INTERNSHIP REPORT
OF
OPERATION AND SUPPLY CHAIN MANAGEMENT OF ESKAYEF PHARMACEUTICALS LIMITED

SUBMITTED TO:

HASAN MAKSUD CHOWDHURY
ASSISTANT PROFESSOR
BRAC BUSINESS SCHOOL
BRAC UNIVERSITY

SUBMITTED BY:

MUHAMMAD ZAHID AL BERUNI
MBA PROGRAM
ID NO. 13264095
MAJOR : OPERATION AND SUPPLY CHAIN MANAGEMENT
BRAC BUSINESS SCHOOL

BRAC University
66 Mohakhali, Dhaka 1212 Bangladesh

LETTER OF TRANSMITTAL

Date: 9 May 2017

Hasan Maksud Chowdhury
Assistant Professor
BRAC University 66, Mohakhali
Dhaka 1212, Bangladesh

Subject: Submission of Internship Report

Dear Sir,

With due respect, I like to take the opportunity to submit my internship report on the topic of "Operation and Supply Chain Management of Eskayef Pharmaceuticals Limited" at your kind disposal. I have tried to compile this internship report according to your direction and requirement.

This report has been prepared for completing a part of my MBA program. I have put my efforts to accumulate together, my knowledge obtained from my course works and my experience of working at the pharmaceutical for preparing this report.

I state profound gratitude to you for examine my report thoroughly and for giving your valuable comments. I would try with best of my knowledge to provide any clarification regarding the report.

Sincerely yours,

_____

Muhammad Zahid Al Beruni
MBA Program
Id No. 13264095
Brac University

DECLARATION

I, Muhammad Zahid Al Beruni, student of Master of Business Administration (MBA) program, under BRAC Business School (BBS) at BRAC University declaring that this internship report on the topic of "Operation and Supply Chain Management of Eskayef pharmaceuticals limited" is my own work, completed under the guidance of Hasan Maksud Chowdhury, Assistant Professor, BRAC Business School (BBS) and it has only been prepared for partial fulfillment of internship program as per requirement for obtaining the Degree of Master of Business Administration (MBA) from BRAC University.

I, hereby also state that this report has been solely prepared by me. And to the best of my knowledge, it do not have any part of previously published or written document by any other person which has been accepted at BRAC University or any other educational institution, except the quotations and references which have been duly acknowledged.

Muhammad Zahid Al Beruni
MBA Program
Id No. 13264095
BRAC University

ACKNOWLEDGEMENT

First, I would like to state my gratitude to the Almighty Allah for giving the opportunity to go the hardship of MBA program, the course of internship and to write a report in this regard.

I would also like to take the opportunity to express my profound gratitude to my supervisor Hasan Maksud Chowdhury, Assistant Professor, Faculty of BRAC Business School, BRAC University who guide, support and help me for writing this internship report.

Then, I also thank all my colleagues of the Eskayef Pharmaceuticals Limited for extending their support and time for enriching my working period. I also give special thanks to Mr. A. M. Fatemy AGM-Plant and Mr. Mohsin Reza, AGM-Commercial of this company for compassionate cooperation, guidance and supervision. It must be mentionable the cooperative working environment and the whole hearted commitment of this company which have enabled me to attend my MBA course works and to observe the business activities.

Finally, I must express my sincerest gratitude to my family and friends who support me in numerous ways to complete the MBA program and to prepare the report as well.

CERTIFICATE OF SUPERVISOR

The Internship Report with the title as "Operation and Supply Chain Management of Eskayef Pharmaceuticals Limited" has been submitted by Muhammad Zahid Al Beruni (ID # 13264095) for partial fulfillment as per requirements for the degree of Master of Business Administration from BRAC University. He has prepared this report by himself under my direct supervision. This report is without any plagiarism and has been accepted, hereby.

Dr. Hasan Maksud Chowdhury
Assistant Professor
BRAC University
66, Mohakhali
Dhaka 1212, Bangladesh

EXECUTIVE SUMMARY

The Internship Report, with the title as "Operation and Supply Chain Management of Eskayef Pharmaceuticals Limited", is prepared for completing partial requirement of Degree of Masters in Business Administration. For organizing this report, I have tried to draw up my observations and working experience at pharmaceutical company. This pharmaceutical company has been delivering unique pharmaceutical with world-class quality products support since its inception in 1990.

This report starts with background, objective and limitations for preparing the report. Then, overviews of pharmaceutical company, its products, department, organogram are described. My major responsibilities are also given here, for presenting a glimpse of my involvement with accounting and administrative tasks of this company.

Afterwards, the key part of this report describes Operation and Supply Chain Management of the company. How operation and supply chain related works are carried out, how company's individual departments assists those, how documentation is done and reports are prepared and presented; all are described concisely in this part. Tax compliance is one of the major responsibilities of every accounts department. In that part of the report, it is also tried to describe briefly how the company ensures this compliance.

Before concluding the report at the final stage, I have put forward few recommendations, based on my observation and knowledge.

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Company Profile

Introduction

Eskayef Pharmaceuticals Limited, a successor of world-renowned multinational pharmaceuticals company, SmithKline & French (SK&F), USA was acquired by TRANSCOM in 1990 in the wake of the merger between SmithKline & French, USA and Beecham, UK. TRANSCOM is one of the leading and fastest growing business conglomerates in Bangladesh. Like TRANSCOM, not many industrial groups in Bangladesh can claim a history of continuous business pursuits stretching back over 100 years. Over the time, its early industrial ventures have moved over to businesses involved in high-tech manufacturing, international trading and distribution, forming strong ties with a host of blue chip multinational companies.

After the acquisition of SK&F by TRANSCOM, the new company was named – Eskayef Pharmaceuticals Limited and it has subsequently culminated to become one of the leading pharmaceuticals companies of Bangladesh. rapid business growth since its inception have propelled Eskayef to a position of eminence among the pharmaceutical companies operating in Bangladesh today.

Table: Eskayef pharmaceutical Limited at a Glance

Company name	Eskayef pharmaceutical Limited
Logo	SK+F
Slogan	Excellence through quality
Type	Private Limited Company
Acquisition from	SmithKline & French, USA
Company inception	1990
Ownership	Transcom Group
Chairman	Mr. Latifur Rahman
Managing Director & Chief Executive Officer	Mrs. Simeen Hossain
Employees	4000+
Business	Pharmaceutical Finished Products, Bulk Pellets, Animal Health & Nutrition Products
Distribution	Transcom Distribution Company Limited (TDCL)
Web address	www.skfbd.com

Source: www.skfbd.com

Major Landmarks

Eskayef Pharmaciticals Limited, a successor of world-renowned multinational pharmaceutical company, SmithKline & French (SK&F), USA was acquired by TRANSCOM Group in 1990. After the acquisition, the new company was named 'Eskayef Pharmaciticals Limited' and it has subsequently culminated to become one of the leading pharmaceutical companies in Bangladesh. Rapid business growth, since its inception has propelled Eskayef to a position of eminence among the pharmaceutical companies operating in Bangladesh today. Owing to its qualified, trained and skilled professionals and through its unswerving standards of quality control, Eskayef is now one of the most respected names in the pharmaceutical industry of Bangladesh. The major landmarks of the company in different years have been shown in the table:

Table: Major Landmarks of Eskayef Pharmaciticals Limited

Year	Landmarks
1979	Incorporation as a subsidiary of **SmithKline & French,** USA
1990	Acquisition of **Smithkline & French (SK&F),** USA by Transcom
1999	Introduction of **Pellet Technology** in Bangladesh
2001	Acquition of old Squibb plant at Tongi by Transcom Group
2001	Commencement of **Animal Health & Nutrition Division**
2006	Inception of state of the art Tongi plant
2008	Achievement of UK MHRA accreditation Initiation of **Cepha Plant**
2010	Starting af Novo Nordisk's **Insulin Manufacturing**
2010	Attainment of **TGA Australia** accreditation
2011	Attainment of **VMD UK** accreditation
2013	Accomplishment of EU GMP accreditation and Launching of **Eye Care** Project
2014	Achievement of **UAE GMP** accreditation

Source: www.skfbd.com

Eskayef Pharmaceuticals Ltd. is currently exporting its quality finished products to 19 countries across 4 continents as the part of the mission of Growing More Global. In the year 2012, Eskayef has entered into the regulated market with excellence through quality. Eskayef is among the pioneers to export products to Australia, United Kingdom, Netherlands and expanding its business horizon to other European countries.

The International Business Department has put a sincere business drive in 2012 and registered a remarkable growth of 54% over the year 2011. The technical knowhow, vision and innovative ideas of the professionals working in the company are the key factors for this achievement. In the coming years, Eskayef is aiming to be a global pharmaceutical company.

The company exports its products in 23 countries of the world through our distribution partners.

Table : Overseas Markets of SK+F

Region	Countries
Europe	Netherlands, United Kingdom
Australia	Australia, Fiji
Africa	Algeria, Burundi, Cameroon, Kenya, Niger, Somalia, Uganda
Asia	Afghanistan, Iran, Myanmar, Nepal, Philippines, Sri Lanka, UAE, Vietnam, Yemen

Source: www.skfbd.com

Mission, Vision and Quality Approach

Mission

To manufacture and supply products with quality and excellence and to contribute to improve the population's health & well-being.

Vision

To lead the national pharmaceutical market, to be recognized as a multinational conglomerate from Bangladesh and stand out as a model of efficiency & trust to our collaborators, consumers, health care professionals & society.

Quality Approach

Eskayef believes that pharmaceutical business is built solely on the blocks of trust and it takes perseverance for a pharmaceutical business entity to earn the trust of the people. Many global best practices are being cultured in the everyday activities of Eskayef, which are contributing in a big way to shape up its future & earning people's trust. "For a holistic working philosophy, the company is governed by three fundamental values: Total Quality Management, Business Ethics and Societal Commitment"

Eskayef is a quality driven and scientific information based company. The EU GMP (European Union Good Manufacturing Practice), UK MHRA (Medicines and Healthcare Products Regulatory Agency of UK), TGA Australia (Therapeutic Goods Administration of Australia), UAE GMP (United Arab Emirates Good Manufacturing Practice) and VMD UK (Veterinary Medicines Directorate of UK) approved state-of-the-art pharmaceutical manufacturing facility has further reinforced high standards of quality, safety and efficacy of Eskayef products. The company is currently exporting medicines to many countries across four continents, including some highly regulated markets in Europe and Australia. Eskayef Pharmaciticals Limited continues the journey of pellets development with pride and perfection since 2001. In addition to the consumption in the domestic market, Eskayef is successfully exporting its pellets to Australia, Indonesia, Iran, Myanmar, UAE and Vietnam.

Since its inception on 2001, across the nation Agrovet Division has been playing an important role in the business sectors of Poultry, livestock & Aquaculture. Quality premixes along with wide range of prominent therapeutic & nutritional brands are its major strengths. Recently commissioned Injectable brands have already attained its fame for premium quality. It is also marketing imported poultry & aquaculture products from world's top class companies. Since 2005 it has emerged as the pioneer exporter of animal health products from Bangladesh.

Eskayef believes that pharmaceutical business is built solely on the blocks of trust and it takes perseverance

for a pharmaceutical business entity to earn the trust of the people. Many global best practices are being cultured in the everyday activity of Eskayef, which are contributing in a big way to shape up its future & earning people's trust. Eskayef Pharmaciticals Limited, owing to its qualified, trained and skilled professionals and through its unswerving standards of quality control, Eskayef is now one of the most respected names in the pharmaceutical industry of Bangladesh.

Overview of Pharma Sector in Bangladesh

In Bangladesh Pharmaceutical sector is one of the most developed hi tech sector which is contributing in the country's economy. After the promulgation of Drug Control Ordinance - 1982, the development of this sector was accelerated. The professional knowledge, thoughts and innovative ideas of the pharmacists working in this sector are the key factors for this developments. Due to recent development of this sector we are exporting medicines to global market including European market. This sector is also providing 95% of the total medicine requirement of the local market. Leading Pharmaceutical Companies are expanding their business with the aim to expand export market. Recently few new industries have been established with hi tech equipments and professionals which will enhance the strength of this sector. The pharmaceutical industries in Bangladesh are gifted with unparalleled potential to grow in the days ahead as they enjoy a number of competitive advantages, industry insiders said.

The $700 million sector with more than 230 manufacturers is continuously expanding with new products to new international destinations. Among all the 50 LDC countries Bangladesh is the only country having quality pharmaceutical manufacturing base with marketing potential, and exporting to at least 80 destinations of the world, they said. The industry's ability to comply with guidelines of quality assurance has put it on a solid base. Almost all companies are equipped with World Health Organization (WHO) Good Manufacturing Practice (GMP) standards. It has the ability to face competition from developing countries like India, China, Brazil and Turkey in its export markets due to strict quality compliance.

However, experts in this sector suggest to form a banner within the 50 LDC's of Asia-Pacific, Africa, Pharmaceutical Union (AAPU) amongst the Ministry of Health and Family Welfare (MoH&FW) or Ministry of Food and Drug Administration (DA) authorities to avoid re- registration of companies and products within the member countries under this umbrella. The export value of pharmaceuticals is small but growing at 50 percent per year. Exports increased from $8.2 million in 2004 to $28.3 million in 2007, while export destinations climbed from 37 countries to 72 during the period. A good number of companies including Square Pharma, Renata and Eskayef have won accreditation from the UK Medicines and Healthcare Products Regulatory Agency (MHRA).

Incepta and Beximco Pharma have been accredited by EMEA (Austria) and the Therapeutic Goods Administration (TGA-Australia), respectively. These accreditations will allow them to enter the lucrative market with very competitive prices and standards as reputed global players.

The most important indicator is the capability of the industry to achieve excellence and go beyond general international standards. Pharmaceutical export market can be categorized into three types, firstly, stringently regulated markets in USA, EU, UK, Australia, GCC which requires USFDA, UKMHRA, TGA, cGMP, GCC certifications and only a few from top ten companies can hardly afford these certifications.

The mild regulated export markets which categories as second consisting the markets of Singapore, Sri lanka, Vietnam, Philippine also need ACTD formats along with bio equivalence clinical test reports of pharma products and these are critical procedures with time and money consuming factors and many of the mid level companies cannot afford. The final category is the less regulated export markets which are the only target markets remain in our hand to explore under the umbrella of AAPU. The products, which are registered by the DG of Drug Registration Authority (DRA), Bangladesh may be treated as registered within these countries, pharma official claimed. If required only Free Sales Certificates/Certificate of pharmaceutical products, Valid GMP Certificate, Product Approved Annexure, DML can be asked directly from our DRA Bangladesh by the importing countries MOH/FDA for the import of pharmaceutical products from Bangladesh. This will not only safe time and money but the current pharmaceutical turnover will grow many fold higher within shortest possible time before the implementation of WTO/TRIPS by the year 2015. Only 39 pharmaceutical manufacturing and marketing companies exported about Tk. 4.21 billion out of around 256 pharmaceutical manufacturers of Bangladesh. Moreover, pharma industry is now exporting active pharmaceutical ingredients (APIs) and a wide range of pharmaceutical products covering all major therapeutic classes and dosage forms to 79 countries. Besides, tablets, capsules and syrups, the country is also exporting high-tech specialized products like HFA Inhalers, CFC Inhalers, Suppositories, Nasal Sprays, Injectables, IV Infusions, etc. The packaging and the presentation of the products of Bangladesh are comparable to any international standard and have been accepted by them, said the official.

According to the UKTI report 2010, the total size of the pharmaceutical market of Bangladesh was estimated to be $700 million in 2007. It also reports that the industry produced medication worth $715 million in 2007 with the market growing over 12pc annually over the last half a decade and firms primarily focus primary on branded generic final formulations by using mostly imported APIs. According to a World Bank report of 2008, about 80pc of the drugs sold in Bangladesh are generics and 20pc are patented drugs. It also reports that domestically Bangladeshi firms generate 82pc of the market in pharmaceuticals and locally based multinational companies account for 13pc, and the final 5pc is imported. There are 240 registered pharmaceutical companies in Bangladesh where 164 of these actively involved in the manufacture or marketing of pharmaceutical products.

Drug Regulatory Authorities in Bangladesh

A regulatory agency is a public authority or government agency responsible for exercising autonomous authority over some area of human activity in a regulatory or supervisory capacity. An independent regulatory agency is a regulatory agency that is independent from other branches or arms of the government. Two organizations regulate drugs and pharmacies in Bangladesh, one governmental and one

semi-government, which are:

1. The Directorate General of Drug Administration (DGDA)
2. The Pharmacy Council of Bangladesh (PCB)

The Directorate General of Drug Administration (DGDA): DGDA is the drug regulatory authority of Bangladesh, which is under the Ministry of Health and Family Welfare. DGDA regulates all activities related to import and export of raw materials, packaging materials, production, sale, pricing, licensing, registration, etc. of all kinds of medicine including those of Ayurvedic, Unani, and Herbal and Homoeopathic systems.

The Pharmacy Council of Bangladesh (PCB):

PCB was established under the Pharmacy Ordinance in 1976 to control pharmacy practice in Bangladesh. The Bangladesh Pharmaceutical Society is affiliated with international organizations International Pharmaceutical Federation and Commonwealth Pharmaceutical Association. The National Drug Policy (2005) states that the WHO's current Good Manufacturing Practices (GMP) should be strictly followed and that manufacturing units will be regularly inspected by the DDA. Other key features of regulation are restrictions on imported drugs; a ban on the production in Bangladesh of around 1,700 drugs which are considered non-essential or harmful; and strict price controls, affecting some 117 principal medicines.

