



GOOD PRACTICE GUIDE:

Operations Management

Supply Chain Management

Manufacturing Operations Strategy
and Management

Key Performance Indicators

Continuous Improvement
and Innovation



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GOOD PRACTICE GUIDE:

Operations Management

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Preface

This ISPE Good Practice Guide on Operations Management has been developed and published by ISPE with the aim to provide to the industry a unique opportunity to integrate in a single document the complex body of knowledge required to all professionals involved in the highly regulated pharmaceutical market.

The Guide is intended to promote excellence and knowledge within the pharmaceutical operations enterprise and systems. The Guide addresses all operations along the supply chain from the selection of raw materials through the distribution of drug products to customers and ultimately patients.

The Guide is a reference source of good practices covering in the most structured way a wide variety of themes, subjects, problems and issues faced across the realm of pharmaceutical operations.

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This Guide is intended to be read in conjunction with other ISPE guidance, International Council for Harmonisation (ICH) guidelines, and industry recognized standards.

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This Good Practice Guide was produced by a Task Team led by Marzio Mercuri (Polpharma Group) and Giuseppe Ravizzini (Recordati Group). The work was supported by the ISPE Operations Management Community of Practice (COP).

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1 Introduction

1.1 Overview

The Pharmaceutical industry is under unprecedented pressure to deliver innovative health benefits at affordable costs. This means that Operations Management is also challenged to maximize the strategic benefit it provides to the company at an acceptable level of cost. As a key driver to delivering on this challenge, the industry has been adopting operational practices which should be understood as coming under the umbrella term of “Operational Excellence”. The effectiveness of these approaches requires the use of practices, procedures, techniques, tools, and relevant Key Performance Indicators (KPIs) across the entire organization.

Until the recent past, the competitive edge in the pharmaceutical industry was built and based on high margin policies, reduction of costs of manufacturing via standardization of processes and increases to manufacturing scales, and relying on technical issues such as front-end design of processes as keys to success.

The 21st Century has seen a change in the portfolio of the innovator company from small molecule blockbusters to a greater focus on specialized biotechnology products. Simultaneously, the use of generic drugs continues to grow, and there is relentless downward pressure on pricing of both generic and innovator products.

Thus the traditional ways of doing business are no longer acceptable and new, innovative ways of working are required. Change is now a constant in pharmaceutical operations. Innovative products, both proprietary and generic, must be developed and integrated into the supply chain while at the same time ensuring that current and legacy products are supported to meet fluctuating global demands and constantly evolving local and global legislative and regulatory expectations.

Efficiencies are needed in individual product manufacturing lines and across multi-plant supply chains to ensure that drug shortages are avoided and to meet the market pricing pressures.

For the purposes of this Guide, operations are defined as the transformative process within a series of activities, along a value chain extending from supplier to customer. Operations Management designs, operates, and improves supply chain systems for getting work done.

The *ISPE Good Practice Guide: Operations Management* aims to provide the pharmaceutical industry with a knowledge base to promote the use of best practices and operational excellence within pharmaceutical operations management.

The Guide addresses all operations along the supply chain, from the selection of raw materials through to the distribution of final product. Topics considered by this Guide include:

- Supply Chain Strategy and Management (see Chapter 2)
- Manufacturing Operations Strategy and Management (see Chapter 3)
- Key Performance Indicators (see Chapter 4)
- Continual Improvement and Innovation (see Chapter 5)
- Methods and Tools for Continual Improvement (see Chapter 5)

A case study (see Chapter 6 – Appendix 1) is also included.

1.2 Scope

The Guide addresses how specialty, bulk Active Pharmaceutical Ingredient (API), and drug product manufacturing systems are organized and operated in order to guarantee the production, storage, and distribution of products while ensuring drug product quality throughout the supply chain. All operations along the supply chain are considered, including:

- Sourcing of raw materials
- Manufacturing of the drug substance (also called the API) and the drug product
- Control over all quality components, the finished product, and critical intermediates process steps
- Adequacy of the manufacturing and control facilities in order to meet compliance and quality objectives
- Distribution of finished products

These responsibilities are achieved as a concept of supply chain. This means that suppliers are adequately audited, facilities are properly qualified, and processes validated, and the finished product checked for the compliance with the expected quality. For example:

- Quality Assurance (QA) is responsible for the compliance of the enterprise with all regulatory requirements.
- Maintenance is responsible for keeping the manufacturing facilities in an adequate state of qualification.

Both compliance and qualification require a multi-disciplinary approach which considers all functions (QA, Validation, Engineering, Manufacturing, Health, Safety, and Environment (HSE), and Logistics). Cooperation is needed between the parties involved to maintain an appropriate qualification and validation status of manufacturing assets and processes.

The manufacturing function is then driven by three major priorities:

- Sustained compliance with all applicable regulatory agencies, e.g.:
 - In the United States, the FDA and the Environmental Protection Agency (EPA)
 - In the European Union (EU), the EMA or REACH¹
- Improved manufacturing performance and efficiency while maintaining control on costs
- Timely production according to demand

In order to fulfill its mission, the manufacturing operations function needs to coordinate with other functions of the pharmaceutical organization, in a spirit of teamwork and with shared objectives, including:

- Awareness of the products in development (to anticipate the future needs of manufacturing)
- Feedback to development based on manufacturing experience (to avoid future scale-up problems)
- Support to clinical supplies

¹ http://ec.europa.eu/environment/chemicals/reach/reach_en.htm

- Timely delivery to distribution to meet the demand (close cooperation with marketing for establishing the sales forecasts)
- Continuity of information between API manufacturing and drug product manufacturing
- Qualification and monitoring of outsourced process

Two interfaces that should be considered are:

1. Between development and manufacturing operations
2. Between API and drug product (within development and manufacturing)

Any change in the sourcing and manufacturing of raw materials, critical package material, in the manufacturing process, and in the facilities should be properly evaluated and validated (in terms of impact on the finished product quality and labeling). Changes should be communicated within the internal organization and be available to the regulatory authorities. Information communication should cover external organizations with a quality notification.

Interfacing with marketing, in order to obtain reliable sales forecasts, can allow organizing production planning with minimum inventories.

For further information on key topics and theories presented in this Guide, see relevant ICH guidance and ISPE publications:

- ICH “Q” series of guides and particularly the latest editions of ICH Q7 [1], ICH Q8(R2) [2], ICH Q9 [3], ICH Q10 [4] and ICH Q11 [5] guidelines, providing the principles and guidance for a quality and risk-based development, manufacturing, and release of quality-based pharmaceuticals
- ISPE Baseline® Guides for design of new and renovated facilities [6].
- The ISPE Product Quality Lifecycle Implementation® (PQLI®) Good Practice Guides (GPGs) [7] providing information on global solutions to implementation challenges of ICH guidance.
- ISPE GAMP® 5 [8] and the ISPE GAMP® Good Practice Guides (GPGs) [9], which provide pragmatic and practical industry guidance to achieve compliant GxP process control and computerized systems fit for intended use in an efficient and effective manner.
- ISPE Guides [10] and ISPE Good Practice Guides (GPGs) [11] that provide information or advise on a particular topic area and underlying technical principles and suggesting solutions in an area where no single answer is correct. The *ISPE Good Practice Guide: Project Management for the Pharmaceutical Industry* [12] and *ISPE Good Practice Guide: Maintenance* [13] may be particularly helpful.

1.3 Purpose

This *ISPE Good Practice Guide: Operations Management* is intended to provide a framework for the management of pharmaceutical operations. It aims to identify and develop industry good practices to:

- Provide reference, guidance, and support to pharmaceutical operations managers in selecting the most appropriate solutions for the identification and completion of the objectives of their manufacturing operations within the framework of their company organization, including external stakeholders and regulatory bodies.
- Provide operations management with a robust basis for understanding how compliance and continual improvement/innovation can be achieved simultaneously.

- Define a common language and provide guidance for performance measurement, benchmarking, and improvement.
- Identify new performance improvement tools, clarifying what is applicable and what is not, for pharmaceutical operations.

1.4 Benefits

This Guide is intended to provide a structured description of processes and technologies within the pharmaceutical industry.

Industry professionals and stakeholders will have the opportunity to build and use a common language and a way to use generic and specific tools while acquiring a deep understanding of the Operations Management processes and supporting technologies.

Additional benefits include:

- Collation of a comprehensive list of current good practices to aid successful operations
- Development of a broader knowledge within pharmaceutical stakeholders at any organizational level
- Knowledge to help to mitigate or eliminate risks common to pharmaceutical projects

This Guide is intended to assist pharmaceutical professionals and others wanting to obtain a detailed understanding of Operations Management in the functions:

- Production
- Quality
- Engineering
- Sourcing and Procurement
- Logistics
- Finance
- Regulatory

1.5 Key Concepts

Traditionally, the pharmaceutical industry has been organized by function, each one playing a “chronological” role in discovering, developing, manufacturing, controlling, and distributing medicines. The model was, essentially, discrete functions “pushing” the product from research to patients.

Recently, this model has changed to some extent:

- The functions still exist but work in closer cooperation.
- The products are “pulled” rather than “pushed” and start from identified patient needs, which in turn drive drug characteristics; these are the basis for the medicine formula and manufacturing process.

- There is increased consideration of the consistency of actions during the entire life cycle of the drug product.

These changes result in concepts such as “supply chain” and “product life cycle management”.

Most functions used to be self-sufficient, fulfilling their mission within the pharmaceutical organization with internal resources. Today, however, the trend is to use selected external resources in order to execute selected tasks that used to be performed internally. External resources may be used when:

- There are insufficient internal resources.
- Production capacities are undersized or are not available in time.
- The tasks involved are not considered “strategic”.
- The tasks involved are not aligned with desired core competency.
- A contractor could have better technical expertise.

The growth of Contract Research Organizations (CROs) and Contract Manufacturing Organizations (CMOs) is significant. Process engineering and facilities engineering are also frequently contracted out (partially). Pharmaceutical organizations now work with a network of contractors and service organizations.

The relationship with regulatory agencies has also changed. They continue to be a government authority controlling the manufacture of product according to the registration file, within facilities meeting this purpose. However, they now provide more freedom for changes and continual improvement, under the strict condition that the manufacturer can prove that the manufacturing process is understood, under control, and designed to produce the expected quality of product. These changes are represented in concepts such as Process Analytical Technology (PAT), “design space”, Quality by Design (QbD), and “continual improvement”.

Increasingly, the notion of “risk management” has been developed, the idea being to proportionate the amount of QA to the risk to the patient (i.e., the quality effort should be commensurate with the risk posed to the patient). All steps of the process are analyzed in terms of risk to the patient, as a tool to prioritize continual improvement actions and minimize the resulting risk.

There is also more emphasis on the potential legal obligation of marketing authorization holders and distributors to maintain continuity of supply, e.g., in the EU requirements for continuity of supply for human and veterinary medicines are defined in Article 81 of EU Directive 2001/83/EC [14]:

“The holder of a marketing authorization for a medicinal product and the distributors of the said medicinal product actually placed on the market in a Member State shall, within the limits of their responsibilities, ensure appropriate and continued supplies of that medicinal product to pharmacies and persons authorized to supply medicinal products so that the needs of patients in the Member State in question are covered.”

