

GDP and Regulatory Compliance

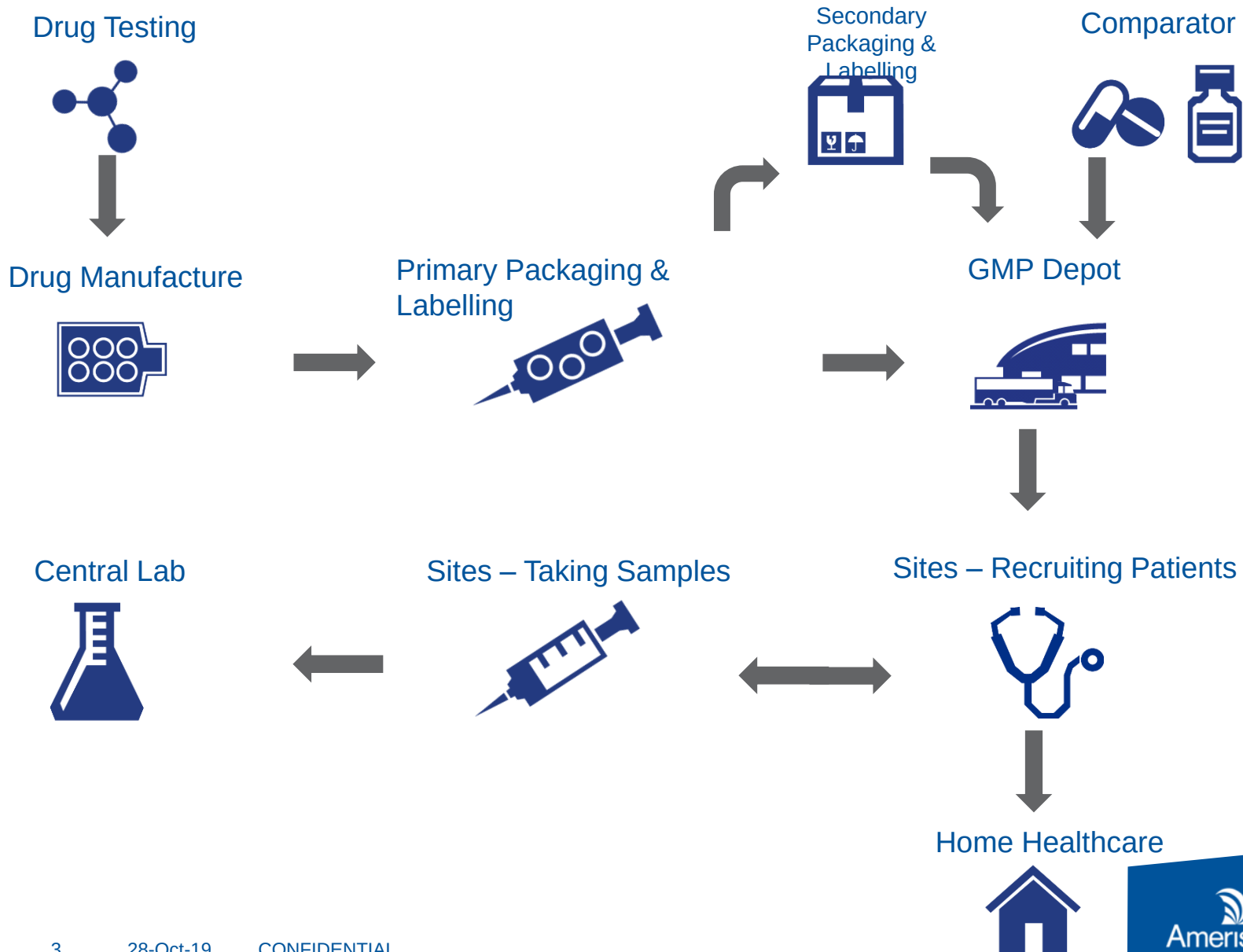
Current Developments and Challenges
for the Pharmaceutical Supply Chain



Pharmaceutical Supply Chain Concepts



Clinical Trial Logistics



Supply Chain of conventional CEP Service Provider

IMP



Samples



Consolidation of multiple shipments after collection

- Danger of mix-up and difficult track & trace
- Challenging process of coolant replenishment (Dry Ice, Gel Packs etc.)