Operation Management
of
Eskayef Pharmaceuticals Limited

Introduction

Operations management is an area of management concerned with designing and controlling the process of production and redesigning business operations in the production of goods or services. It involves the responsibility of ensuring that business operations are efficient in terms of using as few resources as needed and effective in terms of meeting customer requirements. It is concerned with managing the process that converts inputs (in the forms of raw materials, labor, and energy) into outputs (in the form of goods and/or services). Operations management is concerned with managing the operations function in an organization. Operations is one of the major functions in an organization along with marketing, finance and human resources. The operations function requires management of both the strategic and day-to-day production of goods and services.

In managing manufacturing or service operations several types of decisions are made including operations strategy, product design, process design, quality management, capacity, facilities planning, production planning and inventory control. Each of these requires an ability to analyze the current situation and find better solutions to improve the effectiveness and efficiency of manufacturing or service operations.

Although productivity benefited considerably from technological inventions and division of labor, the problem of systematic measurement of performances and the calculation of these by the use of remained somewhat unexplored until Frederick Taylor, whose early work focused on developing what he called a "differential piece-rate system" and a series of experiments, measurements and formulas dealing with cutting metals and manual labor. The differential piece-rate system consisted in offering two different pay rates for doing a job: a higher rate for workers with high productivity (efficiency) and who produced high quality goods (effectiveness) and a lower rate for those who fail to achieve the standard. One of the problems Taylor believed could be solved with this system, was the problem of soldiering: faster workers reducing their production rate to that of the slowest worker. In 1911 Taylor published his "The Principles of Scientific Management",in which he characterized scientific management (also known as Taylorism) as:

1. The development of a true science;
2. The scientific selection of the worker;
3. The scientific education and development of the worker;
4. Intimate friendly cooperation between the management and the workers.

Taylor is also credited for developing stopwatch time study, this combined with Frank and Lillian Gilbreth motion study gave way to time and motion study which is centered on the concepts of standard method and standard time. Frank Gilbreth is also responsible for introducing the flow process chart in 1921.Other contemporaries of Taylor worth remembering are Morris Cooke (rural electrification in the 1920s and implementer of Taylor's principles of scientific management in the Philadelphia's Department of Public Works), Carl Barth (speed-and-feed-calculating slide rules) and Henry Gantt (Gantt chart). Also in 1910 Hugo Diemer published the first industrial engineering book: Factory Organization and Administration.

Pharmaceutical Operation Management includes the total Manufacturing and Quality Assurance of Pharmaceutical Products involving the 3M (Man Machine Material). Depending on the patient safety the operations designed. The efficiency of the operations is controlled by the different competitive strategy. Initiating from Good Sourcing Practice (GSP), the value chain

must consists of Good Warehousing Practice (GWP), Good Manufacturing Practice (GMP), Good Laboratory Practice (GLP), Good Distribution Practice (GDP) and Good Engineering Practice (GEP). The concept of standard operation management already developed in significant manner in Bangladeshi Pharmaceutical Sector particularly in Top 20 Pharmaceutical organization to ensure their own profitability. Meanwhile, the universities and the other educational Institutions are also producing the Subject Matter Experts in operation management who are contributing in adoption of standard operation management and economic development of our country as well.

Overview of Manufacturing Plant of Eskayef Pharmaceuticals Limited

Area (Infrastructure):

Total land area of Tongi Plant is 2,18,000 square feet (approximate)

Facilities:

Manufacturing Dosage facilities:

1. Tablet (Uncoated, Film Coated, Enteric Coated Tablet)
2. Capsule
3. Liquid
4. Sachet
5. Topical Preparation

HVAC System:

Total manufacturing area is under HVAC System.

Power Back up System:

Normally Electricity supplied from Dhaka Electric Supply Company (DESCO) & 24 hours back up power supply available through 03 Generators having capacity of 1250 KVA.

Purified Water System:

Water treatment plant has the capacity of 1000 Liters/hr. following Reverse Osmosis & UV Radiation Technology.

Current Plant Capacity:

Present production capacity in value is 120 Crore Taka & in unit packs 1.61 Crore Packs per year.

Waste Management System:

Have separate area for waste disposal under the supervision of the authorized person according to the standard operating procedure (SOP) following the direction of WHO guideline.

Effluent Treatment Plant (ETP):

To fulfill the requirements of the regulatory body, new Effluent Treatment Plant (ETP) have been established in the year 2007 & functioning well now. Its capacity is about 50,000L/day.

Cehpalosporin Block
Area (Infrastructure): Total area of Cepha block is 45,000 square feet (apx)

Manufacturing Dosage Facilities:

1. Tablet
2. Capsule
3. Vial
4. Dry Syrup

HVAC System:

Total manufacturing area is under HVAC System.

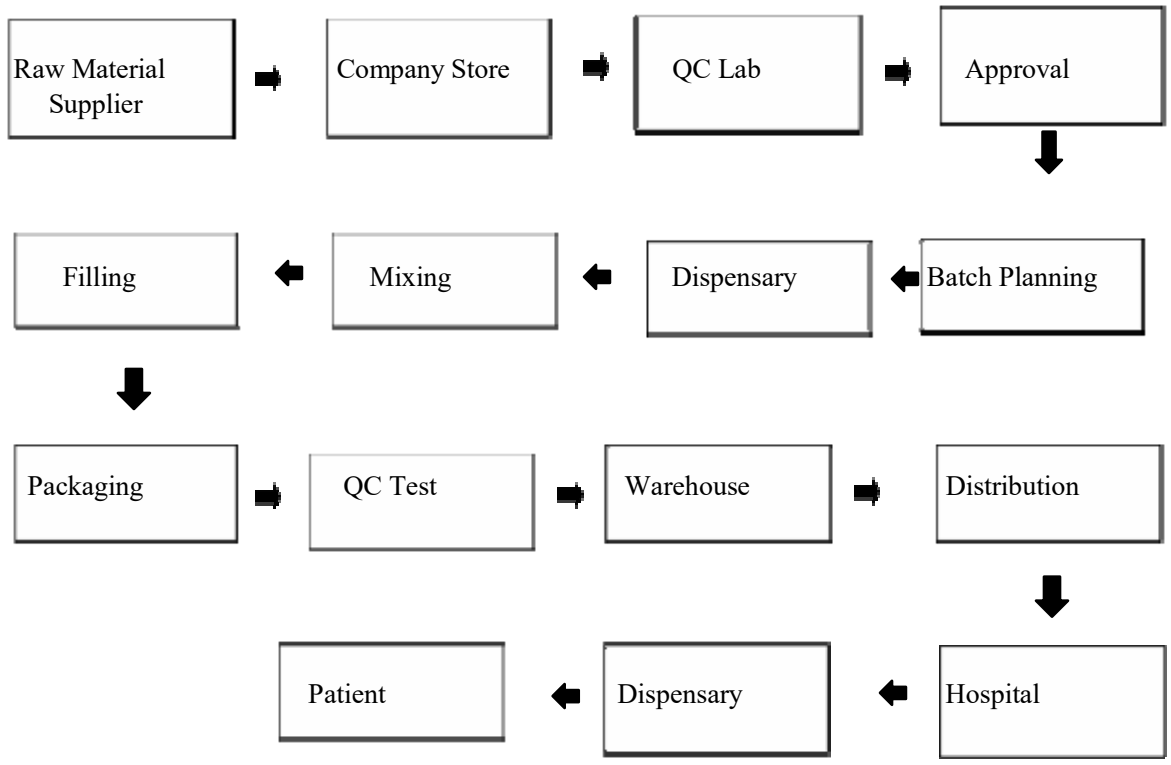
Power Back up System:

Captive own power supply from gas generator of 2.2 MW capacity which is back up by 800 KW diesel generator.

Purified Water System:

Water treatment plant has the capacity of 1000 Liters/hr. following Reverse Osmosis Technology and the capacity of WFI Liters/hr.

Total procedure of production of a drug:



Ware house

Warehouse is an important part of any pharmaceutical industry. Ware house is normally the larger operation in the plant, especially attention should be focused on monitoring cleanliness, freedom from infection and orderliness. Ware house is the place where products are preserved and distributed. SK+F Limited has many products in the market, so its ware house also has many responsibilities. A quarantine area for incoming raw and packaging material, bulk products and finished products. Warehouse
basically deals with 3 types of products:

1. RM (Raw Material)
2. PM (Packaging Material)
3. FG (Finished Goods).

Figure: A typical warehouse

RM can be collected from local and international manufacturers with/without a secondary party/medium. The whole working pattern of a warehouse department can be summarized as below: First, the warehouse receives RM, PM, FG. During receiving warehouse checks some things:

1. Supply data
2. Whether or not the material is from an approved source.
3. In voice- this consist all the necessary information regarding to ensure quality of the supplied product to ensure quality.

Once, The RM is received, a receiving record (RR) is attached to it and it is tagged as “Quarantine” with an identification number like **RM 05 11 0098.**

There is a sampling booth in warehouse. A QA executive collects sample for analysis within 10 days of receiving the product. Then the raw materials are taken in the QC lab for analysis. Here some rules are followed for sampling:

1. For active ingredients: Sample is taken from all the containers.
2. For excipients : Sample is collected from √n +1 containers, where n is the number of containers in a batch
3. For packaging material: it is 6-7 pcs.

After sampling "**SAMPLED**" label is attached to the container

Storage Conditions

Storage	Freeze	Cold	Cool	CRT	Ambient
Temperature	Below 0°C	2-8°C	8-15°C	25°C	Below 40°C
Relative Humidity	-	20%RH	35%RH	55±5%RH	-
Products	-	Injection and vials	Color and Essence	Raw materials	Solvent room

During visit to the warehouse unit we have always maintained SOP guided by the staff of SK+F.

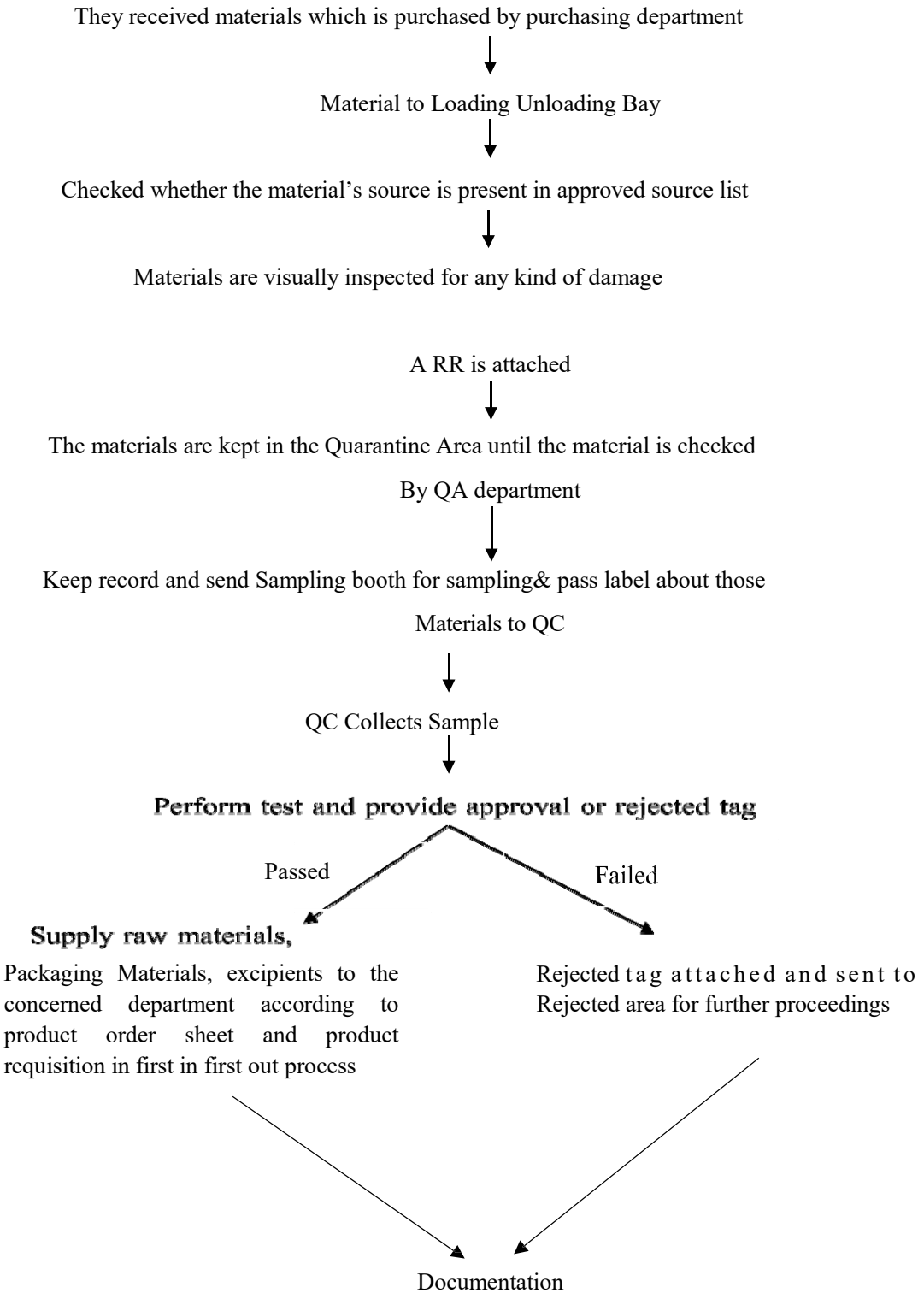
The other warehouses in SK+F are – Ware house-III (for finished goods)

- Warehouse for Cepha unit
- Solvent floor
- EGC shell store room

Different areas of ware house:

1. Quarantine area
2. Passed area
3. Rejected area
4. Office for logistic activity & Lockers for warehouse personnel
5. Cool room (Temp. 18.9 °C)
6. Ambient condition below 40 °C
7. Cold room 2-8°C

Working process of Ware house-I:



Working process of Ware house-III:

Packaging of final product

↓

Stored in ware house-3 with **QUARANTINE** yellow tag in the Shipping carton

↓

After all the performed tests by QC are passed, they give the RELEASED green tag removing the previous one.

(If not passed, a HOLD label is given.)

↓

Then these RELEASED goods are moved to the inner portion of the ware house-III

↓

According to market demand, the released products are distributed in First in first out process to the depots.

Important notes:

1. Sampling for raw materials are done in separate room in ware house-I
2. Not released area, released area and cold storage area of ware house-II are 7000 sq ft, 22000 sq ft and 10 sq ft respectively.
3. GRN, RML and RMI mean for Goods Receive Note, Raw Materials Local and Raw Materials Import respectively.
4. Separate arrangements are there for the products of toll manufacturing (for Beximco, Novartis, General, Unimed-Unihealth, Nuvista etc).
5. Temperature Mapping is done periodically (Every 3 years) for summer and winter season. Temperature mapping is discussed below:

Temperature Mapping:

A temperature mapping exercise is required for any space allocated for the storage and handling of products with a specified labelled storage temperature. This includes freezer rooms, cold rooms, temperature-controlled storage areas, quarantine areas and receiving and loading bays. The permitted temperature ranges in these areas will vary – for example: -25°C to -10°C, 2°C to 8°C, 15°C to 25°C, etc. Temperature mapping may also need to be carried out in spaces without active temperature control.

A mapping study establishes the temperature distribution within the zone being mapped and it locates hot and cold spots. The collected data provides an essential source of information to ensure that all TTSPPs are correctly stored within their labelled temperature range(s). Mapping may also be used to identify zones where remedial action needs to be taken; for example by altering existing air distribution to eliminate hot and cold spots, or by retro-fitting new air distribution equipment to reduce temperature stratification in high-bay warehouses8 .

A temperature mapping exercise involves a four stage process, as follows:

a. Prepare a mapping protocol.
b. Carry out the mapping exercise.
c. Prepare a mapping report.
d. Implement the recommendations by carrying out the remedial and other actions identified in the mapping report. A follow-up mapping exercise may then be needed to verify the effectiveness of the remedial actions.

Objective of temperature mapping:

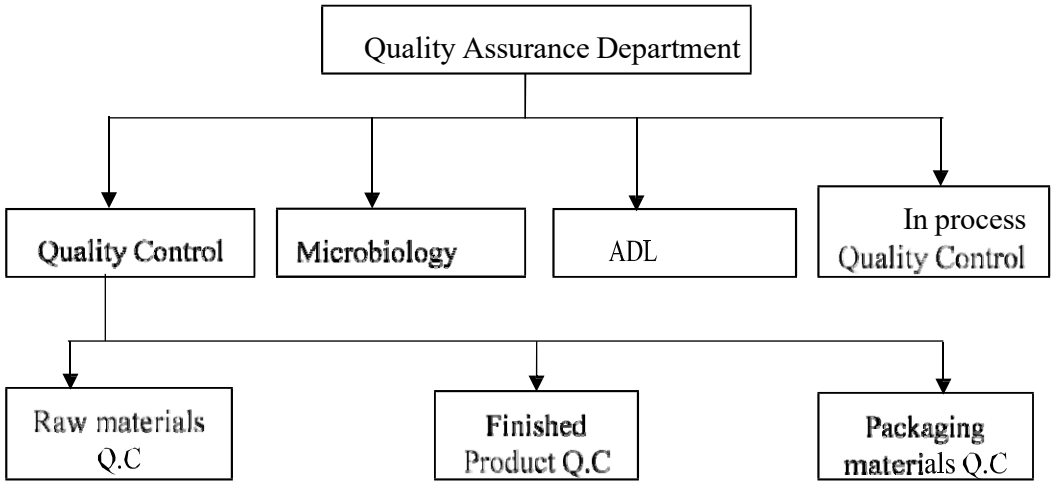
- Mapping temperature variations within the selected storage areas. Typically these areas include freezer rooms, cold rooms, warehouses, packing areas, loading bays and other areas in which temperature sensitive products are stored, or are temporarily held when in transit.
- Measuring temperature variations at each location within the chose area, by day of the week, and time of day.
- Documenting high and low temperature fluctuations caused by the environmental control systems operating at the time of the study – for example, heating, cooling and ventilation.
- Identifying potential airflow issues that may be the cause of temperature variations.
- Recommending where TTSPS can safely be stored in the mapped area. These recommendations should take account of any temperature deviations identified during the study as well as the approved temperature range(s) for the products being stored in the area.
- Identifying the best places to locate temperature sensors, for routine monitoring, in circumstances in which a monitoring system is installed. If a monitoring is already installed, identify the best places to re-locate temperature sensors (if necessary).
- Making recommendations for any remedial actions needed to overcome the problems identified in the study.