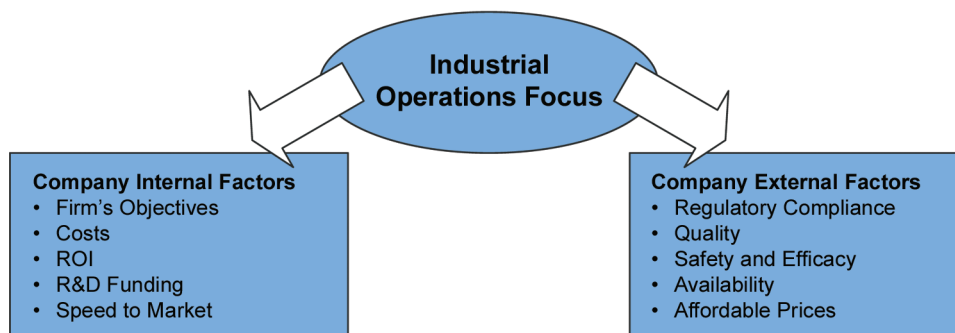
Another trend is the pressure on manufacturing costs. This is the consequence of three main causes:

1. The significant decline of new drug products reaching the market, resulting in research and development (R&D) costs increasing for each new entity entering the market. The industrial operations function is expected to compensate partially by generating more savings.
2. The legitimate wish of the community to access medicines at the lowest cost
3. The increased competition created by the establishment of contract manufacturing facilities and drug products substitutes (i.e., generic therapies replacing original products) to treat the same indication

The “customer” of a medicine (though generally prescribed by a physician) is a patient who expects a significant improvement in their health, with minimum secondary effects. The quality of the medicine is recognized by the marketing authorization delivered by the regulatory authority, based on the facts provided by the pharmaceutical company in the registration file. Companies should be in a position to provide evidence that the medicine manufactured meets all requirements (quality of the raw materials, control of the process, quality of the finished products and packaging, control over the distribution chain, and compliance in all steps with regulations).

The scheme shown in Figure 1.1 summarizes the major constraints that apply to the industrial operations function:

Figure 1.1: Business Factors Driving Operations Strategy



2 Supply Chain Strategy and Management

2.1 Introduction

The supply chain strategy aims to establish a liaison between discovery, R&D, and the final targeted customer of the API or finished product.

Typical nodes of a supply chain network include:

- Sourcing of materials and services (inbound activities)
- Manufacturing and production (primary manufacturing, secondary manufacturing, contract/toll manufacturers)
- Delivery/Logistics and Distribution (Outbound Activities)

Product realization (see ICH Q10 [4]) is part of a life cycle process that describes the process of developing an active ingredient, the finished product and the associated manufacturing processes. Not all phases will be relevant for all sectors of the industry, but the end goal is to ensure a quality product can be sourced and manufactured through the company's supply chain. The supply chain strategy aims to ensure a reliable and robust supply of that pharmaceutical product to the market place, establishing a liaison between suppliers or producers of raw materials, intermediates, the API, the finished product and associated packaging materials through to the distribution chain and final targeted customer.

This chapter provides an insight into aspects to be considered when designing and implementing a supply chain, and emphasizes the importance of seamless integration.

2.2 Supply Chain Fundamentals

Having defined the core functional elements that need to be taken into account for end-to-end Supply Chain Management (SCM), the next step is to consider the activities that take place from concept to consumption.

Supply chain activities and tasks can be performed by participants who are either insource or outsource, and the supply chains can be:

- Local
- Regional
- Global

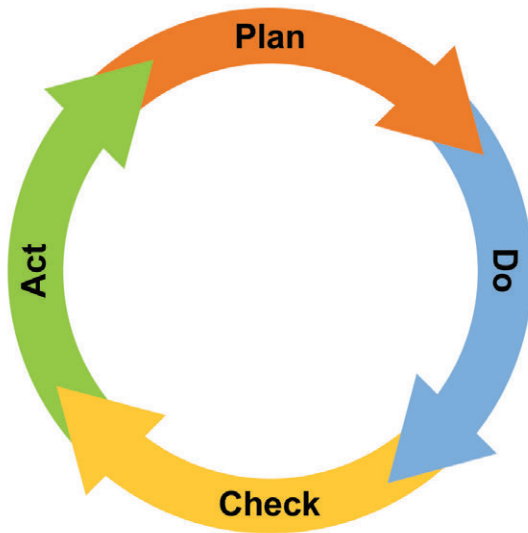
At very high level the entire supply chain process can be represented (see Figure 2.1) by a typical four stage PDCA cycle, such as that from the Lean Enterprise Institute [15]:

Plan: Determine goals for a process and needed changes to achieve them.

Do: Implement the changes.

Check: Evaluate the results in terms of performance.

Act: Standardize and stabilize the change or begin the cycle again, depending on the results."

Figure 2.1: Example Plan-Do-Check-Act (PDCA) Cycle

2.2.1 Supply Chain Planning

There are several key elements that fall within the scope of Supply Chain Planning (SCP), including:

- Organizational alignment
- Supply chain/logistics function reporting structure

The supply chain/logistics function reporting structure can vary according to the size and type of business:

- For smaller companies, supply chain functions usually report to Finance/Accounting
- For medium to large companies, supply chain functions report to technical operations
- For most Fortune 500 companies, supply chain functions report directly to the chief executive officer (CEO).

Traditional logistics functions should report to the head of the Supply Chain function. These logistics functions include:

- Planning
- Distribution and Warehousing
- Strategic Sourcing and Production Procurement
- Import/Export functions (where applicable)
- New product planning

Organizational alignment should be performed via a structured process. This starts with long term planning (from 1 to 3 – 5 years) and with short-term/mid-term planning performed jointly by Commercial and Technical Operations.

The framework on how a business operates should be built around the principles of Sales & Operations Planning (S&OP) and is considered operational best practice.

Key concepts of the S&OP process include:

- Yearly/long term strategic planning
- Monthly business planning cycle/monthly planning calendar/short term planning
- Demand forecast
- Matching supply with demand
- Capacity planning
- Scenario planning
- Distribution planning – network perspective
- Global/regional distribution network design

Yearly/Long Term Strategic Planning

Yearly/three-year planning enables the Supply Chain function proactively to align their capabilities to the commercial vision. An annual review of the business should be performed, where Commercial and Supply Chain functions review and discuss jointly the strategic direction of the business. Key elements of good practice include:

- A review of the external environment of the marketplace, i.e., new competitive factors, new areas of opportunity in market share, new products, etc.
- An update from the Supply function on the state of the supply network. This includes areas of risk and further opportunities to improve the Cost of Goods (COG).
- An understanding, from the supply perspective, of new technology that needs to be built into the supply network (whether internal network or brought in through a CMO), to meet the commercial ambition
- Output from this meeting should be shared with the supply chain organization where appropriate, to ensure understanding (usually shared during the next Supply S&OP meeting).

Monthly Business Planning Cycle/Monthly Planning Calendar/Short Term Planning

The business is driven, month by month, by the S&OP monthly planning cycle. This includes key elements such as:

- The planning cycle, which is coordinated by the Supply Chain Management function or the Technical Operations Management function. The planning cycle includes key elements such as:
 - The Commercial Operations function which develops a new forecast for the month and hands it over to the Technical Operations function (i.e., sales volumes for current products, new launches, etc.).
 - The Technical Operations function which determines the impact of the new forecast on their area, i.e., new capacity profiles, impact on components and raw materials needs, stocks levels
 - Commercial and Technical operations collaborate to discuss risks to supply, based upon the new forecast and the “handshake” between the two parties for the agreed plan

- The monthly structure meeting in which the roles of all parties and how they support the monthly planning cycle is documented. A definition of each meeting should include an Initial Public Offering (IPO) (documented inputs, the process, and outputs), and a planning calendar clearly stating the timing of each meeting.

Demand Forecast

This involves converting sales forecasts to meaningful production volumes, in order to enable Supply to develop a monthly master production schedule.

- This involves a series of Commercial Operations internal meetings to develop the new projected forecast.
- The forecast can be developed using a wide range of tools, depending on the size of the company. Suitable tools range from sophisticated software packages to manual spreadsheets.
- Any changes in the forecast should be documented, in order to highlight changes for the Supply Chain function. (An agreement can be reached regarding the criteria which determines what has to be flagged, i.e., any change $\pm 15\%$ by Stock Keeping Units (SKUs), etc.)

Matching Supply with Demand

Continuity of supply of product to the Commercial function should be ensured. Key elements of good practice (from the Supply side) for this phase include:

- **Planning** – Operating a rigorous supply monthly business planning cycle, where the new master production schedule is generated based upon the new agreed forecast (ranging from automated systems to a manual regeneration exercise, dependent upon the business).
- **Capacity analysis** – Performed by work center, which will indicate and identify potential capacity shortfalls or risks to escalate through the monthly S&OP process (which should include production downtime, such as scheduled maintenance). This should be done on all manufacturing and packaging operational work centers.
- **For captive manufacturing networks** – Robust conversations within key areas of the business (by site, if applicable, that can involve multi-site alignment of the monthly cycle), to discuss and identify potential risks in meeting the plan, which might include Procurement, Planning, Production, QA/QC, Shipping, and Warehousing functions.
- **For external manufacturing networks (CMOs)** – Regardless of where the CMO management accountability falls within an organization, the points discussed in this section should be accomplished on a monthly basis. Depending on established contracts this may prove challenging with the CMO and how much information they can share. Critical to success is to have set monthly meetings with an external network, in alignment with a monthly business planning cycle, which outputs are fed into the process.
- **Sourcing/Production Material Procurement** – This function should have the required capability to identify rapidly and to mitigate/eliminate (with Planning function support) risks to potential raw material/component availability, in order to meet the planned demand.
- **QC/QA** – QC/QA departments may represent a bottleneck. The mitigation effort could identify and involve resources of trained personnel, or analyze the testing function (such as High Performance Liquid Chromatography (HPLC) or Gas Chromatography (GC) units), with a “capacity planning analysis” treating each function as a “work center” (in a similar way to a production line). Value Stream Mapping focusing on reduction of wastes improving lead time (i.e., time between QC order request and analysis completion) and takt time (i.e., the processing time of the specific QC operation to keep up with internal customer demand) may help to remove bottlenecks and improve overall process efficiency.

Capacity Planning

Capacity planning should be employed to avoid any drug substance shortfall in the short-, mid-, and long- term periods. The process should be managed according to specific time limits. A routine capacity planning analysis should be performed on a monthly basis.

A key meeting during this monthly process is a meeting to discuss and review each work center profile by exception (e.g., an agreement can be established to review any work center that is over or under planned capacity by $\pm 15\%$). The meeting team should include members from:

- Planning
- Production
- Manufacturing
- Maintenance
- QA (as appropriate)
- The output of this meeting should include:
- The profile of the work center posing the risk
- Commentary of the issue
- Contingency plans/solutions to mitigate the risk to supply

Data integrity and accuracy are fundamental to well-executed capacity planning. Class "A" Manufacturing Resource Planning (MRP II) states that data accuracy should be 99.9%, measured monthly and reviewed frequently for improvement opportunities, i.e., set up run times inherent in system profiles versus demonstrated actuals.

Scenario Planning

A process should be established for unforeseen changes in demand or supply and to provide the capability to understand the impact of these events on the business. Such events should be understood and internalized, regardless of where the event originated (Commercial or Supply). Supply may have to re-run their production plans to understand capacity or components/raw materials impacts of a change in forecast, or Commercial may have to understand the impact of a supply issue on their financial plans.

Distribution Planning – Network Perspective

As needs change, distribution planning should be included as an area of strategic focus. Changes in demand and changes in supply (or supply locations for existing suppliers), as well as relocation or expansion of manufacturing operations (with technology transfer implications), should trigger a review of distribution planning. Starting with the highest level (the distribution network), an evaluation of key elements should be performed.

Example questions include:

- Do we have changes in supply as well as demand that require an evaluation of our distribution network?
- Does our current network of storage and distribution operations meet the needs of current and future customers and stakeholders?

- Is there a change in our customer demographic that has put additional pressure on the current network configuration? If the answer is yes:
 - Do we understand if this is a temporary situation or one that will require a change in strategy?
- Have we introduced new configurations of products into our network that have different risk factors than those that we have been prepared to handle in the past?
- What has changed and what is the impact on product storage?
- Are there product level characteristics that need to be taken into account, e.g., cold chain, chain of custody, special handling, and storage requirements?
- Are there new requirements that we need to take into account? For example:
 - Packaging?
 - Labeling?
 - Documentation and literature?
- Do we need to perform a detailed analysis in order to have a comprehensive understanding of areas of exposure and risk?
- Are there new challenges related to storage and distribution of our products that we need assistance with? If the answer is yes:
 - What are our options and how should we assess the best path forward?

Having defined the current state, as well as the desired future state, the next step is to develop a “tactical” plan for product storage and distribution.