Outlook – Entire Supply Chain in one Hand



Entire Clinical Supply Chain represented by one specialist LSP (Logistics Service Provider)

- Distribution of IMP direct to site from manufacturer
- Distribution of IMP to storage facility
- Storage at fully GMP compliant depot
- Future: IMP distribution „Direct-to-Patient“

Background: Air Cargo Supply Chain Challenges

From origin to destination pharmaceutical products can be exposed to different climates



Background: Air Cargo Industry Concerns & Challenges

Temperature Excursions: Where do they occur?



An Increasingly Complex Pharmaceutical Transport Market

Factors such as distance, demand, compliance; coupled with the advent of biological therapies are driving the need for innovative and advanced global temperature control solutions.



Pharmaceutical product distribution is becoming increasingly complex & global in scope.



The number of multi-country clinical trials are growing, with increasing activity in the emerging markets.



Growing demand for specialty products and biologics requires greater precision in temperature-control.

What could possibly go wrong?



Weather
problems



Political
action



Mechanical
malfunctions

Qualifications of transport systems



Temperature
excursions

? **Loss of transparency**
in the supply chain

Adverse Conditions – Why Premium Logistics is Mandatory

Transport System

- Airlines are focused on cost
- Many subcontractors in transport system
- Security requirements (x-ray)
- Customs procedures
- Unclear site infrastructure

