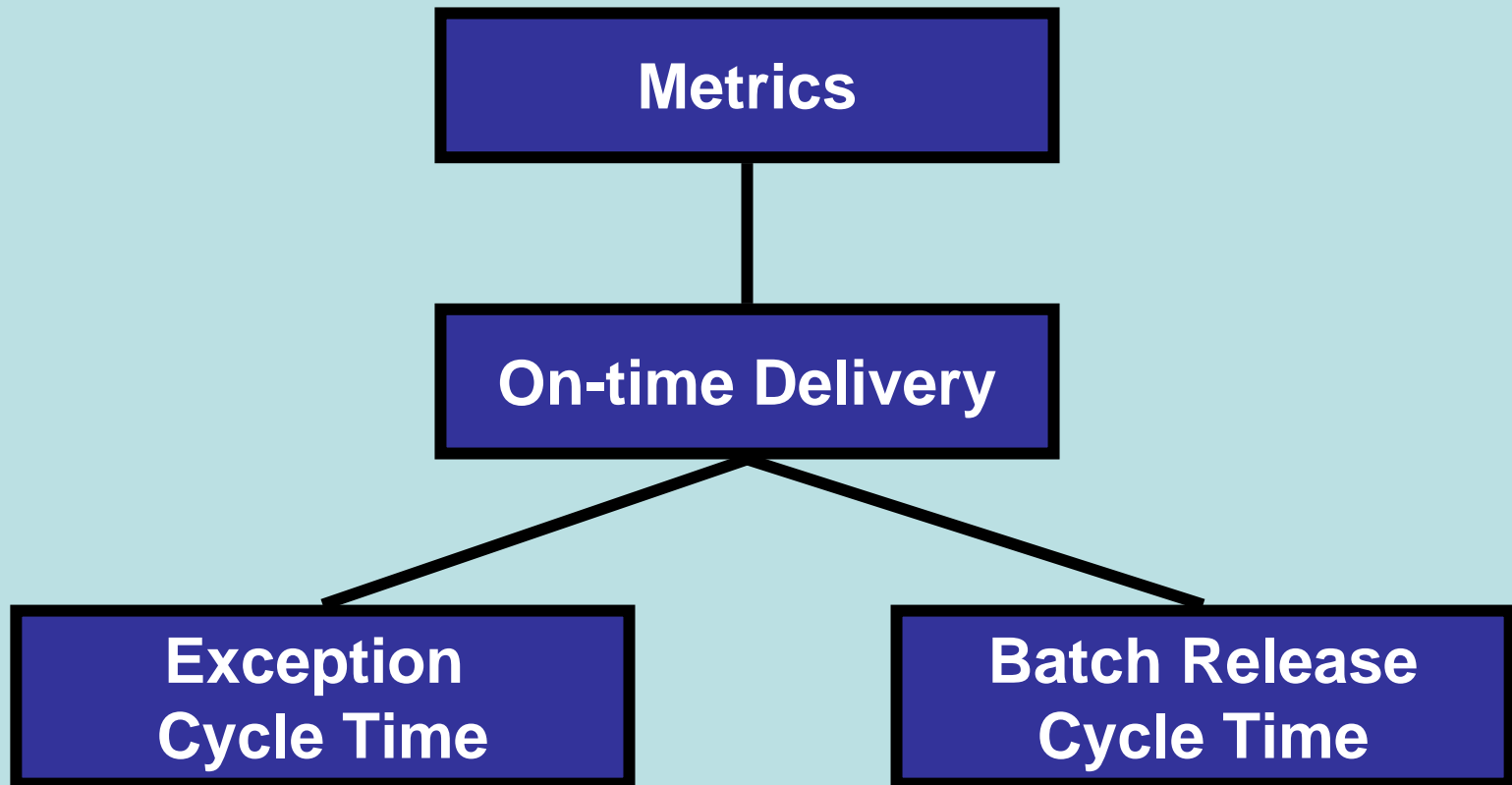
Access

Access to individuals responsible for

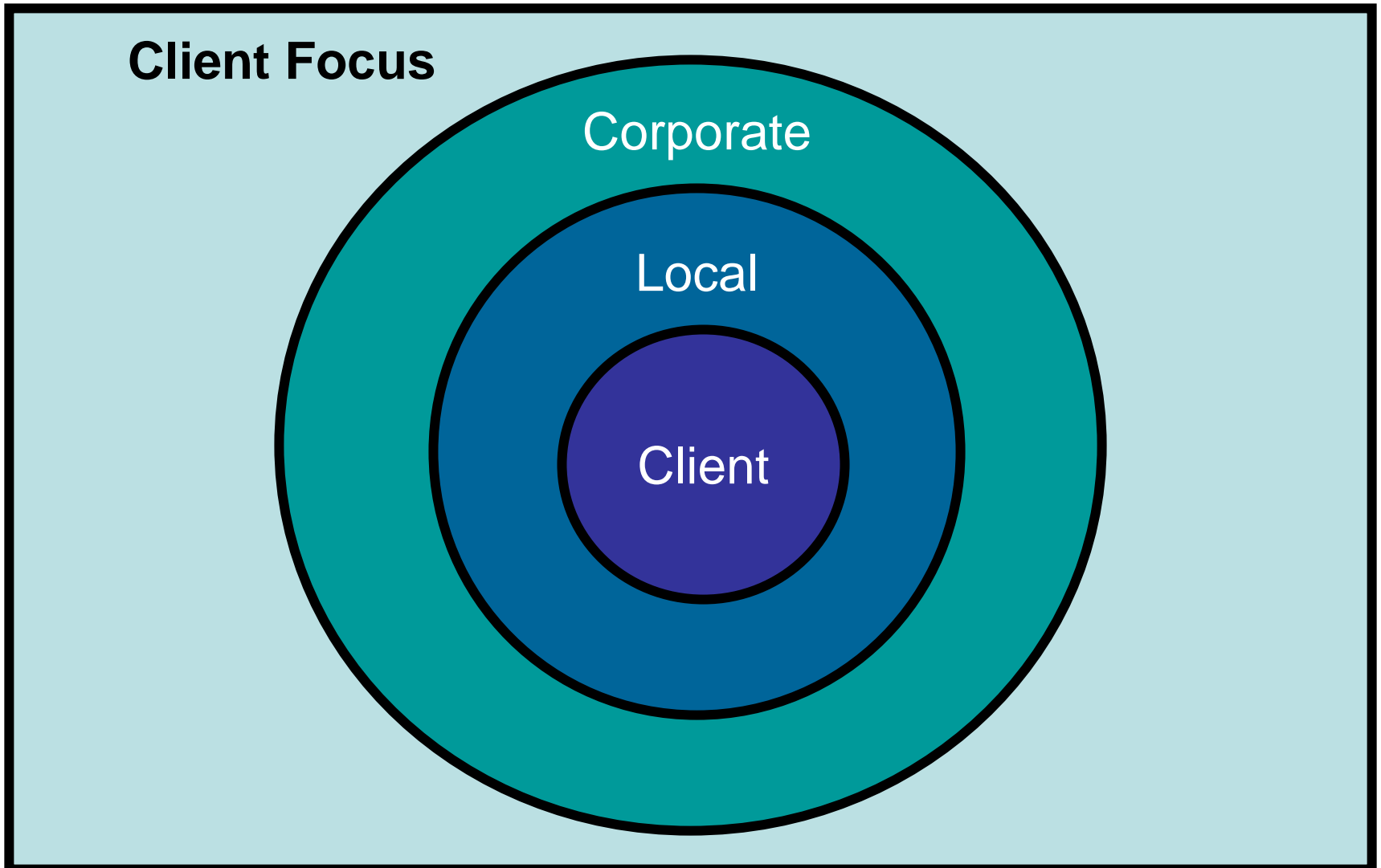


Documentation

Document and agree on Score Cards



Service Level





Q & A





Thank you for your interest in our webinar!

Contacts:

Mike Borlet

michael_borlet@baxter.com

Raul Soikes

raul_soikes@baxter.com

Burkhard Wichert

burkhard_wichert@baxter.com

**For more information on Baxter's
Contract Manufacturing Services,
visit our website:**

www.baxterbiopharmasolutions.com



Trademark Information

- Baxter is a registered trademark of Baxter International Inc.
- NEXAVAR is a trademark of Bayer AG
- GLEEVEC is a registered trademark of Novartis AG
- VELCADE is a trademark of Millenium Pharmaceuticals, Inc.
- SUTENT is a trademark of Pfizer, Inc.
- TARCEVA is a trademark of OSI Pharmaceuticals, Inc.
- DOXIL is a registered trademark of Ortho Biotech
- CAMPTOSAR is a registered trademark of Pharmacia and Upjohn
- ALIMTA and GEMZAR are registered trademarks of Eli Lilly and Company
- TAXOTERE is a registered trademark of Aventis Pharma SA
- Hycamtin is a registered trademark of GlaxoSmithKline
- EXLOXATIN is a registered trademark of Sanofi-Synthelabo Inc.
- VIDAZA is a registered trademark of Celgene Corporation
- ABRAXANE is a trademark of Abraxis Bioscience, Inc.