Global/Regional Distribution Network Design

Building upon the understanding of the requirements for product storage, distribution, and special handling, it should be possible to define the best configuration of warehouse locations (insource and outsource) and transportation combinations. Network optimization includes picking the optimal number, location, and size of warehouses and/or facilities to minimize the total costs including sourcing, production, and transportation to optimize the trade-offs between the number of facilities and service levels. It includes determining which site/supplier should produce which product and which warehouses should service which customers. All factors should be analyzed and compared within the context of service level and cost strategies.

Commercially available network design tools can be used to perform iterations to analyze network scenarios in order to understand the impact of multiple parameters and determine which network configuration best meets business needs.

Major planning components of a distribution network design and optimization are the mapping process and data management.

Mapping (see Figures 2.2, 2.3, and 2.4) allows:

- The visualization of supply chain solutions
- A better understanding of different scenarios for location determination and interconnecting of different locations within the network

- Color coding, sizing, and utilization indicators for further analysis

Figure 2.2: Assessing Customer Population Density

US map used with permission from CH2M HILL, <http://www.ch2m.com/corporate/>

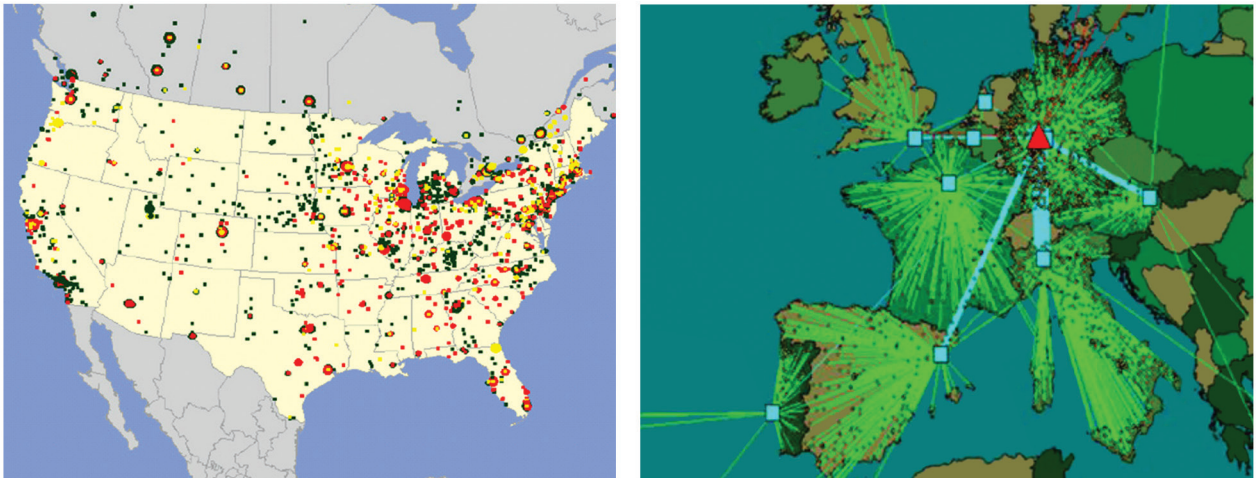
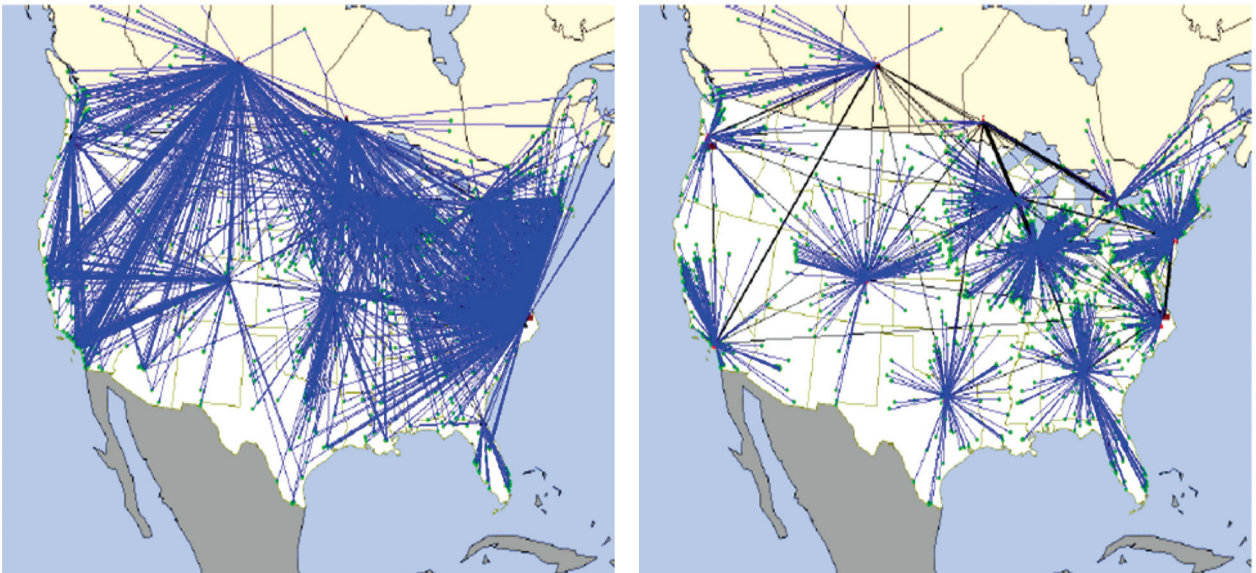


Figure 2.3: Alternatives – Distance versus Service Level

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Data management can help to:

- Specify the costs of the supply chain
- Define a baseline cost data matching accounting data

Typical input data include:

- Customer information: to identify where shipments are going and how much is shipped, by product
- Plant/supplier information: to specify the origin of the product and related costs and capacities required

- Distribution centers: existing and potential distribution centers, cross-docks, warehouses, etc. (For each, the relevant fixed and variable costs along with capacities are required.)
- Products information (volumes, technology information, etc.)
- Transportation costs (the cost to move the product from origin to destination)

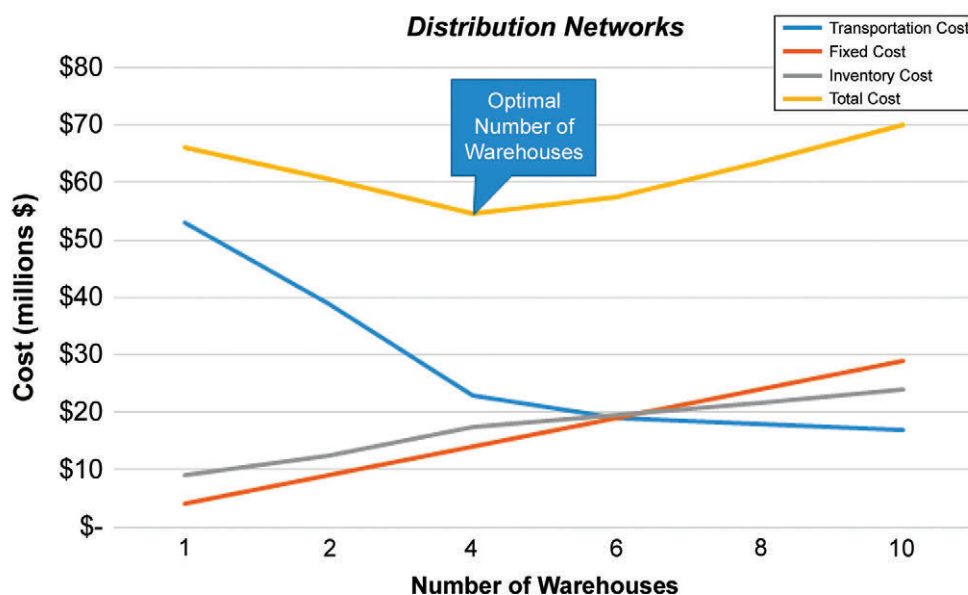
Typical output data include:

- Minimum overall total cost:
 - Manufacturing costs
 - Warehouse costs (fixed, processing, and inventory)
 - Transportation costs
- Optimal number, size, and location of warehouses
- Appropriate allocation of products to different warehouses
- Trade-offs between cost and service levels
- Optimal production quantity at each manufacturing plant
- Efficient supply channels in the logistics network

The output data allow changes to the supply chain to be quantified, and displaying solutions (see Figure 2.5) will help to compare scenarios.

Where product margins are high and the inventory is expensive relative to transportation costs, it is advantageous to minimize the number of warehouses in the distribution network, see Figure 2.4.

Figure 2.4: Distribution Warehouse Network Planning

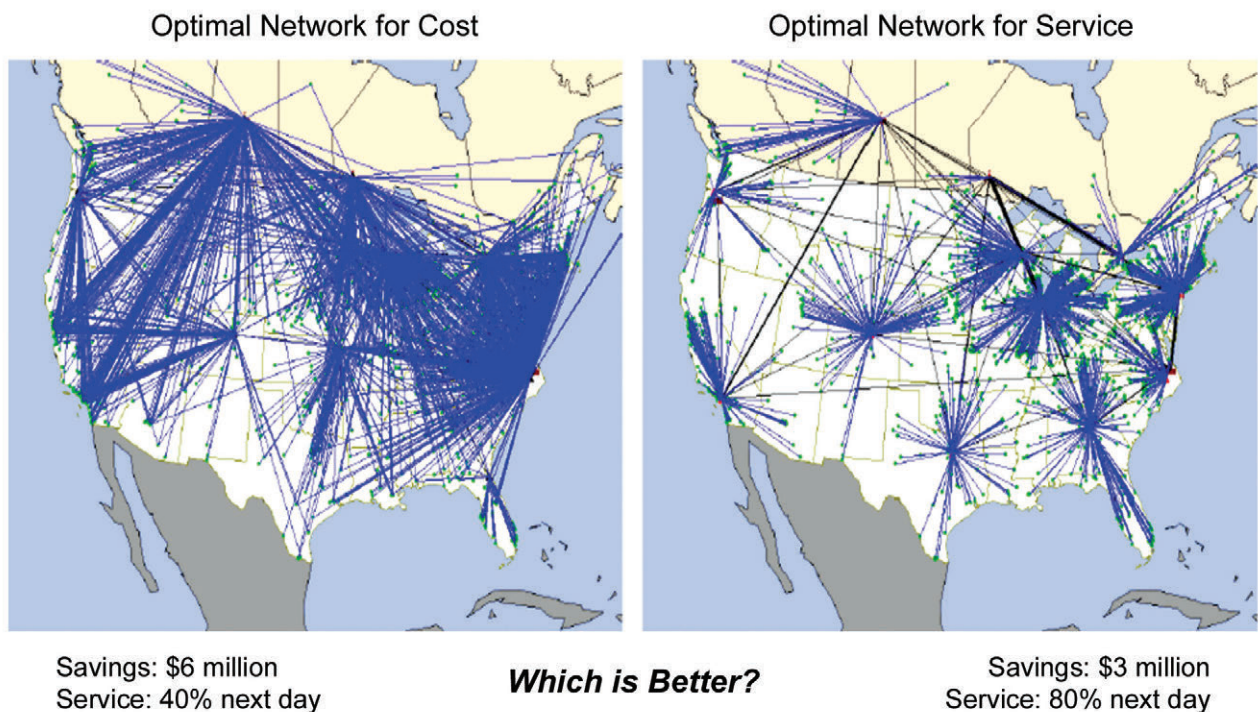


Strategic service levels should also be considered and can be different for individual products. Two service level criteria are often used:

1. Minimizing total miles weighted by demand:
 - Making sure that the highest demand customers are best served
2. Maximizing the weighted demand within a specific radius of a warehouse:
 - Making sure that all customers are provided with the same service

Figure 2.5: Alternatives – Cost versus Service Level

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Inventory levels should be established and maintained in alignment with key success measurements. This requires consideration of stock levels in terms of cost and service levels at a minimum. Metrics can include:

- Demand
- Demand standard deviation
- Service level
- Stock replenishment lead time
- Base stock level
- Safety stock
- Safety stock cost

At a more operative level, the requirements for products handling, storage, and tracking should also consider:

- Implementation of a logistics/distribution scheme/plan based upon:
 - Risk to Product Quality determined by Transportation
 - API/Manufacturing/Packaging locations versus Primary and Secondary Distribution Site
- Addressing the regulatory requirements related to Good Distribution Practices (GDPs) (e.g., in Europe governed by 2013/C 68/01 “Guidelines of 7 March 2013 on GDP of Medicinal Products for Human Use” [16].
- Definition of anti-counterfeit measures, as the pharmaceutical supply chain should be protected against the penetration of counterfeited products. Weak points in the distribution processes of pharmaceutical products provide an avenue for counterfeit as well as illegally imported, stolen, and substandard medicines to enter the supply chain.
- Definition of measures applicable to all persons and outlets involved in any aspect of the distribution of pharmaceutical products from the premises of the manufacturer of the product to the person dispensing or providing pharmaceutical products directly to a patient or their agent. This includes all parties involved in trade and distribution of medicines, pharmaceutical manufacturers, including the manufacturers of finished products and pharmaceutical wholesalers as well as other parties such as brokers, suppliers, distributors, logistics providers, traders, transport companies, and forwarding agents and their employees.
- Implementation of serialization process which requires a comprehensive system to track and trace the passage of prescription drugs through the entire supply chain, e.g.:
 - In the US, this is governed by FDA Guidance for Industry: Standards for Securing the Drug Supply Chain – Standardized Numerical Identification for Prescription Drug Packages, 2010 [17].
 - In the EU, this is governed by the EU Falsified Medicines Directive (2011/62/EU) [18], which stipulates uniquely coded, serialized packs for almost all prescription drugs. Additionally, the EU has defined a second layer of security to be provided by tamper-proof closures that indicate whether a package has been previously opened or tampered with.