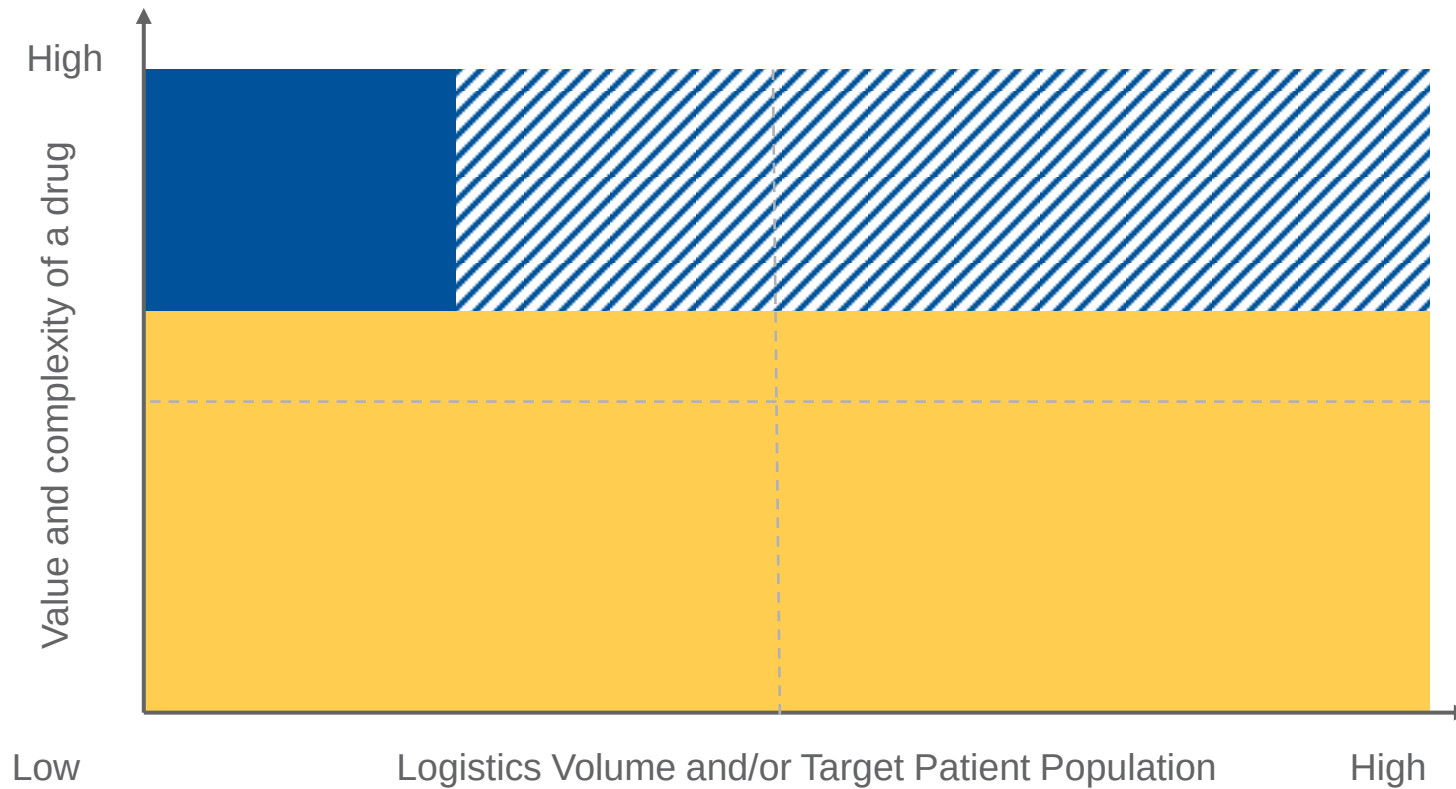
Trial Requirements

- Short cycle times site-manufacturing-site
- Cryovessels
- Patient-specific material
- Potentially live-saving
- Remote QP release

The impact of speciality drugs on today's commercial supply chain



Definition of specialty drugs



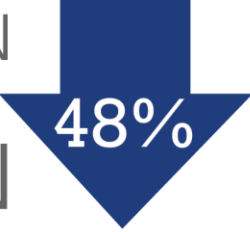
Credit: own illustration

Traditional Clinical Trial Challenges

94%
OF PATIENTS
do not
have access to
TRIALS

30% OF SITES **RECRUIT**

ONE PATIENT OR LESS

RETENTION
rates have
FALLEN  **48%** in
recent
years

1 in **4**
patients
DROP OUT
before study
COMPLETION

Direct to Patient: Current State

Growing within clinical trials, expanded access and commercial programs

- Direct-to-Patient logistical models allow greater numbers of patients access to more treatment options, which can be life-changing
- Home care nursing services are sometimes a focal coordination point for logistics providers
- Today drug distribution often involves local pharmacies that are not always accustomed to temperature-controlled shipping
- DtP models are trending to more centralized dispense / distribution
- Immediate temperature results verification upon delivery is an opportunity for improvement
- World Courier's DtP project volumes, scope of services and geographies have consistently expanded worldwide since 2012
- Includes sustained DtP growth within clinical trials, commercial programs as well as expanded access and compassionate use scenarios

Our processes, dedicated resources and experience position us as the specialty courier of choice for DtP



Comprehensive patient-centric logistics service

Global SOP ensures consistency of project setup and execution

Dedicated resources, including in-country DtP coordinators

Fully DtP trained associates includes customer service, operations and drivers

Focused on continuous improvement, service enhancements and innovations

What's the big deal?

1 in 3

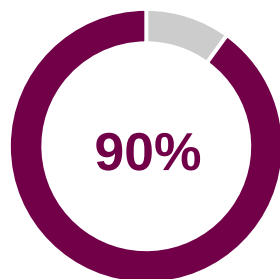
people will develop some form of cancer during their lifetime

1,500+

diseases are caused by a single defective gene



EU approved first gene therapy treatment



Gene-based clinical trials have increased by almost 90% since 2009

By 2020, the global regenerative market is expected to reach over

\$67 billion

1. "Lifetime Risk of Developing or Dying From Cancer." *Lifetime Risk of Developing or Dying From Cancer*. American Cancer Society, 23 Mar. 2016. Web. 04 May 2016. <<http://www.cancer.org/cancer/cancerbasics/lifetime-probability-of-developing-or-dying-from-cancer>>.
2. McCain, Jack. "The Future of Gene Therapy." *Biotechnology Healthcare*. BioCommunications LLC, n.d. Web. 04 May 2016. <<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3564347/>>.
3. Moran, Nuala. "Glybera Gains Official EMA Nod as First Gene Therapy." *BioWorld*. N.p., 2012. Web. 04 May 2016. <<http://www.bioworld.com/content/glybera-gains-official-ema-nod-first-gene-therapy-0>>.
4. "Gene Therapy Clinical Trials Worldwide." *Gene Therapy Clinical Trials Worldwide*. John Wiley and Sons Ltd, 2015. Web. 04 May 2016. <<http://www.wiley.com/legacy/wileychi/genmed/clinical/>>.
5. "MarketResearchReports.Com: Global Regenerative Medicine Market Is Expected to Reach \$67.6 Billion by 2020, Reveals New Report." - *Press Release*. N.p., 2014. Web. 05 May 2016. <<http://www.digitaljournal.com/pr/2120366>>.