Quality Assurance Department

The chain of Quality Assurance (QA) activity stretches from the product design and product development stage up to the end users.

QA need to evaluate the whole system for its smooth and accurate operation while the major effects come from the actions of the supporting departments. In order to meet this objective, the QA staff interacts and coordinates with their other colleagues in the organization such as Finance, Personnel, Product Development, Pack Design, Planning, Purchasing, Manufacturing, Engineering, Warehouse and Distribution, Marketing etc. goal. Quality assurance department is responsible for assuring that the quality policies adopted by a company are followed and in most organization it serves as the contact with regulatory agencies and are the final authority for product acceptance or rejection. It also helps to prepare the standard operating procedures (SOPs) relative to the control of quality.

In SK+F, the Quality Assurance department is divided into the following sections:



Quality Control Section (Cepha unit):

Quality control section involves the operational techniques and activities undertaken within the quality system to verify that the requirements for quality of activities have been fulfilled.

The quality control manager controls the quality control department, which is performed in three stages-

1. Raw materials
2. Finished product
3. Packaging products

Instruments Used in Quality Control Area:

Melting point tester

Optimelt automated melting point system Model:SRS

Karl Fischer Titrator

Metrohm Model: 831

Karl Fischer Titrator

Metrohm Model: 795

UV – visible spectrophotometer

SHIMADZU Model: UV 1601 PC

Kjeltec TM

Foss Model: 2100

Tecator TM scrubber

Foss. Model:2100

Electronic balance Model: Extrohm® Pro (ohaus)

Tecator digester

Foss Model: 707

Microprocessor P^H Meter

Model: HANNA P^H 210

Total organic carbon analyzer

Model: Simadzu

HPLC Prominence Model: Shimadzu (SPD 20AV UV –VIS (detector) & DGU-20A degasser)

HP Laser jet Model: 1320 **Distillation chiller** Model: Buchi B741 **Muffle Furnace**

Model: nasertherm

Fume hood

Laboratory test sieve

Vacuum oven

Memmert

Centrifuge

Eppendorf

Vacuum filter

Waters multipose milliford

Density tester

Logan

Heating Bath

Model: Buchi B491

Refractometer

Model: 3T

Dissolution tester

Erweka Model: 700

Deionized water plant

Nano pure diamond

Vibrator

Edmund Bucler Model: KL-2

Sonicator: use ultrasonic sound to mix solutes with solvents.

Inhaler testing apparatus Erweka

Automatic voltage stabilizer

GPS 1000

Drying oven

Sanyo Gallencamp

Potentiometric titrator Metrohm

Model: 716 DMS Titrino

Orbital shaker

GFL 3017

Atomic absorption spectrophotometer: used for determination of elements such as Ca, K, Zn, Mn, Mg etc.

SHIMADZU Model: AA- 6800

Tests performed in QC department in SK+F:

Tests for starting materials:

1. Appearance and odor
2. Solubility
3. Identity (complies/ not complies)
4. Melting point
5. Weight per ml
6. Acidity/alkalinity
7. Limit test Chloride Sulphate
8. Copper Iron Arsenic
9. Lead/heavy metals
10. Water content by KFR
11. Appearance of solution/Clarity & color of solution
12. Assay Spectrophotometric/ Titrimetric /HPLC/AAS
13. Residue on ignition/Sulphated ash
14. Related substances/Chromatographic purity Microbial limit

Tests for tablets or capsules:

1. Loss on drying at 105 (3 hrs)/ Moisture content by KFR
2. Disintegration test
3. Length/diameter
4. Width
5. Thickness of 10 tablets
6. Friability test
7. Dissolution test
8. Uniformity of weight
9. Appearance of tablets or capsules
10. Average hardness for tablets
11. Assay by titration/spectrophotometric/HPLC/AAS method

    ** AAS – Atomic absorption spectrophotometry used mainly for the assay of vitamins or minerals.

Tests for LCO/Gel/Dry syrup/Pediatric drop:

1. Identification of active ingredient
2. Identification of hydroxy benzoates
3. Microbial contamination (satisfactory/unsatisfactory)
4. P^H value
5. Water per ml at 20± C, gm/ml
6. Viscosity
7. Sedimentation test
8. Total solid
9. Color content
10. Alcohol content
11. PCA content (Parachloro aniline)
12. Assay (Spectrophotometric/Titrimetric/HPLC)

Tests for WFI:

1. Contents of vial/bottle
2. Sterility test
3. P^H value test
4. Ammonia test
5. Nitrates test
6. Chlorides test
7. Sulphate test
8. acidity/alkalinity test
9. Oxidizable substances test
10. Heavy metals test
11. Ca & Mg test
12. Residue on evaporation
13. Conductivity test
14. Water content

Tests for Packaging materials:

1. Description(Appearance)
2. Text(name, label claim, Reg. no, price)
3. Color
4. Dimension(Thickness, diameter)
5. Weight(gm/square meter)
6. Bottle light transmittance

IN PROCESS QUALITY CONTROL

In general, compliance means conforming to a specification or policy, standard or law that has been clearly defined. In process control is a department Quality assurance where all materials are under physical analysis. It coordinates the all department in processing.

Purposes of the company's compliance program:

The company's compliance program is an integrated, enterprise-wide set of policies, practices and internal controls designed to prevent, detect and correct illegal or other improper activity, and to promote compliance with regulatory laws

and company policies. a primary goal of the compliance program is to promote within the company a culture of commitment to the prevention, detection and resolution of situations that may not conform to applicable standards of conduct or business ethics.

Activity of Compliance:

- Compliance personnel can ask any question related to quality to anyone.
- The activity of compliance starts outside the factory. To ensure the raw material suppliers' activity audit is performed.
- Right materials should enter and kept in the right place and each and every material should contain label. If this process is violated, then compliance should raise its voice and record it.
- After QC test, whether the material has passed or failed, it should be mentioned in the label and properly affixed. This process should also be monitored by compliance.
- Compliance or QA department gives release and distribution certificate for passed finished product on the basis of the analytical report of the QC department.
- Market complaint review and investigation.
- If any NCR (non-conformity report) is raised, then at first Hold label is issued by compliance and investigation is done.
- Shelf-life sample collection and maintenance to analyze samples with their corresponding stored samples when market complaint or NCR is aroused.

Microbiology

Microbiology(Cepha unit)

All parenteral drugs, including many oral drugs, must go through rigorous microbiological testing in order to validate certain compounds by United States Pharmacopeia regulations.

Microbial tests are performed for following materials:

1. Raw materials
2. Capsule shell
3. Oral liquid products
4. WFI
5. Syringe

Instruments used in Microbiology:

1. Incubator (Memmert)

For bacteria, temperature: 30-35ºC, incubation period : 3 days For Fungus, temperature: 20-25ºC, incubation period : 2 days

1. Incubator Gallenkamp
2. Air shower pass box.
3. Laminar airflow apparatus
4. Autoclave
5. Microscope
6. TOC
7. pH meter.

Tests performed in Microbiology department:

1. Microbial limit test of raw and packaging material
    a) Total microbial count
    b) Presence or absence of specific Pathogens. The pathogens are: S. aureus, E. coli, P. aeruginosa, Salmonella species, Clostridium species
2. Water test
    a) Total bacteria count
    b) Clostridium
    c) Pseudomonas aeruginosa
3. Environmental monitoring
    a) Monitoring of airborne micro organism
        - Settle Plate
        - Mechanical sir sampler
    b) Monitoring of surface
        - Contact plate method
        - Swab method
    c) Monitoring of personnel hygiene
        - Gloves or hands
        - Garments
4. Sterility Test
5. BET or Bacterial Endotoxin Test (LAL test)
6. Pyrogen Test
7. Potency test for antibiotic

Analytical development lab

Instruments used in Product development – Analysis:

- UV-visible spectrophotometer
- Dissolution tester (Logan)
- Centrifuge(Eppendorf)
- HPLC
- Orbital shaker
- pH meter
- Disintegration tester(Erweka)
- Drying oven

Product development department also use QC lab., production department and SVP department for their test purposes.

Liquid sterile

Parenteral preparation (SVP):

Parenteral preparations or injectables are the sterile solutions or suspensions of drugs in aqueous or oily vehicles meant for introduction into the body by means of an injection under or through one or more layers of the skin or mucous membrane.

Since they are introduced into internal body compartments they must be sterile and free from all types of living microorganisms and microbial products such as toxins, pyrogens, etc., and should be free from particles like dust, fibbers, etc. They should be isotonic with body fluids.

Example: Dextrose injection (IV) Diclofenac-Na-injection (IVor IM)

Instruments used in SVP unit:

a) **For WFI (Water for injection):**

1. Stilmus Redistillator

b) **For sterilization:**

1. Linden (Moist heat autoclave)
2. Hot air sterilizer
3. Reserve vessel
4. Depyrogenation machine (GMS)
5. Sartorius (Pressure vessel)

c) **For washing:**

1. Ampoule and vial washing machine(KCQ60)
2. Rubber stopper washer

d) **For vial labeling, filling and sealing:**

1. Macofar TR
2. Romaco

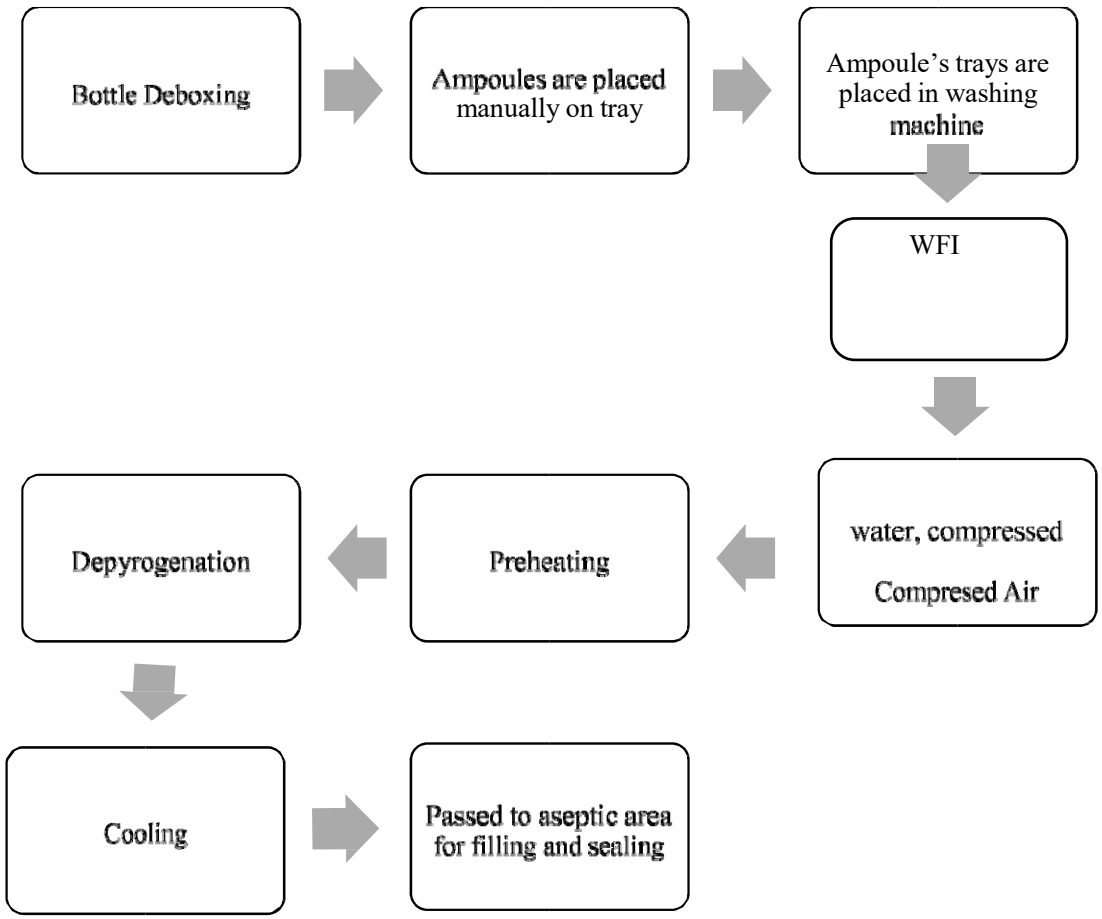
e) **Others:**

1. CFM (Vacuum dust collector)
2. Becker (Vacuum pump compressor)

Classification of clean room on the basis of particulate:

Class	**.5µ/m^3**		**5µ/m^3**	
	Rest	**operation**	**Rest**	**operation**
A	3520	3520	29	29
B	3520	352000	29	2900
C	352000	35200000	2900	29000
D	3520000	Not defined	29000	Not defined
E	Not defined	Not defined	Not defined	Not defined

Mechanism of vial / ampoule washing:

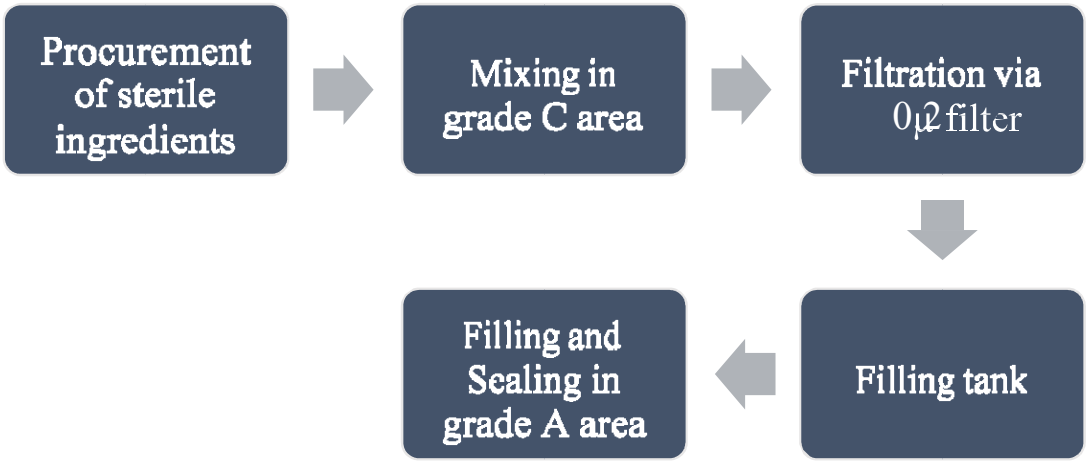


The time and temperature for depyrogenation is different for different vial size. They are given below:

Vial Class	Temperature(°C)	Time (min)
A (7.5 ml)	300	8
B (15ml)	310	11
C (30ml)	320	20

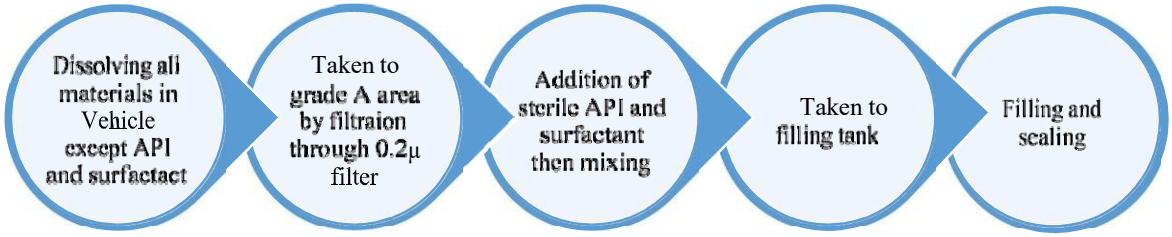
Aseptic manufacture of eye care solution:

In case of aseptic manufacturing following steps are followed:



Aseptic manufacturing of parenteral suspension:

Parenteral suspension cannot be filtered after final formulation is done. So it is prepared in the following way:



Environmental Control of Sterile Area

In SK+F total environmental control is done properly according to the GMP guideline.

- Area control:
  a. Corridor: negative pressure
  b. Room: positive pressure
- Air flow control: Air flow is in between 70-80 feet/mm attained by HEPA filter.
- Air filtration: By HEPA filters with an efficiency of 99. 97% for removing of particles of 0.20 micron or greater than it.
- Temperature control: 22° C
- *Humidity control: 40%-60%
- By using protective clothing
- Fumigation at every weekend by using 40% water solution of formaldehyde (formalin)
- By using UV light (Wave length 254 to 265 nm)
- By using cleaning and disinfecting agents

Sterilization Process followed in SK+F

***Sterilization by heat:**

Moist heat sterilization or Autoclave [under 181 lb pressure for 25 minutes at 121°C] Dry heat sterilization

*** Sterilization by chemicals**

Alcohol (70%), Lysol (cresol with soap)

Test for finished product

- Visual inspection for
  - High/Low volume
  - Cosmetic defect
  - Chips can cracks
  - Glass particles and fibers inside the vial

Comments

- SK+F has a unique sterile section for which they can be proud. The sterile section is fully separated from other section. Rules and regulation are strictly maintained. All necessary tests are performed regularly.