2.2.2 Sourcing

Supplier Qualification

Corporate reputations should be protected from unscrupulous supplier practices. A formal supplier (vendor) qualification process should be established. This should include a prequalification/screening phase and a formal quotation phase (via simple postal audits or Request for Information (RFI) templates).

A preliminary screening phase or received prequalification forms can assist organizations in judging the credibility of a supplier. Companies usually have a questionnaire that is developed by subject matter experts (SMEs), which shortlisted suppliers have to answer (a mandatory requirement) during this phase. Based on the responses, suppliers can then be qualified and rated.

Suppliers should also be asked to submit key information, e.g.:

- Audit requirements
- Company registrations and certifications, e.g., with the International Organization for Standardization (ISO)
- A list of pharmaceutical companies which have already successfully inspected the supplier premises

- Historical data concerning major and minor observations resulting from inspections
- Inspections observations with associated Corrective and Preventive Actions (CAPAs)

This qualification stage can be used to determine suitable suppliers.

Supplier Monitoring and Risk Management

Supplier quality management and performance monitoring are key components of a risk management strategy. Having visibility into supplier operations and quality programs (such as Six Sigma) can help both to ensure that the products meet requirements and to reduce the risks of batch rejections and recalls.

Recommendations for managing supply risks:

- Define and enforce standard performance and risk measures (metrics dashboards) and frequent assessments
- Make risk management a core and repeatable business discipline
- Adopt sourcing methods to balance cost, performance, and risks
- Put in place a robust relationship management process to have open discussions that will improve risk planning, performance monitoring, and responsiveness to potential supply disruptions. Key elements include:
 - Supplier qualification and audit
 - Supplier monitoring and inspection
 - Risk management

2.2.3 Manufacturing (Make)

Internal Manufacturing Activities

Manufacturing/production scope includes:

- Manufacturing and packaging of drug substances
- Manufacturing of drug products in bulk (primary manufacturing)
- Final packaging of drug substance (secondary packaging)
- Contract manufacturing

The Supply Chain function in an organization should participate in the execution of the corporate manufacturing operations strategy. Supporting the execution of this strategy can enable a manufacturing division to meet company strategic drivers and objectives. Key areas for which the supply chain function is usually accountable, in order to drive the strategy, include:

- Role of operational support functions: procurement, planning, shipping, distribution, receiving, and warehousing
- Supporting development of production models (large runs, small runs, specialized, continuous, etc.)
- Operational excellence methodologies

- Facility and capacity planning

External Manufacturing Activities

External manufacturing activities include:

- **Product outsourcing (CMOs):** Identification of the product's internal candidate selection through technical operations network (this is generally driven either by variable costs analysis or by strategic capacity analysis)
- **Services outsourcing (shared services model):** Justification through operations (General and Administrative (G&A) expenses driven)
- **Outsourcing functions/product management:** Definition of the operational model to manage outsourced functions

Outsourcing can allow organizations to eliminate redundant functions across operation units, reducing costs, while allowing business organizations to be focused on their specific business. Considerations for outsourcing efforts include the:

- Relationship between the provider organization and the customer organization
- Communications within the provider organization
- Communications within the customer organization

An organization should evaluate its operations and determine, through current outsourcing best practice, whether operational functions should be:

- Kept internal, streamlined, or discontinued
- Supported by the creation of an internal shared service
- Outsourced

The scope of the outsourcing decision includes on-shoring, near-shoring, or offshoring considerations.

Business drivers that can change the *status quo* for pharmaceutical manufacturers include:

- Industry consolidation, e.g., mergers and acquisitions
- Patent cliff, e.g., cost containment
- Growth into emerging markets
- New products/technologies/portfolio introduction

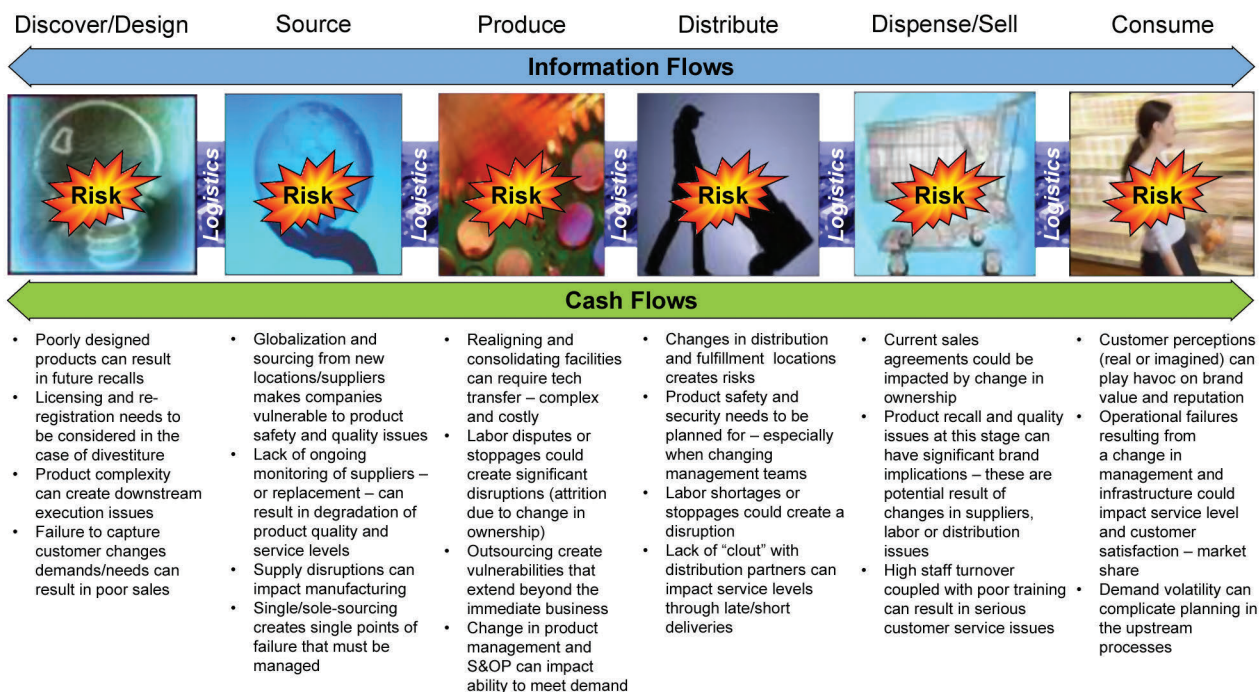
Based on these drivers, there is a move toward consolidation of global operations. This can involve outsourcing the manufacture of both starting ingredients and finished goods to a lower cost manufacturing location, both regionally and globally. Moving the key activities and functions from a known insource environment to a relatively unknown outsourced environment can be a significant task.

Moving the production of key materials, products, and distribution operations to new locations within an enterprise has a high level of complexity. Outsourcing critical functions to a third party can add a new dimension of risk.

Teams should engage in understanding and preparing for risk management. Figure 2.6 illustrates some of the risks that are inherent in the end-to-end product life cycle; network consolidation and outsourcing can elevate the probability and impact of these risk factors.

Figure 2.6: Areas of Risk in the Supply Chain Process and Product Lifecycle

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Product Management (A Key Element of Manufacturing Strategy)

Loosely grouped under the heading of “technology transfer” there are many activities that should be considered when moving a product (or family of products) from one physical location to another or deciding to launch a product in one or another site.

The place element (the subtle change in one of the core components of product management) has a variety of implications that should be reviewed meticulously prior to defining where to launch, more or eventually outsource.

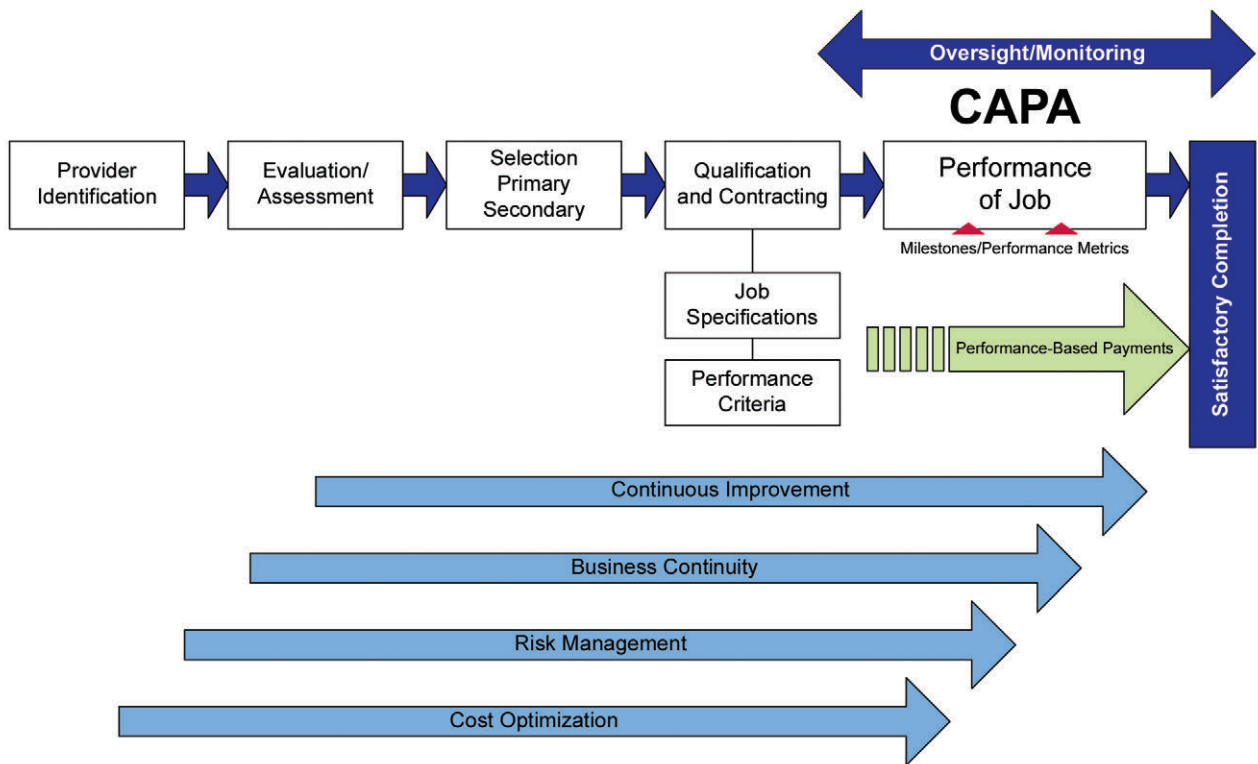
A holistic approach should be taken. All participants, processes, and functions, which are involved across the product life cycle, should be considered.