Challenges and requirements



By 2022, worldwide orphan
drug sales forecast to be

\$209 Billion

By 2020, 27 of the
top 50 selling drugs
will be requiring
2-8 °C cold-chain
storage & handling.

Change of paradigms which influence today's pharmaceutical logistics of finished drugs



Patients & markets

- More tenders from governments
- Patient specific customization



Supply Chain

- Visibility and compliance
- Cost optimization



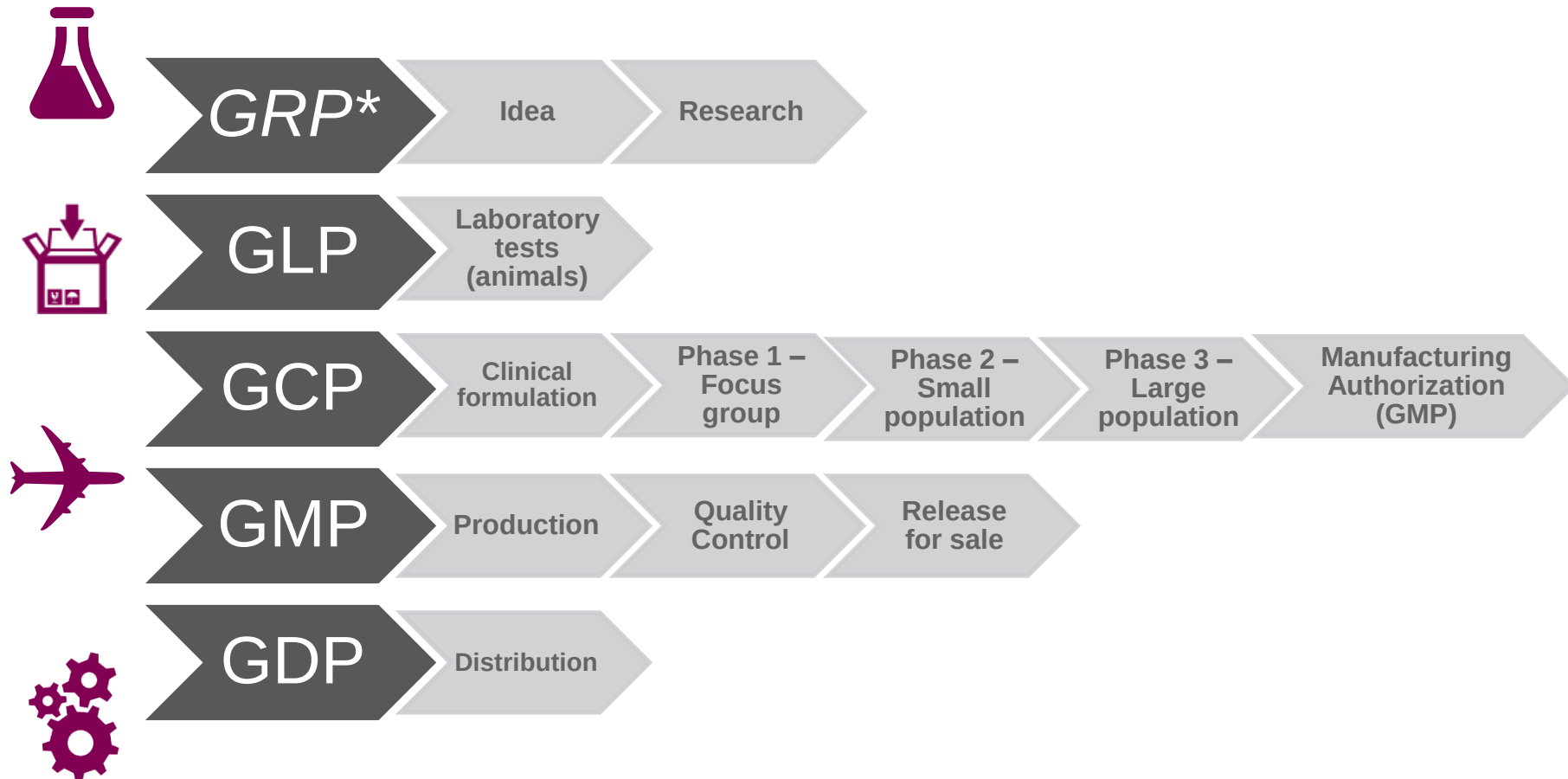
Products

- From small to large molecules
- High-value, low-volume portfolios

GxP and Regulatory Compliance



GxP – Product cycle/phases



*GRP = Good Research Practice

GxP: Topics covered

	Premises
	Organization & Management
	Training
	CAPA
	Contract Activities
	Self-Inspection
	Change Management

	Vehicles & Equipment
	Quality Management
	Documentation
	Qualification & Calibration
	Validation
	Risk Management
	Personnel

GDP Compliance

Why is compliance with GDP provisions so important?

“The quality of pharmaceutical products can be affected by a lack of adequate control over the numerous activities which occur during the distribution process.”

(WHO Technical Report 937, Annex 5, 2006)

“Distribution is an important activity in the integrated supply-chain management of pharmaceutical products.”

“The nature of risks involved is likely to be similar to that for risks encountered in the Manufacturing environment.”

“Counterfeit pharmaceutical products are a real threat to public health and safety. Consequently, it is essential to protect the pharmaceutical supply chain against the penetration of such products.”

(WHO Technical Report 957, Annex 5, 2010)

GDP compliance is paramount not only in the commercial supply chain, but also and particularly during drug development. Achieving market realization (and the corresponding marketing authorization) depends on the ability to show that the integrity of the product could not have been compromised during transportation.

European GDP Development



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Original GDP Guideline 94/C 63/03 (1994)

Guidelines on Good Distribution Practice of Medicinal Products for Human Use

- General Guideline with less than 4 pages
- Legal Basis: Article 10 of Council Directive 92/25/EEC