Product Development Department

Key responsibilities:

- Formulation development.
- Packaging material development
- Scale up
- Existing product development
- Existing product troubleshoot
- Cooperate with analytical development

- DTL for INN drug.
- Documentation.

Instruments used in Product development – Formulation:

- Gansons Coating Machine
- Mixer with heater
- Granulator
- Precision Electric Balance
- Stability chamber
- UV-visible spectrophotometer
- Dissolution tester
- Liquid chromatogram
- HPLC

Activity of PD Formulation:

1. Receive product proposal.
2. Prepare draft recipe & send to marketing.
3. Receive product brief.
4. Develop final recipe & send to marketing.
5. Identify raw materials/packaging materials and send to marketing.
6. Quantity & Raise Requisition for raw materials/packaging materials.
7. Prepare specification.
8. Receive of raw materials for product development.
9. Prepare of packaging materials specification.
10. Prepare experimental batch.
11. Develop and validation and rationale.
12. Prepare final formulation & rationale.
13. Identify aspects and impacts of the product.
14. Prepare pilot batches.
15. Perform initial studies.
16. Put samples on storage conditions.
17. Perform 01 month study.
18. Receive draft design & forward to production.

19. Place requisition for trial production.
20. Perform 1.5 months study.
21. Prepare content of shelf-life.
22. Check change parts & machines performance.
23. Receive final design.

Storage condition:

CONDITION	TEMPERATURE (C)	HUMIDITY (%)
(long term condition)for zone & zone	25	60
(long term condition)for zone & zone	30	70
Accelerated	40	75
Ambient	Ambient	Ambient

Comment:

It is the duty of the development department to make the formula of a new molecule or of an existing molecule. So, it is a very important department and the activities done here need to be well organized and documented.

Production (Generic) Manufacturing Unit-1

Production area is one of the most important areas of a pharmaceutical company where products are manufactured. It may be considered as the skeleton of a pharmaceutical industry. Quality of products manufactured greatly depends on the GMP (Good Manufacturing Practice) and environmental conditions of the production area.

Dispensing booth

Raw materials are dispensed in the dispensing booth where required quantities are taken (mentioned in BMR) and weighted. It consists of a laminar air flow to prevent intrusion of raw materials dust into the room or working area. Its pressure is set for individual materials as directed on SOP. After taking the weight of the required raw materials, they are sent to dispensing bulk and the remaining (extra) are returned back to warehouse.

Air Lock system

Acts as a transit point for raw materials before proceeding into dispensing.

Wash bay

Cleans machine equipment, drums etc. using portable water, hot water, 70 % Isopropyl alcohol and finally purified water and finally rubbed with lint free clean cloth and are transferred to clean room.

Clean store

It consists of negative pressure.

Materials (cleaned) are brought from wash bay and stored until further use.

Stores cleaned accessories such as IPA bottle, Mesh, Drums etc. Empty cleaned container.

Machineries Used In the Tablet Section:

Name of the Machine	Purpose
Planatory Mixer/Granulator	Mixing
Vibratory sifter	Sieving
Fluid Bed Dryer	Drying
Double cone blender	Mixing
High Speed Mixer/Granulator	Mixing
Cadmach Compression Machine(D-type)	Compressing
Cadmach Compression Machine(B-type)	Compressing
Hammer Miller	Milling
Sachet filling machine (Enflax 1 & 2)	Sachet filling and sealing

Liquid section:

The oral use of liquid pharmaceuticals has generally been justified on the basis of ease of administration to those who have difficulty in swallowing solid dosage forms. A drug administed in solution is immediately available for absorption and in most case, is more rapidly and efficiently absorbed than the same amount of drug administered in a tablet or capsules.

SK+F Ltd has mainly three different parts in this section which are-

Liquid Part

a. Syrup
b. Bulk liquid
c. Suspension

The liquid section has got three unit. Unit -1 has got two parts. One part is used for the production of suspension or small volume syrup and the other part is used for the preparation of sugar syrup.

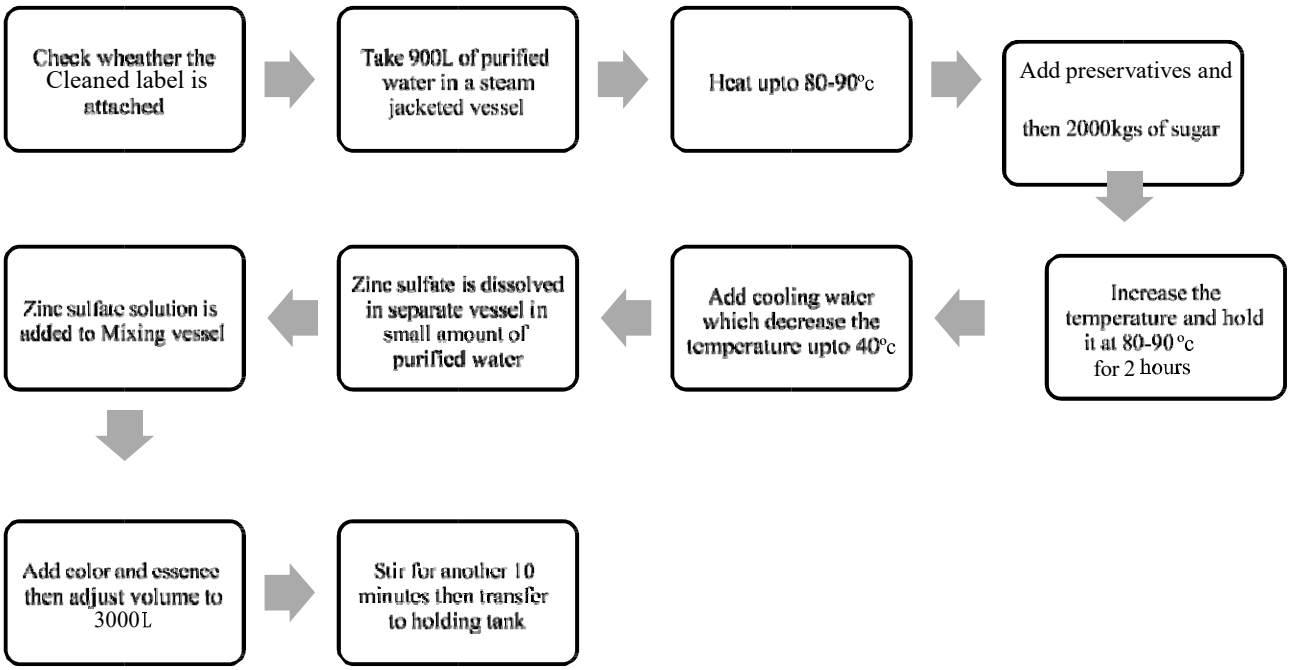
Unit -2 & Unit-3 both are dedicated to certain products. Unit -2 has the following machine

- Bottle washing machine- 24 stations
- Filling station -4
- Cap sealing station -1
- Labeling machine.

The RPM of these machines are set according to the production cycle. Similarly Unit-3 has the following machines:

- Bottle washing machine-can wash 1800 bottles per minute
- Filling station -15
- Cap sealing station -10 Labeling machine.

Observed process of liquid preparation in Liquid unit-3:



Manufacturing Unit-2

Machinaries of unit 2:

- Fluid bed coater:

  Name of the machine :Eurovent Max working vol:150 L

  Mesh size:200

- Spheronizer 500:

  Mnufcturer:Cleva process

  Production cpcity:10 kg

- Extruder35

  Manfacturer:CLEV

  Autofeeder speed:35-105 rpm

  Production cpcity:200kg /hr

- High speed mixer:

  Mnufcturer:Sejong

  Full cpcity:670L

Figure: High Speed Mixer Machine

- Fitzmiller:
  Name of the equipment:Gnson multimiller.

- Fluid bed dryer: Mnufcturer:Changzhou yibu drying.
  Country:China
  Model:FG120
  Max work load:140 kg

Figure: Fluid Bed Dryer

- Double cone blender:

  Manufacturer: Jaw Chuan machinery.
  Country: Taiwan
  Full volume:2000L

Figure: Double cone blender

- Silverson stirrer:
  Nme of mchine:silverson stirrer, England.

- Nicomac coating system:
  Country: Itally
  Max working lod:450 kg

- Rotary tablet press machine:
  Mnufcturer: Shejong Origin:Korea
  No of station;37
  Max pressure force:3 ton Die
  Size :D
  R.P.M of disk :15-115

- C.F coater
  Centrifugal fluidized coater
  Company: Sejong , Korea
  Production capacity: 30 kg

- Balance:
  Manufacturer:Sartorious AG, germany Max
  Capacity:120 kg
  Readbility:20 gm Working
  Range:10-110 kg

Tablet Section

Tablet is a solid unit dosage form of medicament or medicaments with or without suitable diluents and prepared either by molding or by compression. They vary greatly in size, shape and weight which depend upon the amount of medicament and the mode of administration.

Interior Design of Tablet Section in SK+F

- Dispensing area
- Granulation area
- Compression area
- Coating area

The Machineries Used in Tablet Section

- Weighing machine
- Dry granulator
- V - Mixer
- Plenary mixer(sams)
- Fluid bed drier/ granulator(solace)
- Fluid bed Processor
- Double cone blender
- Shifter
- Multimiller
- Sachet filling machin(Enflex)
- Sejong 37 punch double rotary machine
- SEJONG film/ sugar/ enteric coating machine
- Hygrometer
- Homogenizer
- Electric balance
- Hardness tester & Disintegration tester for in process checking
- Dry & wet bulb thermometer for humidity checking

Operation in Tablet Section

a. After the recommendation for the production of a batch, at first the requisition of required raw materials is sent to ware house department.
b. QC & QA approved required raw materials of specific amount is then sent to the dispensing unit.
c. A list of chemicals with corresponding specific weight is hung in dispensing unit.
d. Accurate weighing of chemicals.
e. Remaining materials with a document containing amount used and amount loss is returned to ware house department.
f. Mixing and granulation Compression
g. Coating (if necessary) Packaging and packing
h. Each step is carried out according to Standard Operating Procedure (SOP)

Excipients used for tablet formulation

- Diluents: Lactose, Dibasic Calcium Phosphate, Maize Starch, Mannitol, Sorbitol
- Binders: Povidone, HPMC, Methyl Cellulose
- Lubricants: Mg-stearate, Calcium Stearate
- Glidants: Colloidal silicon dioxide, talc.
- Disintegrants: Sodium starch glycholate, Crosspovidone, Crosscarmellose Sodium o Sweetening agents: Granulated sucrose, saccharine-Na.
- Preservatives: Methyl paraben, propyl paraben. o Shining agents: Tritanium dioxide, Mg-stearate. o Dissolution rate enhancer: Na-lauryl sulfate.
- Multifunctional Ingredients: MCC, Pregelatinised Starch

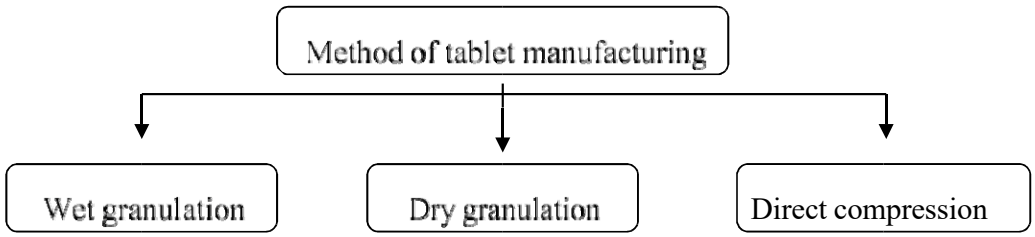
Dispensing unit:

Dispensing unit receive required raw materials which are approved by QC for tablet preparation. It supplies materials to the granulation and coating unit after accurate weighing according to dispensing order sheet and return the remaining materials to store.

Granulation unit:

Granulation is the process in which the powder particles of raw materials are made to form larger particles in order to facilitate compression for the production of tablet.

In SK+F. the following granulation processes are used for tablet manufacturing:



Wet granulation:

This is the most widely used and most general method of tablet preparation. Its popularity is due to the greater probability that the granulation will meet all physical requirements for the compression of both tablets. The wet granulation of tablet production is essentially a process of size enlargement, sticking particles of drug and excipients together using an adhesive to produce a granular product with improved flow properties and increased ability to cohere under pressure.

Wet granulation method is performed with the following steps in SK+F:

Accurate weighing of active ingredient and incipient

↓

Preparation of granulating paste/ slurry by suitable solvent with binder, preservatives etc. and dry mixing of active ingredient(s), diluents etc.

↓

Wet mixing (Dry mixture + paste/slurry).

↓

Wet sieving (granulation).

↓

Drying (usually fluid bed dryer used and required moisture is maintained here)

↓

Dry sieving (granulation).

↓

Lubrication and blending

↓

Discharge (into double polythene bag & close lid of drum tightly and sent to compression unit

Dry granulation

This process is applied for those drugs which are sensitive to moisture. This process is also used for water sensitive powder that needs granule formation before compression.

Steps applied for dry granulation are given below:

Weighing of drugs and excipients

↓

Dry mixing of drugs and diluents

↓

Slugging or precompression

↓

Milling and sieving

↓

Lubrication Discharge for compression

Direct compression

Tablets are produced directly from the powder by compression without modifying the physical nature. It is done for only few selective drugs, which has crystalline nature, e.g.

KCl, NaCl etc.

In SK+F, we didn't observe the production of tablet using this method.

Steps of direct compression:

Weighing of drugs and excipients

↓

Mixing of all ingredients

↓

Sieving

↓

Compression

Oral tablets coated with a layer of sugar or film are called coated tablet. The application of coating to tablets, which is an additional step in the manufacturing process, increases the cost of the product. Again the coat must be dissolved before disintegration and dissolution of the tablet.

Therefore, the advantage to coat a tablet is usually based on one or more of the following objectives:

- To mask the bad taste, order, or color of the drug. To protect moisture sensitive drugs from moisture.
- To provide physical and chemical protection of the drug. To control the release of the drug from the tablet.
- To protect the drug from the gastric environment of the stomach with an resistant enteric coating.
- To incorporate another drug or adjuvant in the coating to avoid chemical incompatibilities or to provide sequential drug release.
- To improve the pharmaceutical elegance by use of special color or contrasting printing.

Process employed in Eskayef pharmaceutical Ltd.

In SK+F, the following three processes are employed for tablet coating:

1. Film coating

Aqueous film coating

Organic film coating

2.Enteric coating

Liquid enteric coating

Powder enteric coating

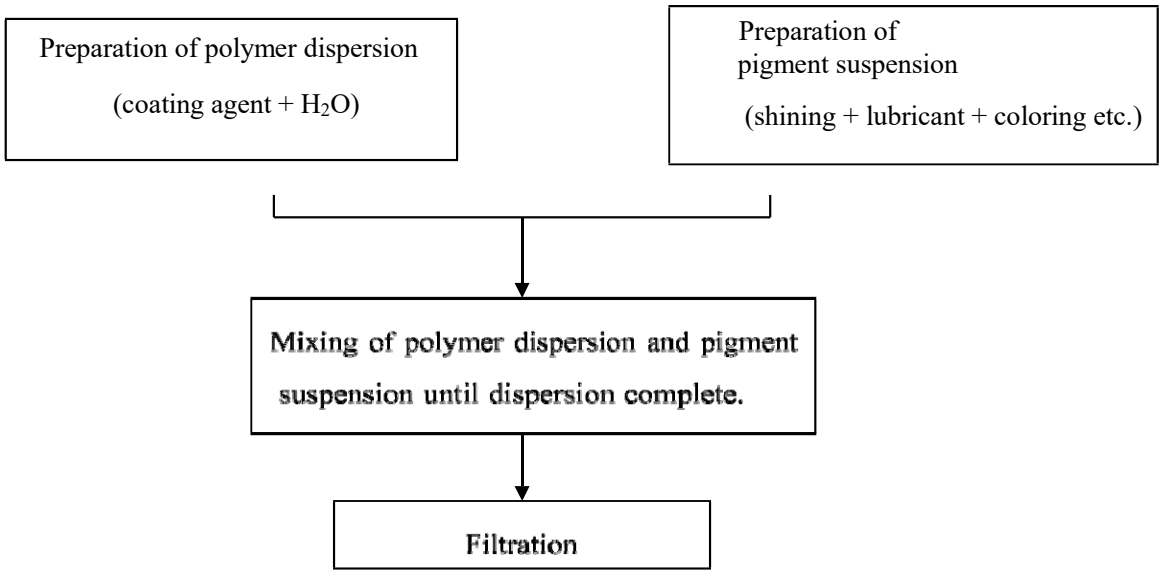
Figure: Sejong (Korea) tablet coating machine

Film coating:

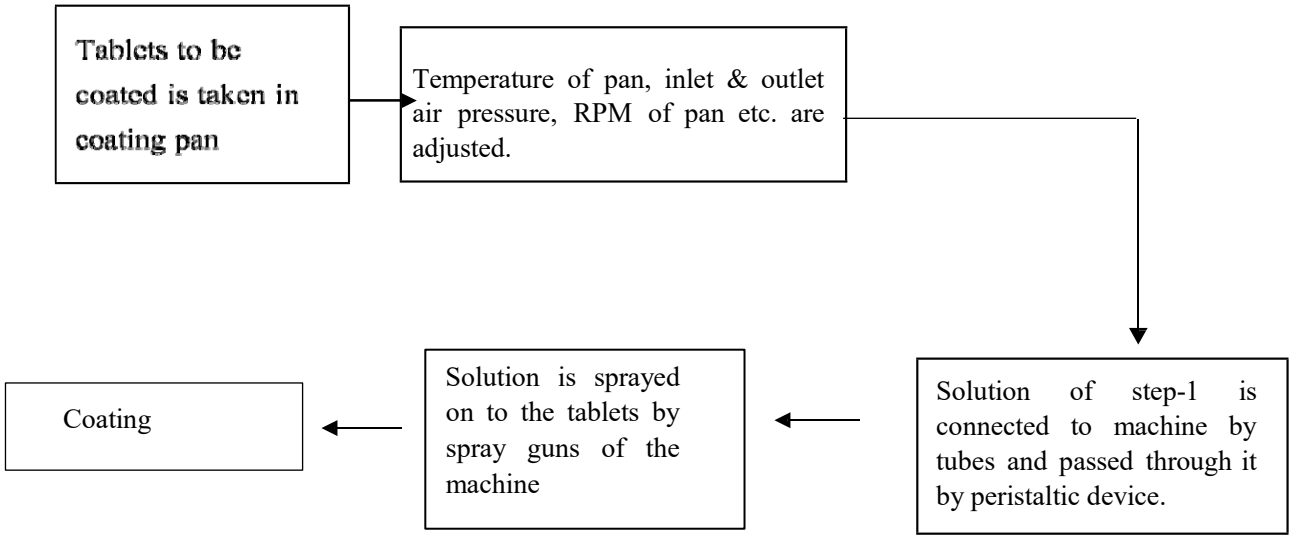
This process involves the deposition of a thin polymeric film onto tablets from solutions that are organic solvent based or water based. Some substances used for film coating in SK+F are mentioned bellow:

- Kollicoat (coating agent)
- HPMC
- PG or PEG400
- Titanium dioxide (increase shining)
- Purified talc (increase flow property)

Aqueous film coating process employed in SK+F



Coating process



Organic film coating process:

1. Pre-coating: Plasticizer and suitable organic solvents are mixed well and initially sprayed onto the tablets to provide a water resistant thin layer.
2. Final coating: film coating agent and suitable organic solvent is used for spraying the tablets

Enteric coating in SK+F:

An enteric coat is usually a special film coat designed to resist its destruction into gastric fluid and to disrupt or dissolved in the small intestine. **Eudragit** is a enteric coating polymer used in enteric coating.