If the decision is taken to outsource, evaluation of potential outsource partners should, as a minimum, include the key steps outlined in Figure 2.7.

For further information, see the *ISPE Good Practice Guide: Technology Transfer (Second Edition)* [19].

Figure 2.7: Strategic View of Outsourcing

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Outsourcing Strategic Drivers

When defining an outsource strategy, it should be ensured that the element of risk has not increased, regardless of perceived advantages.

Factors for consideration include:

- Complexity and Flexibility:
 - Reduction in complexity – is it easier to manage external or internal resources?
 - Does outsourcing provide advantages that provide more flexibility to respond to changes in supply and demand?
 - Does this alternative free up internal resources that can be used for other purposes?
 - May the outsourced process pose a risk to compliance and company reputation?
- Process Improvement:
 - Does outsourcing this function provide some process improvements?
 - Does the outsource partner have capabilities (locations, technology, infrastructure) that will result in an improvement in service levels?

- Cost Savings and Improvement in Asset Management
 - Are there quantifiable cost benefits in outsourcing this function?
 - Does this alternative provide us with a better return on our current asset structure?

How Does an Organization Justify Outsourcing?

There should be defined processes to identify an internal candidate for outsourcing, to develop the business case for the approval of the project, and to successfully implement the approved solution. Elements to consider for the business case include:

- Does the organization want to divest itself of a capability or choose not to create it?
- Is the outsourcing to a specialized services provider chosen for their expertise and focus, instead of performing the work at a lower cost?
- Will the provider's performance/payments be based upon results of their operations or business outcomes, instead of providing resources for doing the work?
- What are the benefits that can be achieved by outsourcing?

The anticipated benefits and risks from outsourcing and their relative importance to the business should be understood. Some of the benefits that can be achieved include:

- Reduction, containment, and cost avoidance
- Improved focus
- Achieving a more variable cost structure
- Access to skills not available internally
- Improved quality
- Increased speed
- Revenue and margin growth
- Reduced Capital Expenditure (CAPEX)
- Innovation
- Opportunities versus risks

Internal Shared Services

Anticipated benefits of internal shared services include:

- Shared services allow internal providers to be more efficient through common processes, economies of scale, and standardization.
- Shared services provide an internal function with enough size to provide a community of expertise, attractive for hiring, training, and retaining.

- A shared service business model allows the business units to discontinue their fragmented focus on non-core support areas, because the shared service group accepts responsibility and accountability for those areas.

These may be achieved through re-engineering of business supporting functions, such as Information Technology (IT) with cloud services, security, internal transports and site housekeeping, up-facility engineering and management.

A typical shared service model should include:

- An internal organization becomes an internal service provider and manages a non-core, but essential, support function.
- Business organizations request products and services from the shared service provider.
- The shared service organization provides services to multiple business organizations within the company.
- The users of the services are charged by the provider for the functions they use.
- The shared service organization is operated like an independent business, covering its costs through revenue (profit center).
- Measurements including external and internal benchmarking assure that the shared services organization is efficient and always improving.

2.2.4 Storage and Distribution (Delivery)

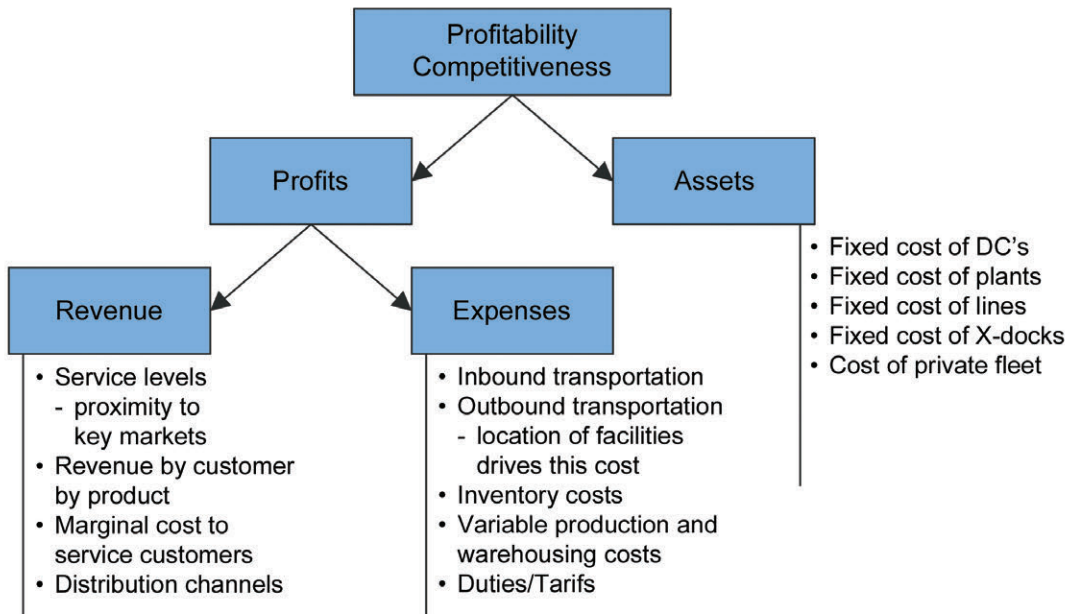
Building upon the understanding of the requirements for product storage, distribution, and special handling, it is possible to define the best configuration of warehouse locations (insource and outsource) and transportation combinations.

In-process fundamentals should focus on:

- Storing facilities
- Transport and distribution models
- Inventory management and working capital

Logistics and distribution models should address best practices to identify the best fit for the given company model/ supply chain strategy. The selected models are normally driven by profitability, minimizing the supply chain “wastes” associated with logistics and distribution. Figure 2.8 shows a KPI tree that provides key indicators to be considered for the model selection (see also Chapter 4).

Figure 2.8: Supply Chain Costs Impacting Profitability



2.2.5 Review of the Organization Set-Up

Supply Chain Metrics/Dashboard

An effective S&OP process should include a robust metrics dashboard that can drive a company forward. Metrics should be developed and agreed with all stakeholders. Metrics should be meaningful, to enable root cause analysis of existing undesirable effects and improvement initiatives, in order to improve the performance of the company. The right set of metrics also drives the right behaviors in the culture of an organization (for a comprehensive set of KPIs, see Chapter 4).

Effective S&OP Process to Measure Cultural Fitness of the Organization

The key success factor to an effective S&OP process is that it should be built into the cultural fabric of the organization.

Who should be involved?

- Technical Operations/Supply Chain:
 - Can include transportation, warehousing, and suppliers (vendors)
 - Provides information on how business runs and what is possible
- Sales/Marketing:
 - Provides information on service level constraints and evaluates how different scenarios will impact sales
 - Provides forecast data
- Finance:
 - Determines cost inputs and validates cost of scenarios

- IT (assists with data collection via Electronic Record Management Systems (ERMS), Manufacturing Execution Systems (MESs), etc.)

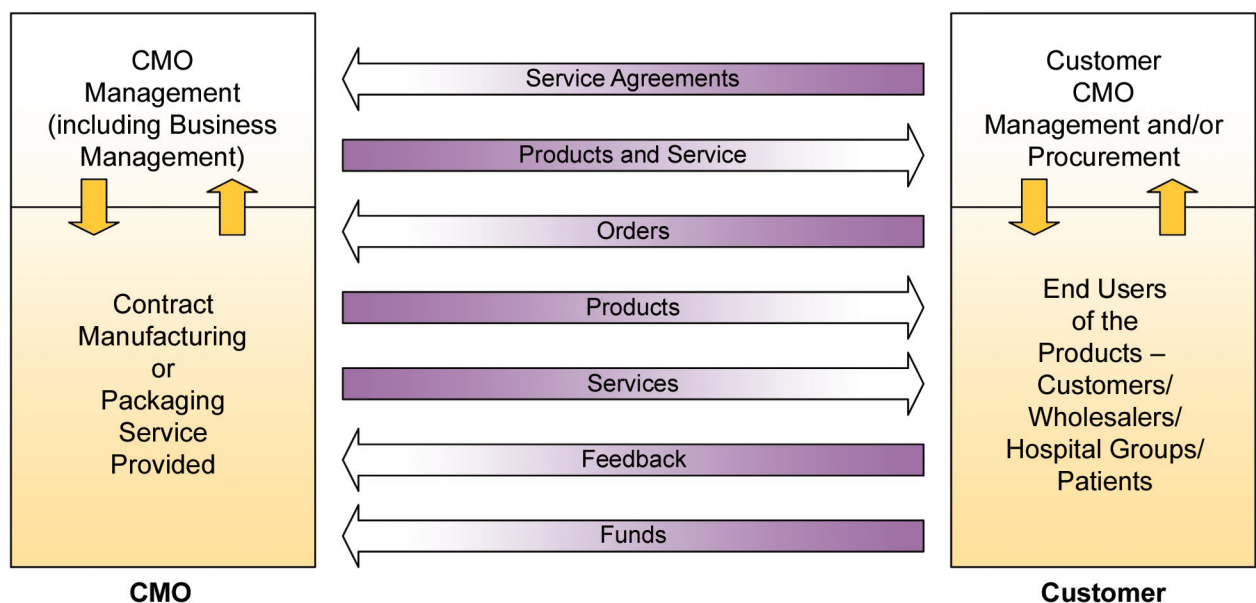
Managing Contract Organizations

Key elements to manage a CMO include:

- A contract with the CMO, including a robust service or supply agreement
- A Quality Agreement (distinct from a contract) including:
 - Formal acknowledgment of the quality requirements of the company
 - The Quality related measures the CMO commits upon
- A defined governance structure between the two parties to manage the relationship
- Defined escalation processes to identify and resolve issues
- An agreed metrics dashboard (aligned to the supply agreement within the contract) to measure the performance of the CMO, pinpoint areas to approve, and satisfy the reporting requirements of senior management
- A monthly S&OP process with the CMO to ensure their understanding of the demand picture, to identify any CMO capacity issues, and to ensure that plans to mitigate risks in supply of product or service are agreed to and established

Figure 2.9 shows a model on how to manage a CMO.

Figure 2.9: Depiction of a Model to Manage a CMO



US Import Compliance

Since the events of 9/11 and the opening up of global trade over the past several of years, the US government has focused a considerable amount of money and resources on further regulating cross-border activities of pharmaceutical products. There are currently nine (dependent upon the classification of the products) different regulatory agencies that can “hold” a shipment at the borders. The three main agencies are the US FDA import division, US Customs (a subsection of the US Customs and Border Protection (CBP)), and the US Department of Agriculture (USDA).

The US FDA, as a response to threats to the supply chain such as counterfeiting, diversion, cargo theft, and importation of unapproved or otherwise substandard drugs and in an effort to safeguard the integrity of the drug supply chain, has launched series of initiatives including:

- Drug Supply Chain Security Act (DSCSA)
- Food and Drug Administration Safety and Innovation Act (FDASIA)
- Secure Supply Chain Pilot Program

Organizations that import pharmaceutical products into the US must comply with all agency (or authority) regulations that apply.

Example key elements to consider for US import compliance include:

- Import cross-border operations
- Record retention
- Physical record retention
- Record retention timeframes
- Penalties
- Contents of records
- Record auditing

For US import procedures, key elements which should be considered include:

- **Entry Process:** When a shipment reaches the US, the importer of record (i.e., the owner, purchaser, or licensed customs broker designated by the owner, purchaser, or consignee) should file entry documents for the goods with the port director at the goods’ port of entry. Imported goods are not legally entered until after the shipment has arrived within the port of entry, delivery of the merchandise has been authorized by the CBP, and estimated duties have been paid. It is the responsibility of the importer of record to arrange for examination and release of the goods.
- **Informed Compliance:** Shared responsibility between the CBP and the import community, where the CBP effectively communicates its requirements to the trade and the people and businesses subject to those requirements conduct their regulated activities in accordance with US laws and regulations. A key component of informed compliance is that the importer is expected to exercise reasonable care in his or her importing operations. Informed compliance benefits both parties. When voluntary compliance is achieved, CBP resources need not be expended on redundant examinations or entry reviews for the importer’s cargo found to be dependably compliant. From the trade perspective, when voluntary compliance is attained, compliant importers are less likely to have their shipments examined or their entries reviewed.