GDP Guideline (2013/C 343/01) - November 23rd 2013

- Greatly expanded
- 10 Chapters
- Legal Basis: Article 84 & 85b subs. 3 of Directive 2001/83/EC
- New Directive 2011/62/EU to fight Counterfeit Medication

GDP Guideline (2015/C 95/01) for active substances - March 19th 2015

Good Distribution Practice of active substances for medicinal products for human use

- Legal Basis: Article 47 of Council Directive 2001/83/EC

European GDP Development

GDP Guideline 2013

1. **Quality Management**
QMS/Risk Mgt/Mgt Review/Change Control
2. **Personnel**
Responsibilities/Training/Hygiene
➤ Key Concept „Responsible Person“
similar to the QP function in GMP (Ch. 2.5)
3. **Premises and Equipment**
Handling/e-Systems/Qualification
4. **Documentation**
Signatures/Archiving/SOPs
5. **Operations**
Storage/Separation/Destruction
FEFO replaces FIFO



European GDP Development (continued)

GDP Guideline 2013

6. **Complaints, Returns, Suspected Falsified Medicinal Products and Medicinal Products Recalls**
Training for Increased Awareness

7. **Outsourced Activities**
New Chapter/Qualification

8. **Self-Inspections**
New Requirement (3rd Party Audits allowed)

9. **Transportation**
Risk based approached/"Ship as stored"

10. **Specific Provisions for Brokers**
New/Broker Activities defined



European GDP Development (continued)

GDP Guideline 2013

Clarification Documents regarding Temporary storage and Holding refrigerated goods

MHRA:* 36 hours

HPRA:** 48 hours

SMI***: 72 hours

NL: 72 hours

For longer holds and for any holds of
Refrigerated Product a WDA is required

* Medicines & Healthcare products Regulatory Agency (UK)

** Health Products Regulatory Authority (Ireland)

***= Swiss Medicines inspectorate current interpretation
(31 January 2012)



European GDP Development (continued)

GMP updates already implemented 31 January 2013

Chapter 7 EU GMP Guideline revised (Published 11 September 2012)

- Review and Control of all Outsourced Activities (Risk based approach)
- Responsibility to assess Legality, Suitability and Competence of subcontractor
- Continuous assessment of Quality and Performance (identify and implement improvements)
-> Audits!
- Review of Records and Results and Conformity of Services rendered.