Capsule Section

Capsules are solid unit dosage form of medicament in which the drug(s) is enclosed in a practically tasteless, hard or soft soluble container or shell made up of a suitable form of gelatin. Hard gelatin shells are used for filling the solid substances whereas soft gelatin shells are used for filling liquid or semisolids.

Instruments used in capsule section:

Sejong auto capsule filling and sealing machine (Sejong Pharmatech Co. Ltd., Korea, Model: 9F-40)

Figure: Sejong (Korea) capsule filling machine

Process:

Capsule shells are filled in hopper

↓

Capsule shells come in a secondary station

↓

Shells are automatically fitted in capsule dies

↓

Caps and bodies are separated by the force created by vacuum pressure through rubber stopper which cause the upper and lower dies to be separated

↓ ← Powders or pellets are given in hopper

Pellets/powder are automatically filled in body of shell

↓

Displaced shells are automatically sealed

↓

Filled capsules are automatically ejected through a metal detector which rejects any capsule containing slight metal impurity

We observed encapsulation of **Losectil** 20mg (omeprazole) in hard gelatin capsule shell during inspection of this department.

Capsule sizes (in theory)

Empty gelatin capsules are manufactured in various sizes, varying in length, in diameter and in capacity. The size selected for use is determined by the amount and density of material to be encapsulated. Generally the capacity varies from 30-600 mg.

Sizes
000 (largest)
00
0
1
2
3
4
5 (smallest)

In SK+F, mainly capsule size 0, 1, 2 & 4 are used. In special cases 00 shells are used

Problems occurred during encapsulation:

1. Blank shell
2. Shell lock in channel
3. Shell breaking
4. Improper filling of shell
5. Improper fitting of shell in dies if compressed air pressure is not adjusted properly. 6. Improper or large size of pellets may cause blockage of nozzle. So shells are left empty.

Bulk Pellets Development System

Bulk Pellets

SK+F is actively engaged in introducing newer molecules and Bulk Pellets to meet the needs of the future. Pellets are the choice of drug administration in future. SK+F feel that to improve the drug action and selectivity. Pellets are the latest drug presentation in the modern world with better patient compliance.

Pellets are the small particle having different size and color. SK+F introduce different pellets such as Diclofenac Sodium, Omeprazol **.Losectil, Zilvit** etc

Apparatus used in bulk pellet:

1. Fluid bed granule coater ; APCG-400
2. GS coater
3. Centrifugal fluidized coater
4. Fluid bed dryer
5. Double cone blender
6. Dusting Pan
7. Nicomac coater
8. Extruder& speronizer(caleva)
9. Sieving apparatus

Materials used in pellet

1. Sugar
2. Lactose
3. Maize starch
4. Povidone K
5. Ethyl cellulose
6. Triacetin
7. Isopropyl alcohol
8. Methyl chloride
9. Hydroxyl propyl methyl cellulose

Type of Pellets:

- Non peril seed(NPS)
- Active Pellets

Non periel seeds production:

Sucrose ⟶ sieving (through 40 meshes) ⟶ sieving (through 60 mesh)

Collect 40/60 sugar ⟶ spray the lactose +maize starch

+ Povidon K dust ⟶ Sieving ⟶ Non peril seeds (NPS) to get 22/36

Pellets Formulation

NPS ⟶ sieving ⟶ spray the API+ diluents + disintegrate seal coating

↓

Enteric coating with FB coater ⟵ drying in tray dryer

It can also directly produced by Fluid bed granulating coater from NPS. When active is used with dusting materials those pellets known as active pellets. If active is not used then it is known as neutral pellets or NPS

Production Unit (Cepha):

In SK+F Ltd. Cepha unit has two parts, which are-

1. **Parenteral:** includes vial filling and sealing. Ampoule and vial filling and sealing are also performed in SVP section if required. Here aseptic condition is also maintained like SVP. For example Triject IV(ceftriaxone)
2. **Non-parenteral (oral):** includes tablet dry syrup and capsule filling and sealing. Example:Kilmax tab(Cefuroxime axetil), Neorex ds capsule (Cephalexin monohydrate), Roxim PFS DS paediatric drop(cefexime trihydrate)

Instruments used:

a) **For parenteral:**

Macofar vial filling-sealing-labeling machine

b) **For encapsulation:**

Sejong capsule filling and sealing machine

c) For dry syrup & tableting:

a) Double cone blender
b) High speed tablet press(ZPT16)
c) Bottle cap sealing machine
d) Drum mixer blender
e) Sifter (sieving machine)

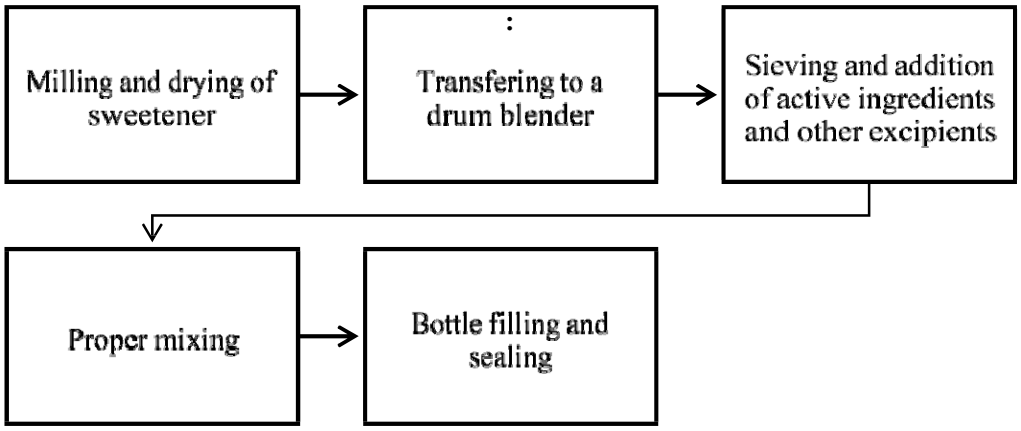
d) **For strip packaging:**

Ganson strip packer machine

The tablet production system is same as manufacturing unit 1&2. Which will be discussed later. The special preparation is Dry syrup.

Dry syrup

- This is a powder dosage form of oral drug used because the drug is unstable in solution.
- It must be reconstituted before use. It is mainly sugar based preparation. We observed the preparation of **Roxim**
- dry syrup (Cefexime trihydrate).The process is shown in the flow chart below



During dry syrup preparation of moisture sensitive products, the humidity and temperature is maintained up to 39 % and 25 C respectively if needed.

Important notes:

1. During dry syrup preparation of moisture sensitive products the humidity is maintained up to 39 % if needed.
2. For parenteral preparation the raw materials come in sealed aluminium container which is opened in aseptic condition and before opening they are cleaned with chlorine solution to free from microbes.
3. The size of membrane filter, HEPA filter and modular or prefilter used are 0.2 µ, 0.3 µ and 0.3 µ respectively.

Packaging unit

The concept of pharmaceutical packaging developed stage by stage with the objectives of presenting a product with physical protection, environmental protection, dosage information, regulatory compliances, perceiving quality and pack security. So, the drug quality is dependent on the packaging quality.

Purpose of packaging:

- To increase the acceptability of the drug To increase the stability of the drug
- To minimize the transport/shipping hazards To improve patients compliance
- To improve the pharmaceutical elegance by use of special color or contrasting printing.

Two types of packing materials are involved-

1. Primary packaging materials (in contact with products) which are:
    - For Blister packing Aluminium foil and PVC film o For Strip packing Aluminium foil only
    - Ampoule
    - Bottle o Vial
2. Secondary packing materials which are Label, Inserts, Inner cartons, Outer carton or shipping carton

Instruments used for packaging:

1. Horn Noack blister machine Model: DPN760 Country of Origin: Germany
2. Hoonga-A (blister packaging machine) Manufacturer: Hoonga-A Corporation, South Korea

Model: Minister-V Capacity: Max 50 rpm

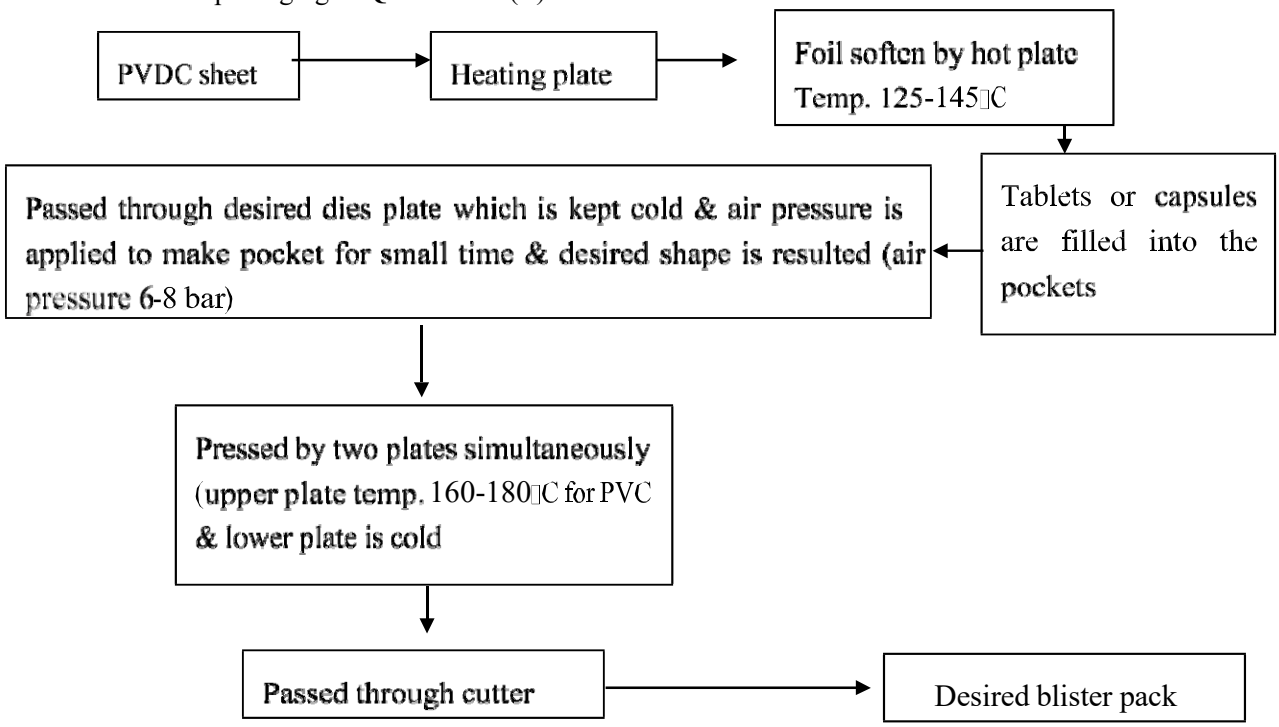
3 . Gansons (strip packaging machine) Gansons Engineers Pvt Ltd, India

Model: G4V

Process:

Blister packaging:

Observed the blister packaging of **Quinox** tab. (C)



Quality Assurance Department (Cepha Block):

Cepha Building is an independent facility so they have a self-sufficient QA unit. Their activity is almost same and will be discussed with QA department of Generic Block.

Calibration, Engineering and Maintenance Department

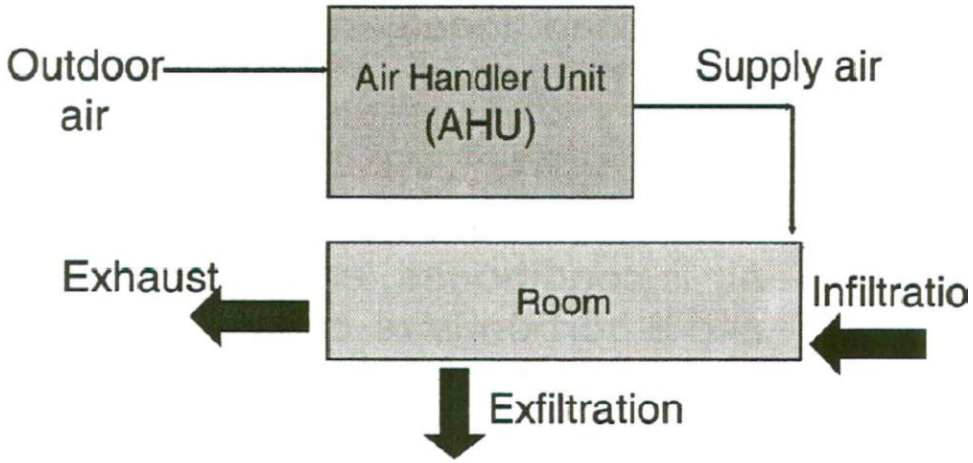
Engineering Department:

SK+F Limited has a strong engineering department, which rendering their services to act as a supportive hand for smooth production

Engineering department:

1. Power house
2. Compressed gas system
3. Chiller system
4. DM Water plant
5. Central heat, ventilation and air conditioning system (HVAC system)
6. Steam generation and supplied plant
7. Effluent treatment plan

Once-thru air schematic



Zoning concept:

Zoning concept is properly maintained in SK+F plant by HVAC system

There are mainly five zones

Zone	Used for
A	**Sterile filling**
B	**surrounding of Sterile filling**
C	**Sterile product labeling & packing**
D	**Non Sterile Production**
E	**Non classified area**

HVAC System:

Total manufacturing area is under HVAC System.

Purified Water System:

SK+F has two water purifying System:

1.Doshion,India(capacity-4000L) 2.Stilmass,Italy(capacity-5000L)

Waste Management System:

Have separate area for waste disposal under the supervision of the authorized person according to the standard operating procedure (SOP) following the direction of WHO guideline.

Effluent Treatment Plant (ETP):

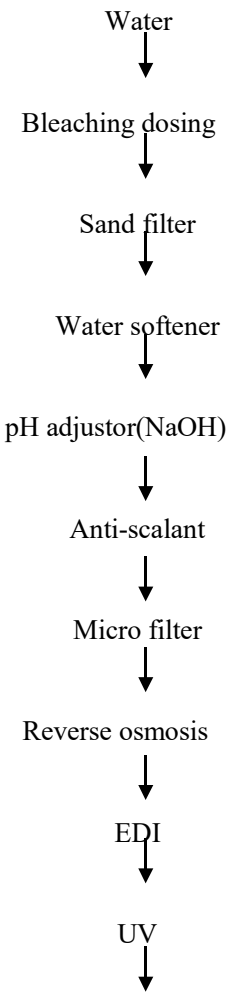
To fulfill the requirements of the regulatory body, new Effluent Treatment Plant (ETP) have been established in the year 2007 & functioning well now.

DM water plant:

SK+F has a well-established DM water plant. At first the water is demineralized by reverse osmosis which reduces the mineral contents about 90% and then passed through the ion exchange resin. The advantages of reverse osmosis are-

- To decrease regeneration time
- To decrease chemical using
- To decrease conductance above 90%

Process:


Water
Bleaching dosing
Sand filter
Water softener
pH adjustor(NaOH)
Anti-scalant
Micro filter
Reverse osmosis
EDI
UV
DM water

Steam generation unit of SK+F (Boiler):

SK+F has the capacity to produce 5.5 tone/hr. This capacity of the boiler is due to proper maintenance of the machine.