- **Product Valuation:** Basic questions that a company should consider when determining the value of goods include:
 - Is the “price actually paid or payable” for the merchandise known?
 - Are the terms of sale known? For example, whether there will be rebates, tie-ins, indirect costs, or additional payments, or whether “assists” were provided or commissions or royalties paid
 - Are amounts actual or estimated?
 - Are the company and the supplier “related parties”?
- **Dutiable Status of Goods/Rates of Duty:** All goods imported into the United States are subject to duty or duty-free entry in accordance with their classification under the applicable items in the Harmonized Tariff Schedule of the United States. An annotated loose-leaf edition of the tariff schedule may be purchased from the US Government Printing Office.
- **Record Retention:** Organizations should ensure that they comply with the Customs Modernization Act (Mod Act), which is part of the North American Free Trade Agreement Act of 1993, amended sections of the Tariff Act of 1930 dealing with recordkeeping requirements for importers, brokers, and others. For further information, see the “Recordkeeping under the Mod Act” [20].
- **Records:** Records should be kept by owners, importers, consignees, importers of record (IORs), declaration filers, entry filers, or other parties (or their agents) to maintain records if they:
 - Import merchandise into the Customs territory of the US.
 - File a drawback claim.
 - Transport or store merchandise carried or held under bond.
 - Knowingly cause the import transport or storage of merchandise carried or held under bond into or from the Customs territory of the US.

Businesses should keep records (referred to as the “(a)(1)(A) list” [21]) that they have to prepare for the entry of merchandise. Others required include business, financial, and accounting records ordinarily maintained for normal business transactions.

- **Retention Timeframes:** The duration for which records must be kept by the IOR, unless otherwise stated and agreed to with the CBP, is:
 - Five years from date of entry
 - OR
 - Five years from the date of the activity, which requires the maintenance of the records
- **Penalties:** Penalties can and will be assessed by the CBP against the IOR, under the following conditions:
 - Failure to maintain or produce “(a)(1)(A) list” records
 - Willful: not to exceed \$100,000 per release or 75% of the appraised value, whichever is lower
 - Negligence: not to exceed \$10,000 per release or 40% of the appraised value, whichever is lower

- In addition, if these records relate to goods eligible for reduced or free duty rates, the merchandise shall be liquidated at the full column one rate. If the goods are already liquidated, they shall be re-liquidated (up to two years from the demand date) at the full column one rate.

- **Contents of Records:** Commonly referred to as “import packets”

In order to comply with the US FDA Import Program (and US Customs regulations) [22], an import packet must include:

- Logistics Service Provider (LSP) bill/invoice for services rendered, i.e., freight costs, clearance charges, port charges, etc.
- Department of Homeland Security – Entry Summary Form #7501 [23]
- Department of Homeland Security – Entry/Immediate Delivery Form #3461 [24]
- An FDA “May Proceed”
- Commercial invoice for the import of the shipment
- Packing list/bill of lading
- USDA letter

Whether the manufacturer of product is internal to a corporate network or to a third-party CMO, the manufacturing site is accountable for creating/providing the following documents upon booking the shipment at the origin: a packing list, a commercial invoice, a USDA letter, and the product certificate of analysis.

Traditionally, an LSP/broker service receives the above-mentioned documents, logs them into its brokerage system, and assigns an entry number (randomly generated by its system). Through the clearance of the shipment by US CBP and the FDA, the FDA “may proceed” and form #7501 [23] and form #3461 [24] are also received by the LSP.

These documents are then combined with the original documents that have followed the shipment, and the import packet is created. The LSP then performs its billing function, and the LSP charges for the shipment (the bill/LSP invoice) are also added to the packet.

- **Record Auditing:** Organizations that import pharmaceutical products into the US must also comply with both the FDA and US Customs regulations on import records auditing.

Where organizations are audited by either agency, those organizations are accountable for:

- Producing a documented process
- Showing evidence of an active auditing program that is in place
- Providing a random selection of import packets (by entry number) requested by the agency. They will audit the packets and verify their completeness and accuracy. If errors are found, they will record it in their final report as a “finding.”

For further information on import cross-border operations in the US, see “Importing into the United States: A Guide for Commercial Importers” [25].

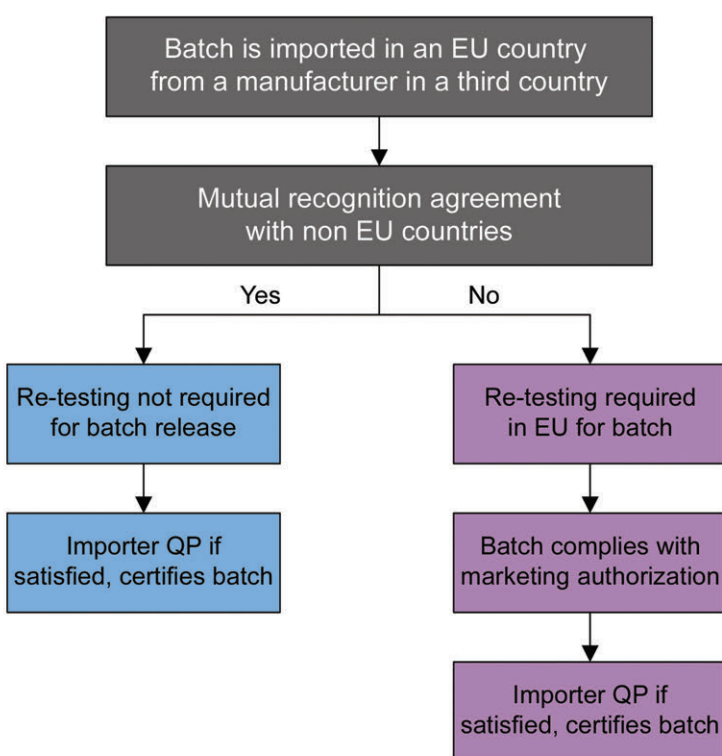
EU Import Compliance

For import into the EU, refer to the EU Export Help Desk [26], which provides necessary information to businesses willing to export goods to the EU market.

Example key elements to consider for import into EU countries include:

- Annex 16 to the *EU Guide to Good Manufacturing Practice* [27] requires a Qualified Person (QP) of the importer to certify the finished drug product before the batch is released for sale in EU countries. The same annex allows for the QP of one country in the EU to accept certification of a QP from another EU country. A schematic of the retesting batch release follows (see Figure 2.10).

Figure 2.10: Retesting Batch Release Schematic



- From July 2013, the EU authorities required a good manufacturing practice (GMP) certification for every API imported into the EU. The certification should be issued by the competent authority of the exporting country.
- According to the EU Directive 2001/83/EC [14], marketing authorization holders in the EU are required to use APIs that are produced in accordance to the Current Good Manufacturing Practices (CGMPs). At the time of application submission, the QP of the finished product manufacturing authorization holder signs a declaration stating that the APIs are manufactured in compliance with the GMPs for starting materials. In addition, EU Directive 2001/83/EC [14], requires applicants to submit a copy of a written confirmation from the manufacturer of the API that they will inform the applicant of any modification in the manufacturing process or specifications of the API.
- EU Directive 2011/62/EU [18] (relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products and substances) imposes the requirements for the importation of medicinal products and active substances to the EU member states and is setting up the obligation to prove that drug substances are sourced from qualified suppliers. Such requirements are usually reinforced further by local national regulations.

In China, for example, GMP certificates can be obtained only by companies producing drug substances after patents have expired. Local manufacturers can apply for GMP certificates only after patent expiration, and it usually takes 2 years to obtain the GMP certificate.

- In addition, GMP certificates are issued as product specific (therefore, if the patent on a product has not expired, then the GMP certificate is not available). These requirements can make the import of drug substances to the EU increasingly complex.

2.3 Supply Chain Planning

Functions outlined should be included in operations planning activities, followed by execution and analysis. Defined improvements should be integrated into future processes.

- Source:
 - Everything related to the procurement and acquisition of goods and materials
 - Constituents/stakeholders of the processes are finance, procurement, quality/compliance/regulatory, and logistics (as inbound perspective)
- Make (manufacturing):
 - It involves transformation/production – activities and functions that are engaged in the transformation of materials into a saleable item.
 - It could include composite models of internal production, technology transfer and outsource operations, contract packing, and other activities.
 - Constituents/stakeholders of the processes are finance, manufacturing/production (plan and execute), facility engineering and maintenance, project engineering (or corporate engineering), quality/compliance/regulatory, and third-party providers.
- Deliver:
 - The storage and distribution infrastructure and network required in order to bring finished goods/materials to market
 - This should cover the warehousing function (internal and outsourced) as well as the transportation entities for chain of custody/cold chain compliance, authentication, and return and destruction for recalls or expired products.
 - Constituents/stakeholders of the processes are warehouse and materials management, transportation personnel, security, logistics and regulatory compliance, and quality and control.

The functional areas should be reviewed, and best practices reviewed and discussed, from the perspectives of people, process, and technology.

2.4 Supply Chain Management

Traditionally, the practice of Supply Chain Management (SCM) has been accepted as an area of core competence. In many cases, it may be considered a competitive advantage for companies that have mastered the complexities of their supply chains. Comprising a series of activities that take place across the product life cycle, from product conception through commercialization, supply chains tend to be global and are increasingly complex.

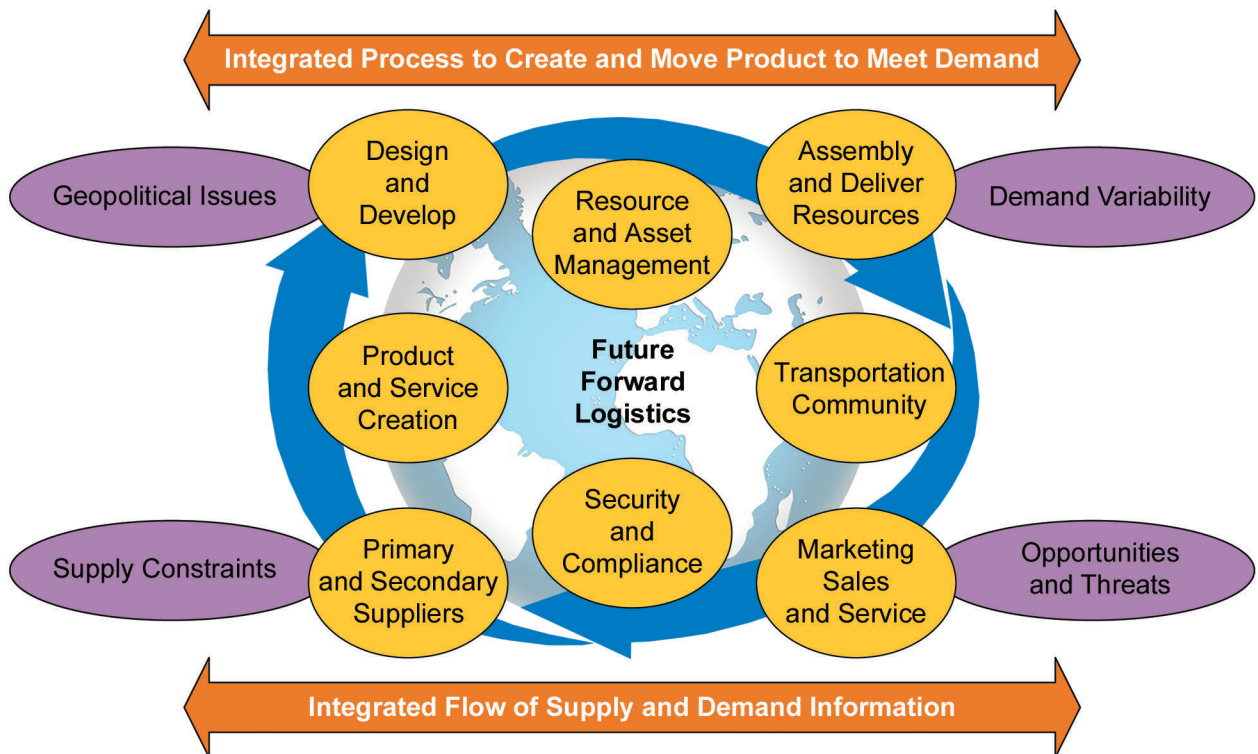
Understanding the interdependencies of all supply chain participants, both internal and external to an enterprise, is considered key to managing this complex series of processes and functions, i.e., in that process, mapping and RACI (responsible, accountable, consulted, informed) diagrams help establish the interdependencies and responsibilities of each function.