GDP adopted by PIC/S

Pharmaceutical Inspection Co-operation Scheme

PIC/S Guidelines on the Principles of Good Distribution Practice of Active Substances for Medicinal Products for Human use

- Chapter 1 - Scope
- Chapter 2 - Quality System
- Chapter 3 - Personnel
- Chapter 4 - Documentation
- Chapter 5 - Premises and Equipment
- Chapter 6 - Operations
- Chapter 7 - Returns, complaints and recalls
- Chapter 8 Self-inspections

(July 2018)

WHO GSDP Outlook

GOOD STORAGE AND DISTRIBUTION PRACTICES

(May 2019)

DRAFT FOR COMMENTS

Please send any comments you may have to Dr Sabine Kopp, Group Lead, Medicines Quality Assurance, Technologies Standards and Norms (kopps@who.int), with a copy to Ms Claire Vogel (vogelc@who.int) by **15 June 2019**.

Consolidation of comments received and review of feedbacks. Preparation of working document for discussion.	June 2019
Discussion of working document and feedbacks received during the informal Consultation on Good Practices for Health Products Manufacture and Inspection.	July 2019
Revision of the working document based on comments received during the informal Consultation on Good Practices for Health Products Manufacture and Inspection.	End of July 2019
Mailing of revised working document to the EAP inviting comments and posting the working document on the WHO website for public consultation.	August – September 2019
Consolidation of comments received and review of feedbacks. Preparation of working document for discussion.	End of September 2019
Presentation to the Fifty-fourth meeting of the ECSP.	14 -18 October 2019

EAP= Expert Advisory Panel

ECSP= Expert Committee

on Specifications for Pharmaceutical Preparations

WHO GSDP Outlook

GOOD STORAGE AND DISTRIBUTION PRACTICES

(May 2019)

DRAFT FOR COMMENTS

Please send any comments you may have to Dr Sabine Kopp, Group Lead, Medicines Quality Assurance, Technologies Standards and Norms (kopps@who.int), with a copy to Ms Claire Vogel (vogelc@who.int) by 15 June 2019.

Pronounced Focus on two areas:

- Integrity of the Distribution Chain
- Quality Risk Management

Integrity of the Distribution Chain

GOOD STORAGE AND DISTRIBUTION PRACTICES

(May 2019)

DRAFT FOR COMMENTS

Please send any comments you may have to Dr Sabine Kopp, Group Lead, Medicines Quality Assurance, Technologies Standards and Norms (kopps@who.int), with a copy to Ms Claire Vogel (vogelc@who.int) by 15 June 2019.

New Definition of GDP

„That part of quality assurance that ensures that the quality of a pharmaceutical product is maintained by means of adequate control over the numerous activities which occur during the distribution process as well as providing a tool to

secure the distribution system from counterfeits, unapproved, illegally imported, stolen, counterfeit, substandard, adulterated And/or misbranded pharmaceutical products“

Quality Risk Management

GOOD STORAGE AND DISTRIBUTION PRACTICES

(May 2019)

DRAFT FOR COMMENTS

Please send any comments you may have to Dr Sabine Kopp, Group Lead, Medicines Quality Assurance, Technologies Standards and Norms (kopps@who.int), with a copy to Ms Claire Vogel (vogelc@who.int) by 15 June 2019.

New devoted chapter

„There should be a system to assess, control, communicate and review **risks identified at all stages in the supply chain**“

„Appropriate controls should be developed and implemented to **address any risks identified.**

The effectiveness of the controls implemented should be
Evaluated at periodic intervals“

WHO GSDP Outlook

GOOD STORAGE AND DISTRIBUTION PRACTICES

(May 2019)

DRAFT FOR COMMENTS

Please send any comments you may have to Dr Sabine Kopp, Group Lead, Medicines Quality Assurance, Technologies Standards and Norms (kopps@who.int), with a copy to Ms Claire Vogel (vogelc@who.int) by 15 June 2019.