Brand: Stilmass

Water is supplied into steam producing tank

↓

Heated at 140 °C

↓

Produced steam

↓

Supplied to respective area where required through Mild-Steel Line

Figure: Boiler

Effluent treatment plant:

SK+F has got MHRA certificate for its environmental policy. So as a part of their, commitment, all the effluents are released after well treatment. SK+F has an effluent treatment plant having capacity of 2.5 L/hr

Effluent Treatment plant consists of:

- Collection tank
- Coagulation and sedimentation tank
- Aeration tank
- Neutralization and disinfectant tank.

Figure: A typical ETP

Process:

Water in collection tank

↓

Alum, lime water, polymer, urea +DAP are added in mixing tank

↓

Coagulation and sedimentation occurs

↓

Decantation

↓

Aeration

↓

Again decantation

↓

Filtration by sand filter (20μ)

↓

Calibration Department:

Disinfection

This department have a crucial role to play. They periodically calibrates all the machine against a definite standard.

Documentation & Validation

Documentation is strictly maintained in SK+F. Everything is well documented here, because it follows this concept that without having documented you did nothing. Each and every stage of the process and method is documented and also validated which ensure the EU-GMP.

The documents which are reserved in SK+F are following-

- Site master file
- Validation master plan
- S.O.P
- Validation protocol
- Specification
- Batch documentation.
- Q.M.S documentation
- Others

Specification contains:

- R.M. specification
- Packaging mteril specification.
- In process specification
- Finished product specification

Batch Document contains:

- BMR
- COFA
- Line clearance
- Cleaned tag
- BPR
- Print outs.

QMS document contains:

- Deviation management
- OOS
- CAPA
- Change control
- Marketing complaint handling
- Rejection
- Audit report

Vendor evaluation Other documentation contains:

- Validation report
- Control direction
- Log books
- Maintenance record
- Calibration record
- Environmental maintenance record.

Validation literally means the act of proving that a process, equipment, method actually works and gives the desired outcome. All the works regarding these validation are compiled in main archive and from there the documents are supplied according to the need of the specific department. So, validation can be classified as follows:

- Process validation
- Method validation
- Equipment validation
- Cleaning validation etc.

Supply Chain Management

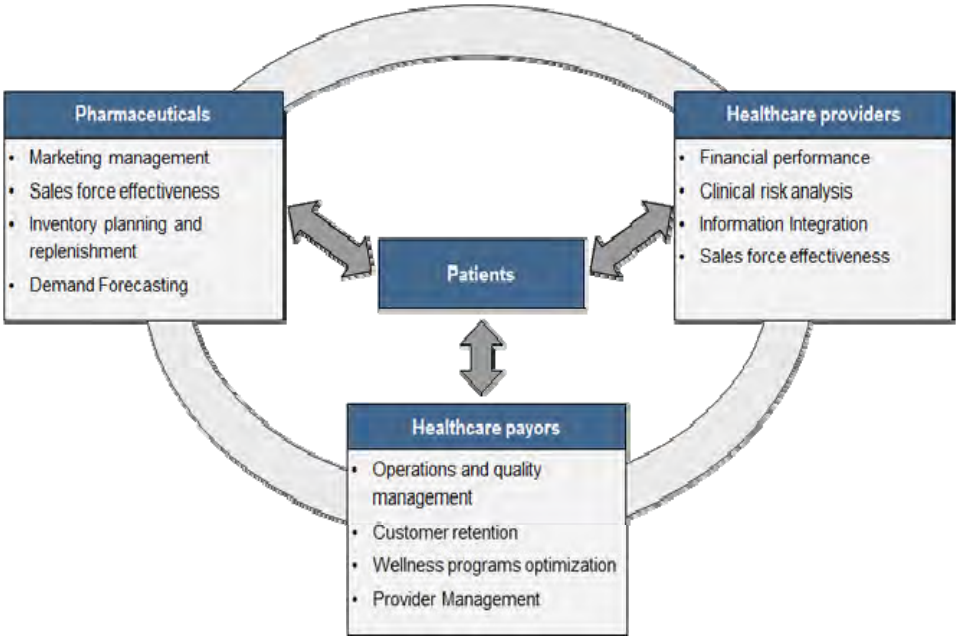
Introduction

Supply Chain Management (SCM) is the process of planning, implementing and controlling the operations of the supply chain with the purpose to satisfy customer requirements as efficiently as possible. Supply chain management spans all movement and storage of raw materials, work-in-process inventory and finished goods from point-of-origin (POO) to point- of–consumption (POC). SCM is a conscious and deliberate control, integration, and management of the business functions. SCM contributes and affects that supply flow through the business for the purpose of improving performance, costs, flexibility etc, which bring the ultimate benefits of the end customers or consumers. The supply chain function includes many sub-areas such as: forecasting and planning, purchasing and procurement, logistics, operations, inventory management, transportation, warehousing, distribution, customer service etc. However, it is difficult to find a standard model of Supply Chain Management operating in the business community particularly in the pharmaceutical sector.

Supply chain management **(**SCM**)** is the oversight of materials, information and finances as they move in a process from supplier to manufacturer to wholesaler to retailer to consumer. Supply chain management involves coordinating and integrating these flows both within and among companies. SCM is both a horizontal business function (i.e. Managing the supply chain in a business) and a vertical industry sector (i.e. Businesses involved in managing supply chains on behalf of their clients). A company may operate as a supply chain services provider within the vertical supply chain industry sector. But each of the clients serviced by a company will employ supply chain staff within their business operating on a horizontal basis across their organizations.

All business needs to forecast and plan. To look forward and predict what will be required in terms of resources and materials in order to deliver their products or services to their customers in a timely manner. In this area we find SCM activities such as demand planning, inventory planning, capacity planning etc. The commercial part of the supply chain is purchasing or procurement. This is where a business identifies suppliers to provide the products and services that it needs to acquire in order to create and deliver its own service or product. Costs and terms of business are negotiated and agreed and contracts are formed. Thereafter the suppliers' performance and future contractual arrangements will be managed in this area. This area of the business is sometimes referred to as purchasing, sometimes, procurement, buying, sourcing, etc. In its strictest definition purchasing is limited to the actual commercial transaction and no more, whilst procurement includes the wider elements of the acquisition, including logistics and performance management.

Figure : Basic Model of Pharmaceutical SCM

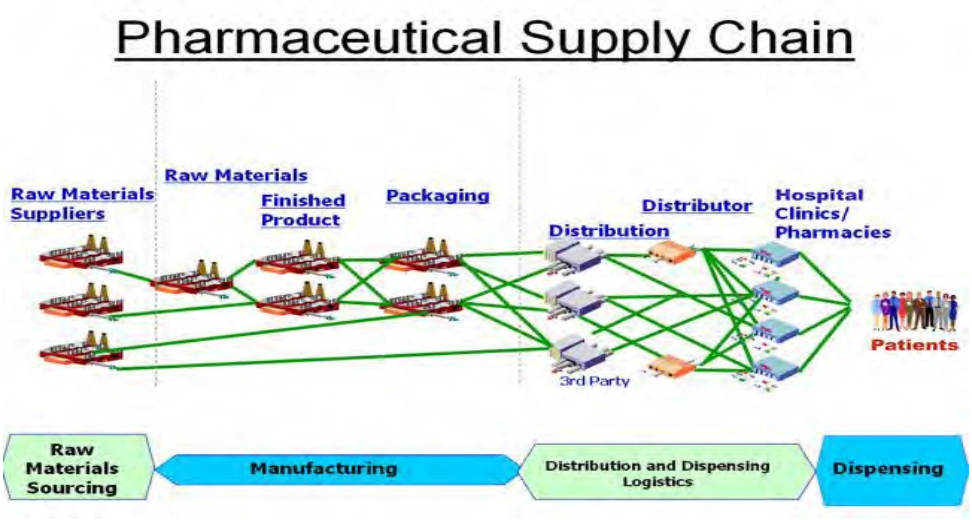


Source: www.slideshare.net/pharma-chain

A General View of Pharmaceutical Supply Chain

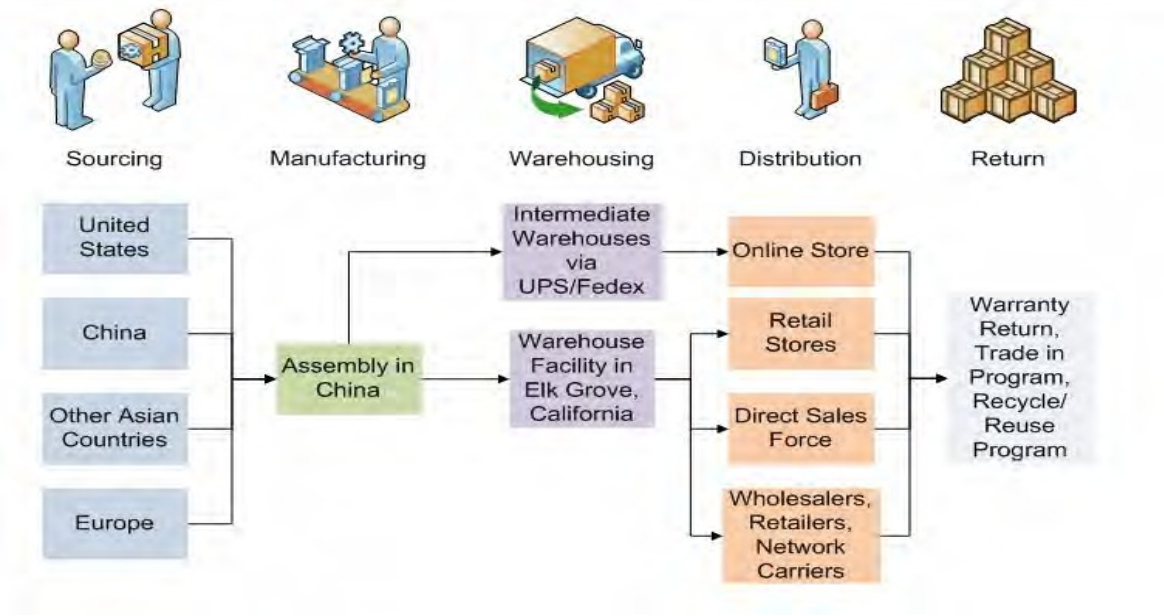
The pharmaceutical supply chain is somehow different from other supply chains of physical goods because of its urgency, importance, storage, transportation, regulation etc. The following figures help understanding the SCM in pharmaceutical sector.

Figure : Pharmaceutical Supply Chain



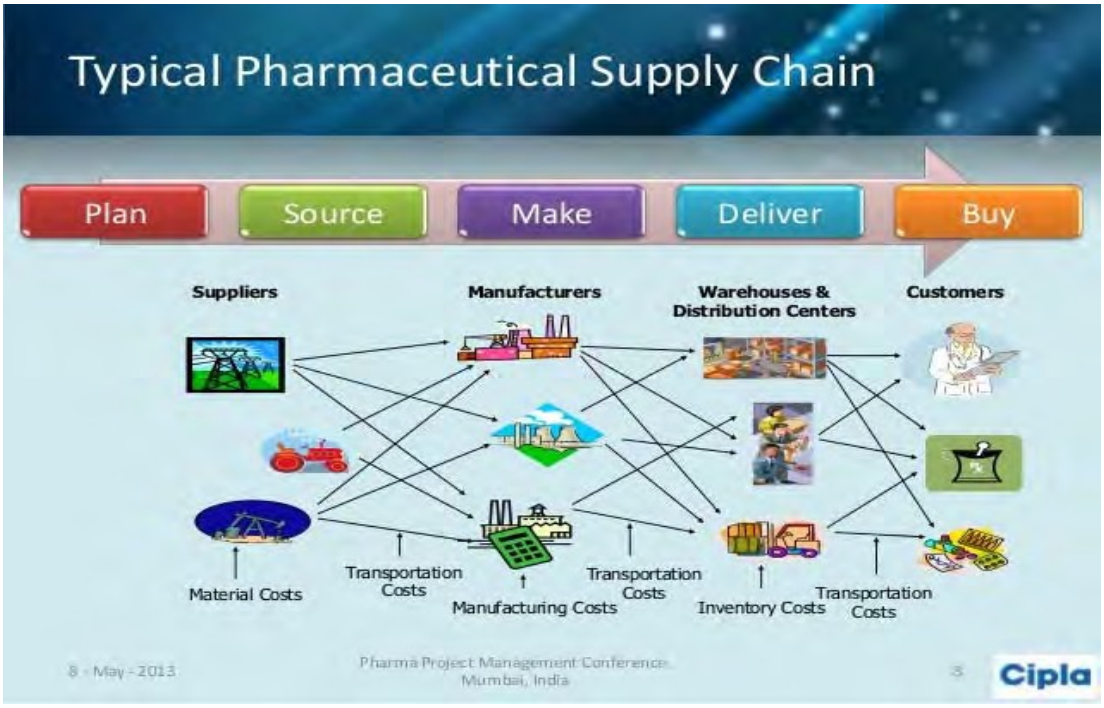
Source: www.slideshare.net/pharma-chain

Figure: Operations of Pharmaceutical Supply Chain



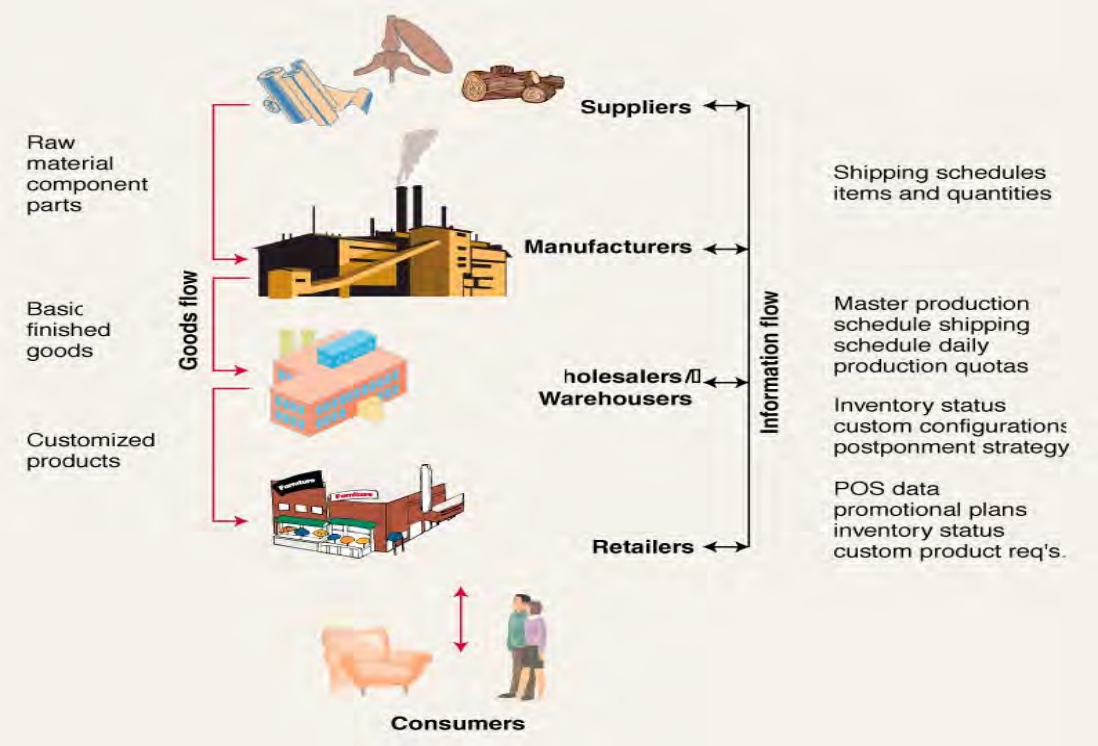
Source: www.slideshare.net/pharma-chain

Figure : Typical Supply Chain Management - Main Components



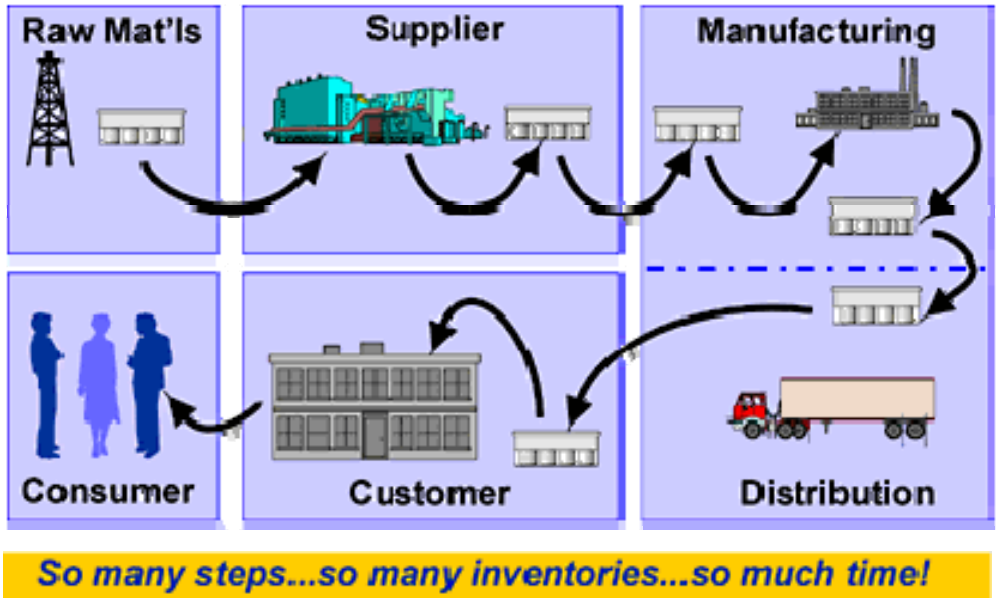
Source: www.slideshare.net/pharma-chain/accessed on 28-12-2015.