The supply chain may be thought of as a system, comprising functional entities, information, and physical goods flows along with cash flow, or reduction in cash-to-cash cycle time.

2.4.1 Supply Chain Model

Optimizing the end-to-end supply chain requires an understanding of interrelationships across a holistic supply chain environment: source, make, and deliver (see Figure 2.11).

Figure 2.11: Holistic Supply Chain Model – Understanding All Elements across a Complex Global Landscape
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One approach to developing an understanding of supply chain is from a process level. This Guide uses the Supply Chain Operations Reference (SCOR) model as a baseline (SCOR is a commonly accepted model developed by the Supply Chain Council² (SCC)) [28]. Although there have been many iterations of this model, the basic functions include:

- **Source:** Acquisition of materials, components, and services
- **Make:** Transformation of materials and components into saleable products
- **Deliver:** Distribution of materials, components, and finished goods, to include:
 - Network design

² The SCC is now merged with the American Production and Inventory Control Society (APICS).

- Storage
- Retrieval
- Transportation

These key functions are repeated through the product life cycle; from the initial research and development of new products; and through clinical trials, commercialization, and end of product life (see Section 2.4.2 and Figure 2.12). Although stakeholders and business drivers vary across this product life cycle, the fundamentals remain the same. Variables and constraints should be considered, and, where possible, a SCM strategy should be developed that can support changes across this product life cycle. The key criteria – that is, product quality, safety, and regulatory compliance – should be the primary focus for all supply chain-related activities, establishing a set of Standard Operating Procedures (SOPs) across the supply chain network.

Key issues include:

- Consideration of the key principles/concepts of the supply chain
- Inclusion of external partners in the product life cycle

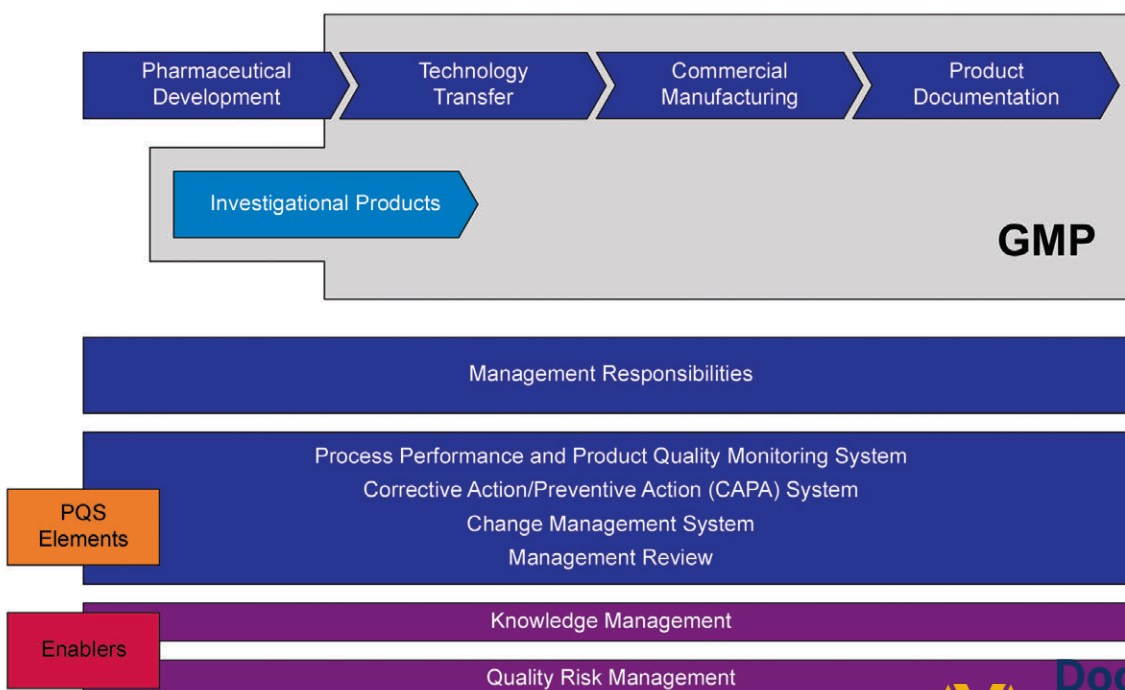
2.4.2 Life Science Product Development

The mission of the pharmaceutical industry is to bring effective therapies to patients, which are safe, affordable and produced via sustainable processes and practices.

This requires the deployment and coordination of multidisciplinary activities which may range from understanding the disease (pre-discovery phase) and new molecule identification (target) to final manufacturing, commercialization and post-marketing clinical tests (Phase 4 Clinical Studies).

Figure 2.12 outlines the product life cycle development process.

Figure 2.12: Diagram of the ICH Q10 Pharmaceutical Quality System (from ICH Q10)



Increased outsourcing of key functions, including contract research, clinical trials, and manufacturing, has intensified the need to establish clearly defined procedures, roles and responsibilities, and related Service Level Agreements (SLAs). The clinical environment includes activities prior to product approval and commercialization. A framework should be established to ensure that CGMP practices are followed by all participants depending upon the specific clinical phase.

Based on an increasingly global network of research, clinical trials, and manufacturing operations, logistics (or transportation factors) should be planned for, in order to ensure a robust logistics model across the product life cycle. The interdependencies of all participants across the chain of custody, with associated controls and digital data capture, should be understood. Strategies for risk mitigation should be developed.

Supply disruptions can impact raw materials, starting materials, and finished product.

The foundation of a sustainable model for SCM requires an understanding of the functions of:

- Source
- Make
- Deliver

This enables development of a strategy that can be adjusted across the product life cycle.

Starting with the first step in this life cycle (i.e., R&D), questions that should be asked include:

- Source:
 - Is this supplier able to meet our needs beyond preclinical?
 - Can the supplier support us as we move to production?
 - Can the supplier scale up to meet global demand?

Where the answer is NO, alternatives should be considered at the detailed bill of material level (i.e., API, excipients, and critical packaging material).

- Make:
 - Where is the optimal location to manufacture this product after commercialization?
 - Is this a product that should be outsourced in order to meet projected demand/cost constraints?
 - If so, what is the best approach to transfer these products into a commercial manufacturing environment?
- Deliver:
 - Are there any specific product characteristics that should be taken into account? For example, is the product, or any of the ingredients or components, susceptible to variations in temperature, altitude, or vibration?
 - What transportation devices, packaging components, and distribution channels should be planned for to ensure product protection and efficacy?

A team approach should be used to design a sustainable model; core team members and constituents should consider aspects such as:

- **Sourcing:** Develop short-, medium-, and long term strategies to reduce the risk of supply disruption.
- **Quality and Regulatory Compliance:** Adopt a Quality by Design (QbD) approach at the process level from preclinical through commercialization, taking into account all risk factors at the product level. Develop guidelines and SOPs that can be adopted by all participants, internal and external, to ensure compliance, safety, and product level quality.
- **Packaging:** Extended supply chains include multiple partners; transportation links; and variations in temperature, altitude, and humidity. Designed product level packaging, including packaging for raw materials, APIs, and finished product, should ensure that the product arrives at the desired destination in optimal condition. Designing this into the product life cycle can provide a baseline that can be adjusted as required in the future.
- **Logistics and Trade Compliance:** Variations in supply locations, and related demand locations, can impact both cost (up or down) and have other implications that should be taken into account. Origin and destination pairs can impact modes of transportation, availability of transportation assets, product packaging, and material handling requirements. Understanding and including these variations in planning can help to prevent future adverse events. Considerations include:
 - Cold chain/cool chain requirements: product level and container level monitoring and control
 - Documentation (literature, labeling): language and regulatory requirements across the supply chain landscape (taking into account potential trans-shipment locations and hazards)
- **Risk Management:** Diligence and good practices can enable an understanding and management of risk factors associated with these areas. It will facilitate the development of a strategy that protects brand owners, their business partners, and patients. A risk assessment should be performed across different phases in the product life cycle, especially when transferring manufacturing from clinical to commercial or to outsource partners across geographical borders.

3 Manufacturing Operations Strategy and Management

3.1 Introduction

The manufacturing operations strategy connects a company's competitive strategy with manufacturing operations' technologies, assets, planning, and management team in order to meet company strategic drivers and objectives through:

- Production technologies selection
- Manufacturing sites and facilities setup
- Systems and methods supporting manufacturing operations
- Organizational structures
- Operational/work policies
- Quality, safety, and environmental manufacturing aspects

The manufacturing operations strategy should aim to maximize capital/resource effectiveness in order to support achievement of business objectives and deliver additional value to the supply chain.

This chapter focuses on:

- Objectives of manufacturing operations
- Role of manufacturing and operations in the company's strategy, with respect to other functions (e.g., R&D, marketing, medical, regulatory)
- Role of the operational support functions: QC/QA, engineering, maintenance, procurement, planning, shipping, distribution, receiving, and warehousing
- Production models (large runs, small runs, specialized, continuous, etc.)
- Organizational models: vertical/by function, horizontal/by product line, or other
- Operational excellence methodologies (for further information, see Chapters 4 and 5)
- Quality, safety, and environmental issues management
- Facility and capacity planning

The overall objective of the manufacturing operations within the established strategy is to design quality into the production, storage, and distribution of drug substances and products for their customers and, ultimately, their patients (for further information, see the ICH Quality Guidelines series and particularly the ICH Q9 on Quality Risk Management) [3].

Considerations include:

- Consistent production of products meeting all quality and conformance specifications

- Timely production and delivery of finished products to patients with appropriate safety stock considerations to meet the patients' needs
- Cost-effective manufacturing facilities and processes

3.2 Production Technology

Production technology selection is dependent upon the intended purity of both the drug substance (API) and the drug product (finished product). Other factors should also be considered in the selection of product technology, including:

- Required production volumes including lot/batch size
- The type of process – is it aseptic or non-aseptic?
- Is an API (either chemical or biological) being manufactured?
- Is it an oral solid dosage, powder, liquid, or injectable?
- Is packaging integral to the manufacturing?
- Is this a single product or multiproduct facility?
- Occupational Exposure Limit (OEL) for the API
- Stability
- Cold chain requirements
- Does the product contain a hormone, a cytotoxic compound, a β -lactam, or a cephalosporin as the API, which requires special containment and cleaning strategies?
- Safety issues from a flammability, explosivity, asphyxiation, or toxicity perspective
- Overall material flow through the facility
- Skills of the available personnel from an operational/maintenance perspective
- Value of the product being produced
- Environmental impacts of wastes and emissions produced for the facility

User requirements should be considered based on current and potential requirements and should reflect the market conditions, local regulatory considerations, and how the facility is intended to be used.