New items

- Cross reference to WHO TR 996 Annex 5 (WHO GDocP)
New Concept for minimum Document retention:
Shelf life of product transported/stored +1
- **New requirement:**
Pharmaceutical products may only be dispatched and shipped, when there is a valid and documented order by an authorized party to do so.

Risk Management

- **Force Majeure Risks:** external risks can not be influenced

- ☐ Natural disasters, strikes, terrorism, wars

- **Climatic impact:** Environment

- ☐ Weather, climate, season

- **Supply- and Process Risks:**

- ☐ Depending on the selected thermo container system

- ☐ Transportation modus (aircraft, ship, truck, train)

- ☐ Transit time

- ☐ Human language skills. Information exchange: Qualified and trained personnel

- ☐ Counterfeits, theft

- **Demand Risks:** Market / customer related



Pharmaceutical Quality Management

Risk Management (ICH Q9)

- Quality risk management process
 - Risk assessment
 - Risk control
 - Risk communication
 - Risk review
- A robust process will incorporate consideration of all the elements at an appropriate level of detail.



Partner selection and qualification

Chapter 7 GDP Guideline - Outsourcing

The “Holistic Approach” of a PQS* and nearly all regulatory guidelines agree upon that the management of outsourced activities and purchased materials must have processes in place which:

- Assess suitability of contractors / suppliers before use
- Ensure use of approved suppliers and a defined supply chain
- Define responsibilities and communication processes for quality related activities
- Review performance and make improvements

*PQS = Pharmaceutical Quality System

Partner selection and qualification

Quality Agreements



Topics that should be covered include:

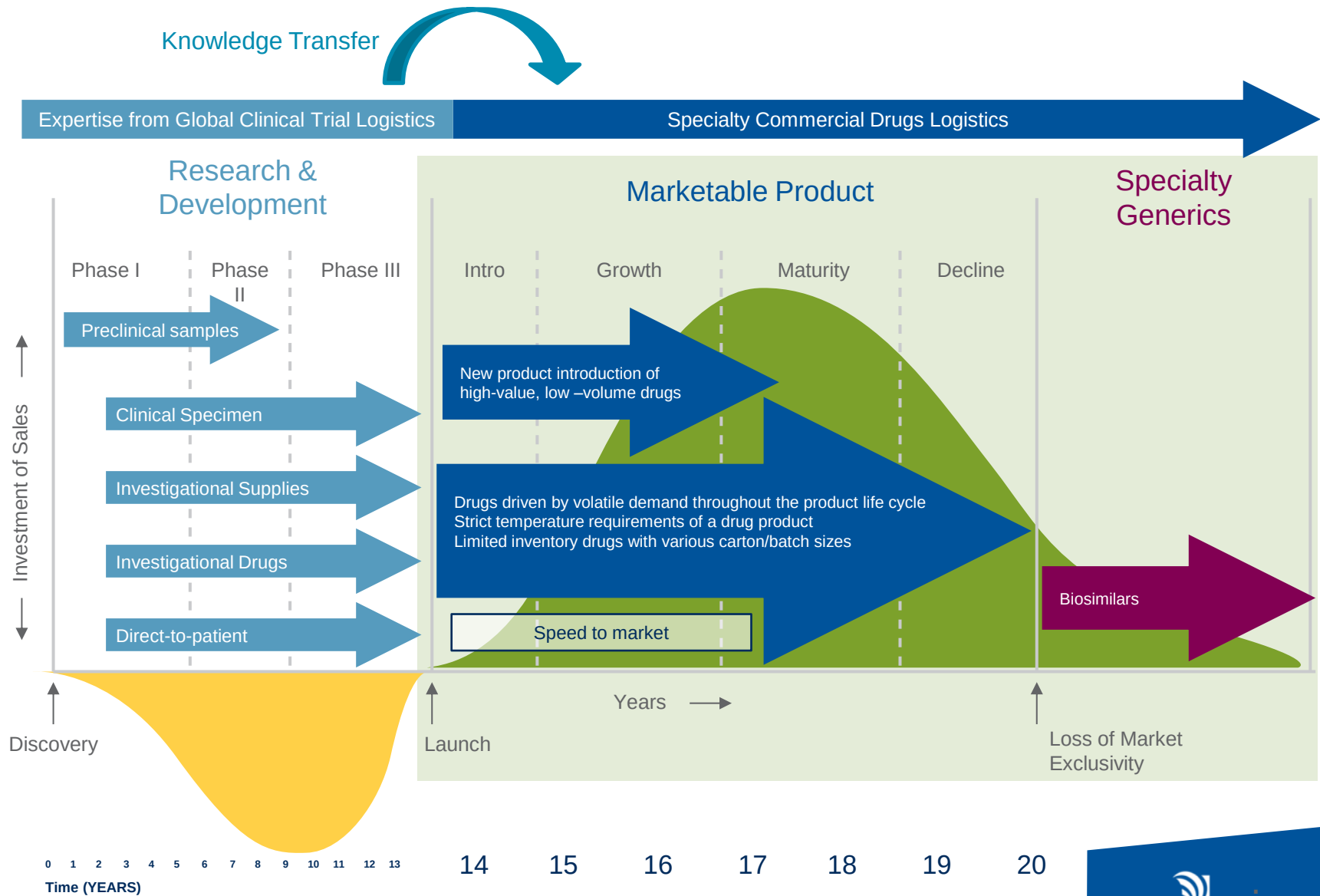
- Contact details
- Hours of operation
- **Public & company holidays**
- **Products and special requirements**
- Packaging components
- Documentation
- Labeling
- Pickup
- **Re-icing**
- **Special requirements at origin & destination**
- Pre-alerts
- Irregularities
- **Tracking & tracing**