Figure : Flow of Goods and Information in SCM Processes



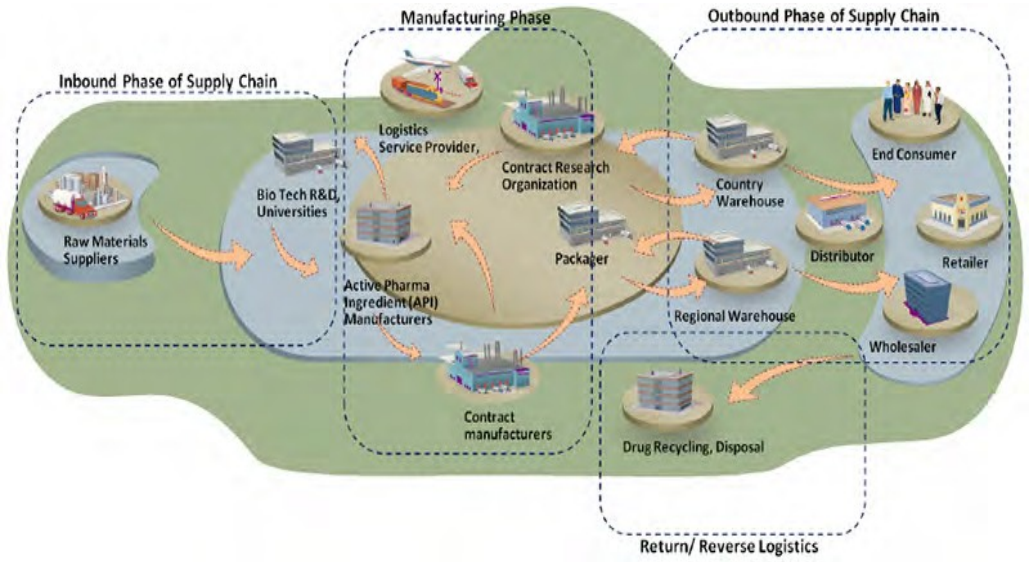
Source: www.slideshare.net/pharma-chain

Figure : Supply Chain Management: Raw Materials to Consumers



Source: www.slideshare.net/pharma-chain

Figure : Extended Pharmaceutical Supply Chain Management



Source: www.slideshare.net/pharma-chain

Figure : Supply Chain Management- Key Issues

Source: www.slideshare.net/pharma-chain

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Local Market Overview

The Bangladesh pharmaceutical marketplace is predominantly a branded generic marketplace. Pharmaceutical firms in Bangladesh can either sell to the private sector pharmacies, to the government and its public health care facilities, or to international organizations operating in Bangladesh (e.g. UNICEF). Bangladesh pharmaceutical industry is mainly dominated by domestic manufacturers. Of the total pharmaceutical market of Bangladesh, the local companies are enjoying a market share reaching around 97%, while the MNCs are having a poor market share. Out of the top ten pharmaceutical companies in Bangladesh, all are local pharmaceutical companies. The top two domestic manufacturers, namely Square and Incepta Pharma are having a combined market share of more than 30% of the total pharmaceutical market of the country.

Bangladesh Association of Pharmaceutical Industries (BAPI) was instituted in 1972, since then BAPI playing a pivotal role in shaping up the industry. Association's member include large, medium, small, national and foreign companies who together are responsible for manufacturing 97% of the country's pharmaceutical production.

Marketing Strategy of Pharmaceuticals in Bangladesh

Marketing is the process by which companies create value for customers and build strong customer relationships in order to capture value from customer in return (Kotler, 2005). Marketing is the backbone of all industries. Though pharmaceuticals produce life saving drugs, they also need marketing. But their marketing is to some extent different from other industries. Some major characteristics of marketing sector are given below:

- Their distributional channel includes invoice system, own distribution channel.
- Medical representatives are the key persons in marketing.
- For promotion, the groups such as doctors, surgeons are targeted.
- Major promotional strategies include printed promotional materials, physical sample, and clinical materials.
- Special incentives are given to the doctors. For example, the doctors are given honeymoon packages, the cost of which is borne by the pharmaceuticals.

The field level executives are playing the imperative role for marketing division. Basically, they have taken the responsibility to market the products of their companies. So, the success of a pharmaceutical industry intensively depends on the efficiency and effectiveness of the medical representatives. If an organization wants efficient employees in this section, he should to satisfy this representative.

Drug Distribution

Bangladesh's drug distribution marketplace is composed of small independent pharmacies. This structure combined with an under-regulated industry, few firms manufacturing pharmaceuticals, and companies competing to sell branded generics based on brand names provides ample opportunity for the sale of low-quality drugs at higher prices. And this partly explains why the quality of drugs available for sale varies significantly in Bangladesh. The pharmacies

sell from 200-22,000 types of medicines each. Each type of medicine has one to twenty five possible brands. Large pharmacies reported buying medicines according to sales trends – e.g. what sells the most. Medium and small pharmacies reported being linked with a medical doctor and thus sales are usually skewed towards that medical professional's preferences. Most pharmacies are individual shops, though some chains are starting to develop, especially in urban areas. On average, each pharmacy visited has 10-50 pharmaceutical firms that supply them medicines on a daily basis.

For example, Beximco Pharmaceuticals has 1,200 people visiting pharmacies daily to take orders for drugs. None of the pharmacies visited will keep restocking any medicine that they consider a slow item. Small pharmacies report of keeping a medicine for a maximum period of six months.

Although there are approximately 300,000 private pharmacies in Bangladesh, the government has only 26,000 pharmacies officially listed. The rest are illegal pharmacies as they have no license / licensed pharmacist on staff. Pharmacists have varying levels of education and many lack adequate training. For example, while the four large urban pharmacies visited each had one professional pharmacist (with four years of coursework), two of the medium-sized pharmacies visited had one person trained for one year along untrained coworkers working as pharmacists. Rural pharmacists can have high school graduates with approximately two weeks training. The Bangladesh Pharmacist Society is currently implementing the first phase of a three-phased program to improve the skills of pharmacists. The three-phased program should be complete in seven to eight years.

While about 95% of the consumers in big pharmacies visited purchase medicines with a prescription, as few as 50% of people in medium and small pharmacies visited have a prescription. If people don't have a prescription, they either come in and ask for a specific drug or come in and describe their ailment to the pharmacist who then makes a diagnosis and recommends a drug on the spot. Popular products include antibiotics of various levels, pain-killers, and gastric remedies. People purchase one to ten tablets or capsules at a time. The amount purchased depends more on the financial capacity of the consumer than on the required dose of medicine.

Performance of pharmaceutical companies as a main player in pharmaceutical supply chain has significant effect on supply chain management efficiency. Risk identification and mitigating them in pharmaceutical companies not only can lead to process optimization, productivity increase and minimizing business risk, but also will help health systems to meet goals of supply chain management; Accessibility, Quality and Affordability. Many risks reported in this study are internal risks due to processes, people and functions mismanagement in a firm which could be easily managed by suitable mitigation strategies. Although only a few of the risks are external ones but their impact on business disruption have not studied. Therefore identifying their risk impacts of risks on business processes and functions and investigating mitigation strategies to manage them should be considered in future studies.

API/Raw Material Production Plant: The major advancement of Bangladesh pharmaceutical sector has been occurred only in the production of finished products. Manufacturing of pharmaceutical products are vastly dependent on imported raw materials, as almost 90% of raw materials are now being imported. This dependency on imported raw materials is resulting in increased production cost of the finished products. Ultimately the competition to offer export prize is becoming tougher, which is one of the major challenges of pharmaceutical sector of Bangladesh. Setting up of a standardized Active Pharmaceutical Ingredient (API) plant is very essential. Local

production of raw materials will greatly contribute to pharmaceutical export to extend export volume, and also can potentially contribute to the country's economy.

Some APIs are now produced within the country, and the range is increasing. The government and industry are jointly planning the development of an "API Park" at Bausia, about 40km from Dhaka, to concentrate API process development and production in a single location. Services and infrastructure (such as an incinerator and an effluent treatment plant), can be shared. Approximately 40 pharmaceutical businesses are likely to establish API production in the Park. There were hopes that the API Park can become operational in 2012.

API Park

Name of the project: API (Active Pharmaceutical Ingredient) Industrial Park Project Project Implementation Period: January 2008 to December 2012 Location of the project: Bausai, Upazila-Gazaria, Dist: Munshigonj (37 Kms. aways from Dhaka by Dhaka-Chittagong highway)

The regulatory authorities of Bangladesh: The documents provided by the Drug Administration of Bangladesh are not impressive; represent the poor status of drug regulatory authority of Bangladesh to the business community and to the regulatory authorities of importing countries. Besides, the website of DGDA is still lacking lot of necessary and up to date information, required and inspected by the business partners and regulatory authorities of importing countries.

Regulated Markets: To register pharmaceutical products in regulated markets it requires highly standardized documents. There are regulations directed by the regulatory authorities of United States of America, European Union, Australia and Japan along with other highly regulated and semi regulated countries. To meet all their requirements sophisticated and accredited manufacturing plant, standardized manufacturing process, proper quality control and above all highly skilled professionals are required. It is tough to meet all the requirements by small pharmaceutical companies of Bangladesh.

Medicine export should be emphasized to LDCs than any other countries: Some companies are aggressive to enter the highly regulated overseas markets, such as, USA, Australia, Europe, Canada, France, and Golf countries. But the practical observation is that getting export status to those countries requires huge investment in the manufacturing plant to achieve certification from different international drug regulatory authorities, highly sophisticated documentation, and huge initial capital investment. Actually the export volume to the highly regulated countries will not be easily feasible; rather we can perform pretty well and can potentially increase our export if the exporters become more attentive to LDCs. Among 50 LDCs, only Bangladesh has its strong fundamental and modern manufacturing base, hence we can easily share the drug market of rest of the LDCs. So, considering the practical situation, the LDCs should be the targeted markets of our pharmaceuticals, of course, side by side, moderately regulated and highly regulated markets may be explored gradually. However, we can establish joint-venture, tool manufacturing, and contract- manufacturing business with the companies of developed countries, not only for exporting medicines.

Establishing Export cell by the govt./private Consultancy firms may promote Pharma export: Government can establish specialized Export Cell to promote exports of pharmaceuticals to grab and capitalize the huge export opportunities in LDCs. Some private Consultancy firms having experience and expertise in drug export

professionally can be ngaged to assist the pharmaceutical companies who do not have the technical and expertise know-how to go through the entire process of export, or have lacking in documentation skills or even do not have the skilled man power to deal with the drug export. Thus, Consultancy firms can play a significant role to explore export to maximum countries, accelerate export activities, and to reduce the overall cost of export. Even some small companies having International Marketing Department (IMD) can explore the benefits of outsourcing by hiring Export Consultants to reduce its overhead expenditure and make a comparative study of cost- benefit ration to justify having IMD.

Export of Pharmaceutical Products

Pharmaceutical exports from Bangladesh rose 15.65 percent year-on-year to Tk 553.3 crore in fiscal 2013-14 due to growing global demand, high quality products and competitive prices. Demand for Bangladeshi pharma products is growing in Asia, Africa and European markets as manufacturers follow international standards that ensure better quality. Exports grew 24 percent to Tk 478.4 crore in 2012-13 from the previous year, according to data from the Export Promotion Bureau. Bangladeshi medicine makers meet 98 percent of domestic demand and export to 88 counties. The country exported 30 pharmaceutical items in fiscal 2013-14. The sector incurred losses in the first six months of last fiscal year due to internal problems which almost broke the supply chain down.

The major problem is Bangladesh import raw materials due to lack of an API park in Bangladesh. India has API park and as a results it can offer competitive price in global markets compared to Bangladesh. As Bangladesh exports medicine to Europe which is known as stringent regulatory standards it gives impetus to our pharma industry and creates awareness among global customers particularly from emerging and developed markets. Although Southeast Asia and Africa are traditionally Bangladesh's major markets for generic drug exports leading companies have now focused on advanced markets. Top companies have registered products in countries like Netherlands, Latvia, Azerbaijan, Costa Rica, Estonia and Lithuania.

Supply chain management of Eskayef Pharmaceuticals Ltd.

The pharmaceutical supply chain is the means through which prescription medicines are delivered to patients. Pharmaceuticals originate in manufacturing sites; are transferred to wholesale distributors; stocked at retail, mail-order, and other types of pharmacies; subject to price negotiations and processed through quality and utilization management screens by pharmacy benefit management companies (PBMs); dispensed by pharmacies; and ultimately delivered to and taken by patients. There are many variations on this basic structure, as the players in the supply chain are constantly evolving, and commercial relationships vary considerably by geography, type of medication, and other factors. The pharmaceutical supply system is complex, and involves multiple organizations that play differing but sometimes overlapping roles in drug distribution and contracting. This complexity results in considerable price variability across different types of consumers, and the supply chain is not well understood by patients or policymakers. Increased understanding of these issues on the part of policymakers should assist in making rational policy decisions for the Medicare and Medicaid programs.

Supply chain stages of Eskayef Pharmaceuticals Ltd

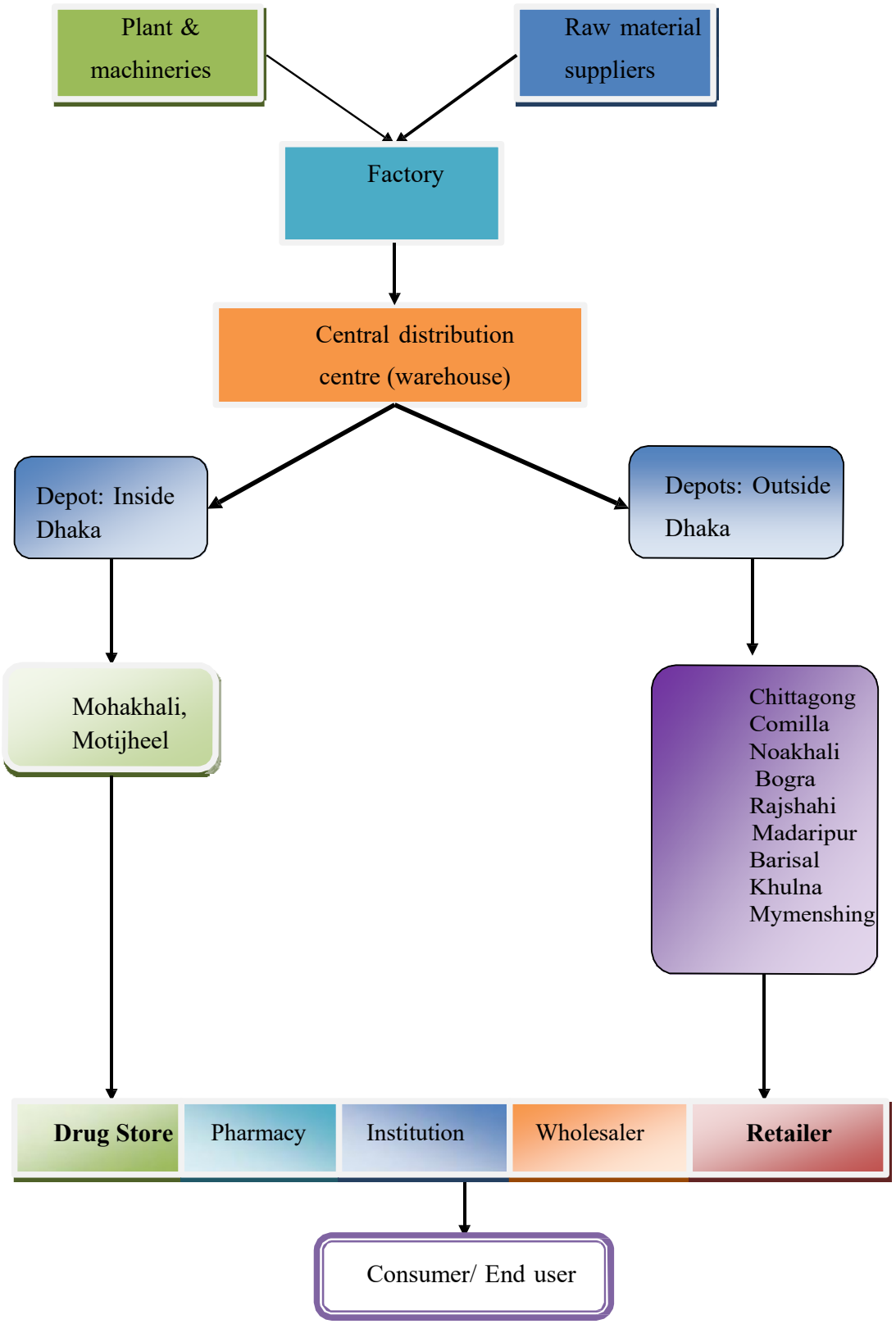
A supply chain consists of all parties involved, directly or indirectly in fulfilling customer's requirement. It includes not only manufacturers and suppliers, but also transporters, warehouses, retailers and customers themselves.

The key players and their financial relationships-

- Pharmaceutical Manufacturers:
- Wholesale Distributors:
- Pharmacies:
- Pharmacy Benefit Managers (PBMs)

Distribution channel of SK+F is shown in Figure:

Figure: Distribution Channel of SK+F



Suppliers of SK+F

Major raw materials of SK+F include many different types of dyes and chemicals. Suppliers of this company are Weifang Shengtai, MSM Prai Berhad, Sainor, Magaldrate, Active Fine Chemicals Ltd, MEGAWIN, Implex Corporation, Drug International Ltd etc. provides these raw materials. Plant & machineries are imported from India, U.K, China, Taiwan, Korea, Japan by SK+F.