3.2.1 Process Design and Selection

Process design factors vary from product to product. Considerations when developing a process include:

- The type of product (drug substance/drug product) being produced, e.g.:
 - Biologic/large molecule
 - Chemical/small molecule

- Gel, solid, liquid, or powder
- Sterile or nonsterile
- In some markets, authorities may require that a specific process cannot be modified without additional bioequivalency studies.
- Availability of existing facilities and equipment – can existing equipment be used to manufacture the product?
- Process safety considerations – is the material at each step of the process stable?
- Yield and throughput of the process being designed
- Level of waste generated and the strategy/cost of managing this waste
- Applicable regulations
- Critical Quality Attributes (CQAs)
- Critical Process Parameters (CPPs) needed to manufacture the product
- Is there a significant benefit of using a continuous process, or is a batch process preferred?
- Use of Process Analytical Technology (PAT)

3.2.2 Equipment Selection

Equipment selection is dependent on the type of process, the type of facility, the technical capability required, the maintenance needs, and the volume of product needed to be produced. Equipment selection should consider, e.g.:

- Production capacity – capability of meeting the desired throughput with required spare capacity to cover production volumes for future growth
- Standard designs for equipment areas including:
 - Cleanability of product contact surfaces: can they be cleaned to acceptable CGMP levels?
 - Suitability of product contact surfaces (transmission lines, gasket materials, etc.) and items that are compatible and do not impact product quality
 - Use of food grade lubricants, when appropriate
- Level of product containment appropriate for the material handled in production
- Compliance with industry accepted air classification standards when systems are located in controlled environment
- Cost of the machines, associated tooling, operation, and level of automation
- Single usage/disposable or multiple usage equipment options
- Timing of equipment delivery
- Availability of spare parts

- Supplier capacity, capability, and reliability
- Anticipated routine downtime due to Preventive Maintenance (PM)
- Energy consumption per unit produced of the machine and ancillary equipment
- Utilities to support the equipment, e.g., steam pressure, compressed air pressure, electrical voltage and amperage, waste line connections
- Desired level of automation and integration with the entire plant
- Appropriate level of automation versus human intervention
- Computer systems managing the equipment and the applicable design or regulatory requirements (e.g., US FDA Title 21 CFR Part 11 [29])
- Availability of project management programs designed using a standard technique such as Failure Mode and Effects Analysis (FMEA)
- Level of skill needed by the local personnel to operate and maintain the equipment
- Time and skill set needed to change tooling
- Availability of training for local technicians and availability of the equipment service technicians
- Amount of waste material/water generated

Fitts' List can be used to help to determine when to apply automated equipment or whether to use manual intervention (see Table 3.1).

Table 3.1: Fitts' List

Source: MIL-HDBK-763: Human Engineering Procedures Guide, Department of Defense (DoD), 1987, Washington, D.C.

Humans Excel In	Machines Excel In
• Detecting certain forms of very low energy levels • Sensing an extremely wide variety of stimuli • Perceiving patterns and making generalization about them • Storing large amounts of information for long periods and recalling relevant facts at appropriate moments • Exercising judgment when events cannot be defined completely • Improvising and adopting flexible procedures • Reacting to unexpectedly low-probability events • Applying originality to solving problems (i.e., alternative solutions) • Profiting from experience and altering course of action • Performing fine manipulations, especially where misalignment appears unexpectedly • Continuing to perform when overloaded • Reasoning inductively	• Monitoring (both machines and people) • Performing routine, repetitive, or very precise operations • Responding very quickly to control signals • Storing and recalling large amounts of information in short time periods • Performing complex and paid computations with high accuracy • Sensing stimuli beyond the range of human sensitivity (e.g., infrared, radio waves) • Multi-tasking • Exerting large amounts of force smoothly and precisely • Ignoring extraneous factors • Repeating operations very rapidly, continuously, and precisely the same way over a long period • Operating in environments that are hostile to or beyond the endurance of humans • Deductive processes

Process innovations, such as continuous processing and single-use equipment, are being deployed to apply “lean” processes, particularly in the biopharmaceutical industry. These innovations require the use of specialized equipment that is specifically designed to support and obtain the maximum benefit from new ways of operating.

3.2.3 Facility Considerations

Facilities should be designed and maintained in compliance with CGMP expectations (or their regional equivalent), generate only minimal safety and environmental hazards, be in compliance with the appropriate regulatory bodies, and operate in a cost-effective manner. Facility considerations include:

- Appropriate material and personnel flows, including considerations for products produced, product segregation, and efficient manufacturing processes
- Considerations on internal and external expandability to accommodate in a mid-long-term horizon future growth of product portfolio and/or volumes requiring investment in new equipment and/or facility spaces
- Fit-for-purpose wall, ceiling, and floor finishes
- Fit-for-purpose door design
- Sufficient and fit-for-purpose lighting
- Appropriate heating, ventilation, and air conditioning (HVAC) and cooling/heating systems, including meeting generally accepted practices for cleanrooms, as established in part 1 of the ISO Cleanrooms Standards 14644 Series [30] and applicable ISPE Good Practice Guide on HVAC [31]
- Appropriate process utilities (purified water, water for injection, clean/pure steam) and site utilities systems (i.e., steam, chilled, and hot water for HVAC, compressed air, etc.)
- Air filtration, based on facility requirements
- Appropriate storage areas for raw materials, work in progress, finished products, manufacturing consumables, and maintenance and repair parts
- Appropriate electrical grounding, classification, design, and maintenance, to address possible hazards such as electrocution, arc flashing, or dust/solvent explosion
- Infrastructure/utilities connection locations
- Differences in regional and national building practices and building codes/regulations including:
 - Practices
 - Techniques
 - Building systems materials
 - Personnel skills

Modular construction can provide ease of expandability or replication and contribute to reduced process changeover times. Modular facility designs can also be integrated with modular single-use process equipment.

3.2.4 Containment

Industrial hygiene and HSE regulations and practices are intensifying due to the increasing potency of drug substances (e.g., with OELs of 10 µg/m³ or lower), see the CDC Guidelines [32]. Increasing emphasis is being placed on containment of drug substances in order to reduce the risks to operator health, environmental contamination, and product loss.

Containment is an engineering- and science-based approach to ensure contamination control from a product and personnel safety perspective. It involves multidisciplinary functions and expertise such as:

- Facility planning and architectural design
- Process design
- HVAC and mechanical design
- Validation and QA
- HSE
- Pharmaceutical toxicology
- Risk management expertise

Equipment, process, and facility design should result in personal protection equipment being the last, rather than the first, protection barrier for personnel.

An Occupational Exposure Band (OEB) and an appropriate containment strategy, based on available technical solutions, can be determined from the:

- Assessment of the specific chemical and physical (e.g., powder) characteristics of an API (e.g., from the Material Safety Data Sheet (MSDS))
- Intrinsic ability of the API to generate a dusty environment
- The hazard group of the substance
- Features of the process (e.g., small, medium, or large batch sizes)
- Duration of the process operations

Table 3.2 outlines a typical example of an OEB categorization based on substance properties.

Table 3.2: Example OEB Categorization

Occupational Exposure Band	OEB 1	OEB 2	OEB 3	OEB 4	OEB 5
Typical OEL ($\mu\text{g}/\text{m}^3$)	1000	100	10	1	< 1
API PROPERTY					
Acute Toxicity					
Oral LD ₅₀ rat (mg/kg)	> 2000	200 – 2000	50 – 200	May – 50	< 5
Dermal LD ₅₀ (mg/kg)	> 2000	400 – 2000	50 – 400	May – 50	< 5
Inhalation LC ₅₀ (mg/m)	> 2000	1000 – 2000	250 – 1000	25 – 250	< 25
Potency (projected clinical dose, mg/day)	> 500	50 – 500	May – 50	0.5 – 5	< 0.5
Irritancy/Corrosion (skin and/or eye)	Non-irritating	Mild Irritant	Irritant	Severe Irritant/Corrosive	Corrosive
Sensitization	(Not a Sensitizer)	(Not a Sensitizer)	Low-Incidence Dermal Sensitizer	Dermal Sensitizer	Dermal Sensitizer
Mutagenicity			EU phrase R40: Possible risk of irreversible effects + positive results from assays showing mutagenic effects	EU phrase R46: May cause heritable genetic damage + positive results from assays showing mutagenic effects	EU phrase R46: May cause heritable genetic damage
Reproductive/Developmental Toxicity			EU phrase R62: Possible risk of impaired fertility or R63: Possible risk of harm to the unborn child	Substance with clear evidence in animal studies to create impair fertility or cause developmental toxicity in humans EU phrase R60: May impair fertility or R61: May cause harm to the unborn child	Substances known to impair fertility or cause developmental toxicity in humans – EU phrase R60: May impair fertility or R61: May cause harm to the unborn child
Repeat Dose Toxicity (e.g., 28-day)					
Oral NOAEL, rat (mg/kg)	> 500	50 – 500	May – 50	< 5	
Oral NOAEL, dog (mg/kg)	> 300	30 – 300	30 – Mar	< 3	
Dermal NOAEL, rat/rabbit (mg/kg)	> 1000	100 – 1000	10 – 100	< 10	

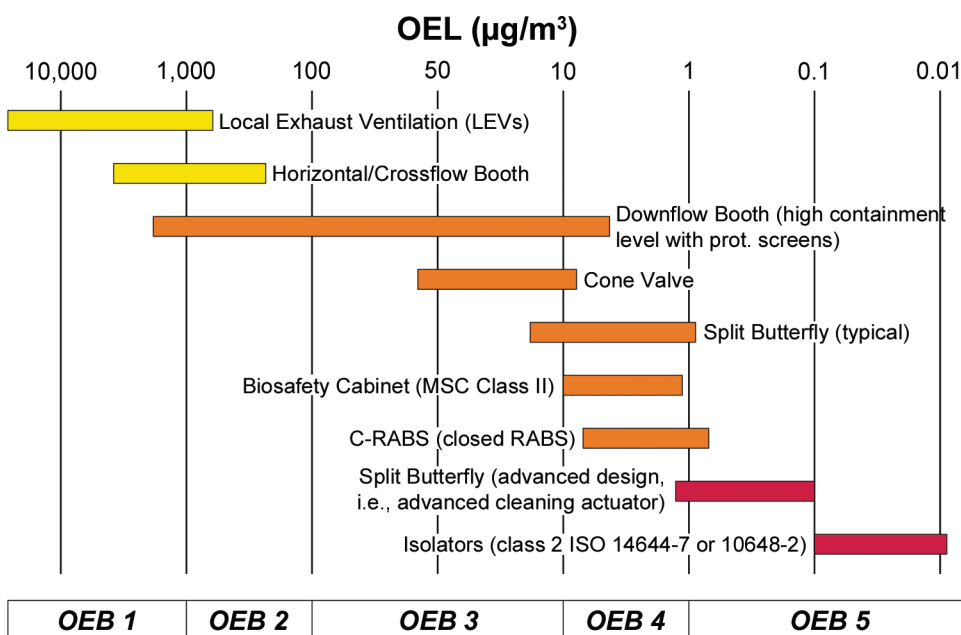
Appropriate containment solutions should be based on OEB categorizations and a risk-based approach.

Figure 3.1 outlines a potential containment strategy with selection of specific technical solutions for each OEB category (these are engineering solutions that are commonly used in the pharmaceutical industry for each OEB).

Each solution should be selected based on a risk-based approach that should also consider:

- Physical status and properties of active ingredient (solid or liquid, fine powder or granule, etc.)
- Batch size (grams, kilograms, or tonnes) and the quantity of the handled active ingredient as a percentage of batch size
- Characteristics of the operation (loading, unloading of a specific material) and its duration
- Frequency of operation

Figure 3.1: Example of Potential Containment Engineering Control Applications



Typical manufacturing scale (kilo and above) OEB range. The containment level achievable will vary depending on several factors (i.e., equipment performance).

For further information on a holistic approach for the design of suitable containment solutions, see ISPE Baseline® Guides on API [33] and Oral Solid Dosage Forms [34]. For further information on containment solutions, see the: *ISPE Baseline® Guide: Risk-Based Manufacture of Pharmaceutical Products* [35] and the *ISPE Good Practice Guide: Heating, Ventilation, and Air Conditioning (HVAC)* [31]. For further information on containment testing, see the *ISPE Good Practice Guide: Assessing the Particulate Containment Performance of Pharmaceutical Equipment* [36].

3.2.5 Ergonomics

When designing a process and purchasing equipment, ergonomic considerations can significantly impact decisions made on what equipment to purchase or the layout of a facility.