Concluding Remarks



Key considerations to customize the commercial supply chain

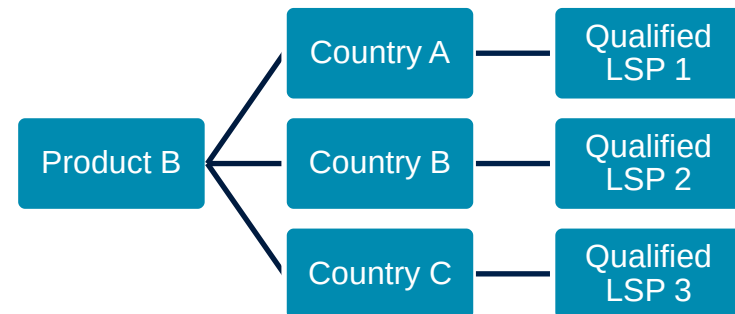
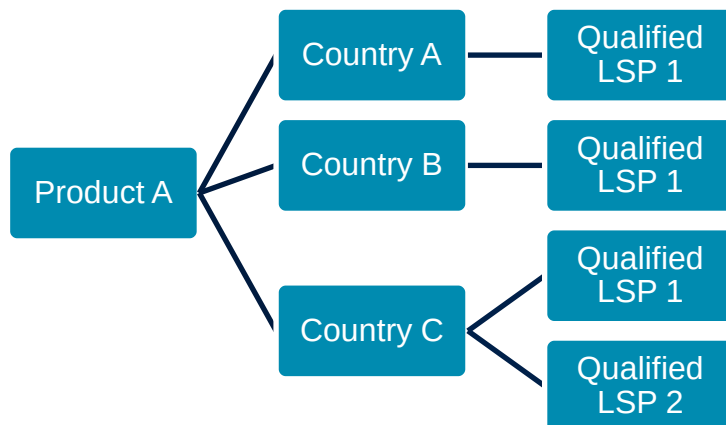


Summary

There are similarities of handling of global clinical trials and certain specialty drug scenarios.

Assessment of specifications/ requirements is key with regard to:

Product	Country	Demand
Value	Regulations	Population
Volume	Customs	Consignees
...	...	...



Thank you!

Michael Fleischer
Director, Quality - Transport
GMP Compliance & QA Manager
Certified Lead Auditor





When time is of essence, trust is
absolutely essential and confidence
is key, choose World Courier.