Table 3.4: Source of Major Raw Materials Procurement

Name of Items	Suppliers	Quantity(Kg)
Dextrose	Weifang Shengtai Pharmaceutical Inc., is a leading producer of pharmaceutical-grade glucose in China. The company estimates that its pharmaceutical glucose products account for about sixty percent of the total China pharmaceutical glucose market.	570000
Sugar	MSM Prai Berhad (*formerly known as Malayan Sugar Manufacturing Company Berhad*) operates the Prai sugar refinery in Penang. Located on the northwest coast of Peninsular Malaysia, the facility is the country's largest sugar refinery with an annual production capacity of 960,000 tonnes of refined sugar, accounting for up to 86% of MSM's total production capacity.	1500000
Omeprazole Pellets	SAINOR Established in the year of 2005, and today it is one of the fastest growing organizations in the niche area of drug loaded pellets. With combination constant product innovation and adaptation to suit the spirit and intent of customer requirements, constructed according to WHO GMP Specifications. The people behind this organization are young technocrats with an ambition to make SAINOR one of the topnotch companies in INDIA, to make a mark in the NATIONAL SECTOR and became a force through exports to Global Markets.	153000
Magaldrate	SPI Pharma is a global leader serving over 55 countries in the manufacture and marketing of antacid actives, excipients, taste-masking technology, drug delivery systems for tablets, fast-dissolve technologies, chewables, lozenges, and a variety of other patient- friendly dosage formats. SPI also specializes in drug development services, delivering in-vitro data packages in CTD Module 3.2 format.	128800

Source: SK+F Main Office, Dhaka

Manufacturing Facilities: Located at Tongi (outskirts of Dhaka city), Mirpur and Bhulta, Rupganj SK+F's manufacturing site is spread over an area of 20 acres which houses a number of self-contained production units including oral solids, metered dose inhalers, intravenous fluids, liquids, ointments, creams, suppositories, ophthalmic drops, injectables, nebulizer solutions etc. The bulk drug unit for producing paracetamol is also located within this site. SK+F has its own utility infrastructure to ensure adequate generation and distribution of purified water at all times.

The manufacturing and packaging facilities have been designed to minimize generation and maximize containment of dust particles using closed transfer system and clean in place facility. All practicable measures have been taken to ensure that members of the staff are not exposed to unacceptable concentrations of dust particles. Process area, cubicles, storage area have been connected to vacuum dust cleaning. The design of the plant ensures automated materials handling systems and multilevel designs to enable gravity feed between processing stages. The building design has also allowed maximum engineering maintenance access without entering into the production areas.

Warehousing: Storing of raw and packaging materials to meet the requirements of production and also storing and dispatch of finished products as per concept of Good Storage Practice of pharmaceuticals per concept of Good Storage Practice of pharmaceuticals. After manufacturing, SK+F stores these products in their warehouses.

Depots: Then, from the storehouse TDCL distribute these products to its depots inside and outside Dhaka. SK+F can achieve responsiveness to customers demand by locating large inventory in the depots to the customers. This distribution centers distribute them to a variety of customers, including pharmacies (retail and mail-order), hospitals, and long-term care and other medical facilities (e.g., community clinics, physician offices and diagnostic labs). SK+F is successfully operating distribution of medicine throughout 54 districts out of 64 districts in Bangladesh.

Retailers (Pharmacy): After that, SK+F provides the medicine to many pharmacies all over the country. Pharmacies are the final step on the pharmaceutical supply chain before drugs reach the consumer/patient. Pharmacies purchase drugs from distribution centre and MPO's and occasionally directly from manufacturers, and then take physical possession of the drug products. After purchasing pharmaceuticals, pharmacies assume responsibility for their safe storage and dispensing to consumers. Pharmacy operations include maintaining an

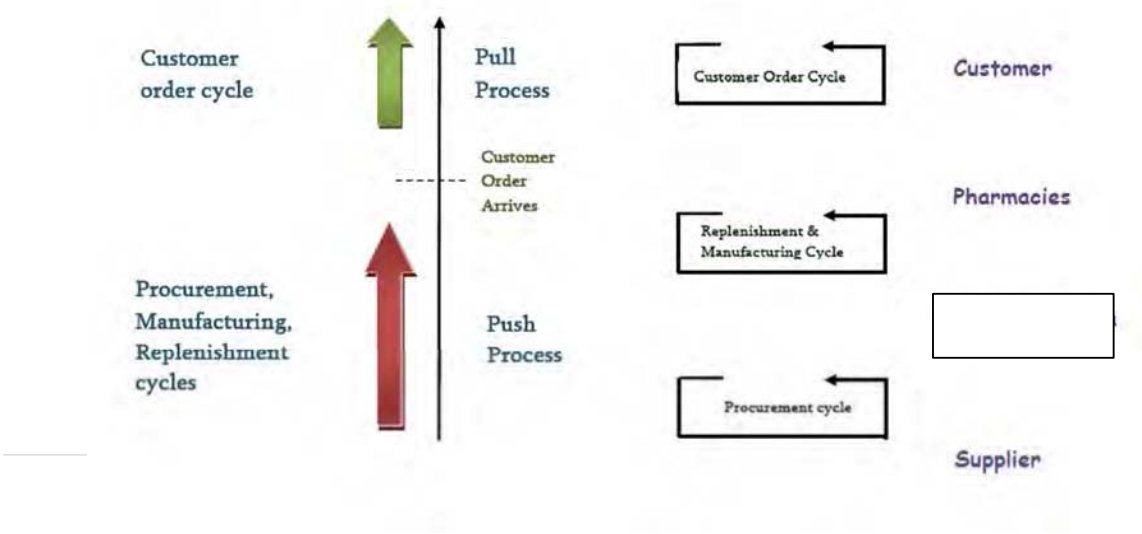
adequate stock of drug products, providing information to consumers about the safe and effective use of prescription drugs, and facilitating billing and payment for consumers participating in group health benefit plans.

Consumers: The ultimate destination is consumer. For different promotional activities, the doctors prescribes medicine to the customers and customers can get the medicine from many pharmacies and drug stores of hospitals.

Push/Pull view of the supply chain of Eskayef Pharmaceuticals Ltd.

All the processes in a supply chain fall into one of two categories depending on the timing of SK+F's execution related to end customer demand. With pull process, execution is initiated in response to customer order. With push process, execution is initiated in anticipation of customer orders. Therefore, at the time of execution of a pull process, customer demand is known with certainty, whereas at the time of execution of a push process, demand is not known and must be forecasted. Push processes operate in an uncertain environment because customer demand is not yet known. Pull processes operate in an environment in which customer demand is known.

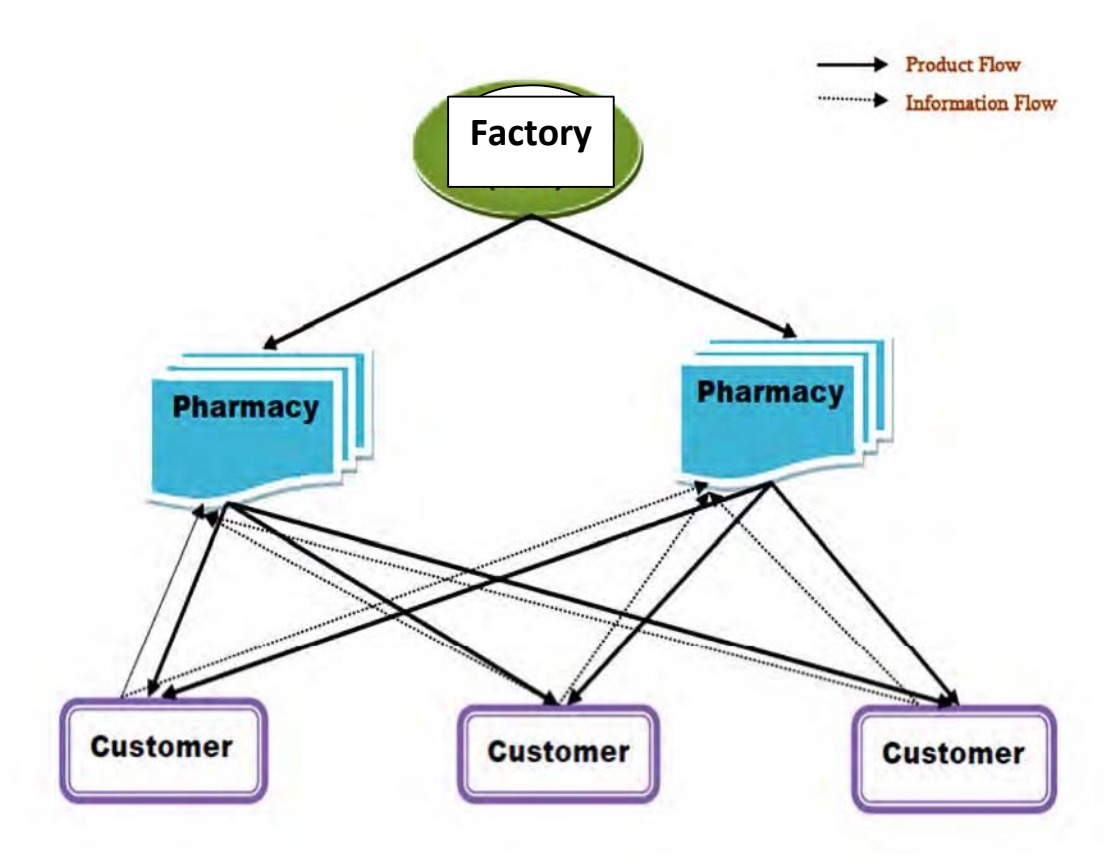
Here, SK+F Pharmaceuticals execute all process in the customer order cycle before the customer arrives. So, all the manufacturing activities procurement cycle, replenishment cycle are performed in anticipation of demand and are thus push process. The goal of replenishment cycle is to ensure product availability when a customer order arrives. In fact, raw materials such as chemicals are often purchased six to nine months before customer demand is expected. SK+F produce the medicine three to six months before the point of sale. And all processes that are part of the customer order cycle are pull process. The order fulfillment takes place from product in inventory that is built up in anticipation of customer orders. SK+F is often constrained by inventory and capacity decisions that were made in the push phase. The processes in the SK+F Pharma supply chain break up into pull and push processes, as shown below:



Design option for a distribution network of SK+F: Distribution refers to the steps taken to move and store a product from the supplier stage to a customer stage in the supply chain. Distribution is a key driver of the overall profitability of a firm because it affects both the supply chain cost and the customer experience directly.

Manufacturer storage with carrier delivery: Here, SK+F follows "Manufacturer Storage with Carrier Delivery" design as distribution network system. Under this option, inventory is held by SK+F in their depots and store house, and then distribute the medicine to many pharmacies all over the country by the delivery van of SK+F. Then, the customers get the medicine through these pharmacies. Pharmacies as retailer carry no inventories. Information flows from the customer, via the retailers to SK+F.

Figure: Product Flow and Information Flow



Performance Characteristics of manufacturer storage with carrier delivery of SK+F: The supply chain strategy determines how the supply chain should perform with respect to efficiency and responsiveness. The supply chain of SK+F must use three logistical and three cross-functional drivers to reach the performance level the supply chain strategy dictates and maximize the supply chain profits. The ideal supply chain will emphasize efficiency but also maintain an adequate level of responsiveness. The biggest advantage of manufacturer storage with carrier delivery is the ability to centralize inventories at

SK+F. It can aggregate demand across all retailers that it supplies. The key issue with regard to manufacturer storage with carrier delivery is the ownership structure of the inventory at the SK+F. The benefits from centralization are highest for high value, low demand items with unpredictable demand.

Table 3.5: Factors and Performance

Cost Factor	Performance
Facilities & handling	➢ Lower facility costs because of aggregation. ➢ Some saving on handling costs as CPL can manage small shipments or ship from production line. ➢ Increase efficiency at each distribution channel.
Inventory	➢ Lower costs because of aggregation. ➢ Benefits of aggregation are highest for low demand & high value medicines.
Transportation	➢ Higher transportation cost because of increased distance & disaggregate shipping and to keep responsiveness.
Information	➢ Significant investment in information infrastructure to integrate manufacturer and retailer.
Service Factor	**Performance**
Response time	➢ Quick response time because of availability of Medical Promotion Officers. ➢ Response time may vary by complicating receiving.
Product variety	➢ Allows a high level of product variety to be available to the customer.
Product availability	➢ Easy to provide a high level of product availability because of aggregation at CPL.
Customer experience	➢ Good in terms of delivery at pharmacies with drop shipping.
Time to market	➢ Fast, with the product available as soon as the first unit is produced.

No of Foreign Suppliers of Raw Materials and Major Items of Procurement

Table: Number of Foreign Suppliers

Year	. of Foreign Suppliers	% increase
2010	180	-
2011	185	2.78
2012	204	10.27
2013	270	35.35
2014	356	31.85
2015	375	5.33

Source: Eskayef Main Office, Dhaka

Total Import Raw Materials during last Five Years

Table: Total Import Raw Materials during last Five Years.

Year	Imports (in Million US$)	Growth Rate (%)
2011	22.30	-
2012	25.45	14.13
2013	32.27	26.80
2014	34.61	7.25
2015	41.02	15.52

Source: Eskayef Corporate Office, Dhaka

Yearly Sales of during the last Five Years.

Table: Yearly Sales of during the last Five Years.

Year	Sales in Crore	Growth Rate (%)
2011	451	-
2012	573	14.13
2013	618	26.80
2014	740	7.25
2015	855	15.52
2016	1050	22.80

Source: Eskayef Corporate Office, Dhaka

Steps of Raw Materials Import Procedure

Eskayef Pharmaciticals Limited has been maintaining the following steps for imports of required raw materials:

Material Requirements Planning (MRP)

MRP is a planning and inventory control system used to manage manufacturing processes. It provides answers for questions e.g. what items are required? How much quantity is required and when are they required? Procurements of required raw materials usually start once they received MRP.

Block List

After getting MRP they have to apply for block list permission and it is must for each imported raw materials which is usually held twice in a month and it is authorized by the drugs regulatory department.

Block List Amendment

If the price varies from the block list they have to apply for the amendment usually takes seven working days or more for low price amendment and if they require high price amendment then they have to wait for the next block list meeting.

Pricing

After that they have to ask price from their approved sourced through their local agent, sometimes they collect the price directly from the supplier if there is no local agent.

Vendor Selections

They usually select the vendors carefully after checking price feasibility and other compatibilities

Asked for Indent or Proforma Invoice

After the proper selection of source they have to ask for the Indent or PI which is issued by the local agent or supplier or manufacturer.

Approval from Quality Assurance

They send the PI/Indent to the QA department through fax/e-mail for getting approval from General Manager of QA department.

Purchase Order

Once they received the approval they have to make purchase order in ACCPAC.

Apply for Cover Note

They should apply for cover note which usually takes two or three working days.

L/C Proposal: In the mean time they have to make L/C proposal which must be signed by Import Manager and General Manager (Commercial)

L/C Typing

After that they have to arrange for L/C typing.

Signing

Once the typed L/C is received at their end, they should check it very carefully and do the correction where there is any mistake found and then they have to send it for signing.

Sending L/C Application to Bank

Then they arrange to send the signed L/C application to the bank with keeping proper copies in their respective files.

Draft L/C

After sending L/C application to the bank they have to wait for draft L/C which usually takes two working days.

Final L/C Confirmation

They have to confirm L/C by sharing it to the suppliers, after deleting or adding clause in accordance with suppliers they have to arrange it to swift and share it to the supplier.

Following up with the Source/Supplier

They should follow up regularly with the suppliers to get the materials on due time.

Document Processing

Once the shipment has been made they have to process the shipping documents as follows:

(i) Drug Clearance: After getting the shipping documents they have to apply for drug clearance to the drugs regulatory department anf usually it takes two days to get permission from the drug authorities.

(ii) Marine Policy: They usually apply to the Insurance Department to get policy and a single day is required for getting it.

(iii) Shipping Guarantee (for Air Shipment): if the mode of shipment is by air then they should apply for shipping guarantee to the bank with the non-negotiable copy and the application should be duly sign by their authority.

(iv) Retirement(for sea shipment): if the material is shipped by sea then they have to apply to the bank for teturing the original documents after getting the conformation from the bank and application of retirement must be properly signed by our respective authorities.

(v) Customs Clearance: Once they received all the documents which is required they usually go for customs clearance and arrange to take over customs documents to their C & F agent accordingly.

Receiving and Inspecting Materials: Receiving Report is issued after getting the RM at their warehouse and after receiving the RM their QC or warehouse department confirm them whether there is any rejection or not.

Compensation or Insurance Claim: If they found there is any rejection then they have to go for compensating with the supplier or insurance claim which depends on some factors.

Compensation: If they receive complain regarding the quality of the RM then they have to arrange the compensation from the suppliers which is related to the following steps:

(i) Firstly they inform the suppliers over the mail regarding the quality issue.

(ii) If they agreed with them (SK+F) then they fix the amount of compensation with proper discussion to their accounts department which considers the whole cost including landed cost.

(iii) Suppliers usually provide the payments by cheque and then it goes to the accounts

department with taking proper copies in their file for further inspection.

(iv) In the mean time they have to arrange to send the faulty RM back to the suppliers.

(v) Sometimes the suppliers can arrange to make compensation by adjusting with the next consignments.

(vi) **Insurance Claim:** if they get company regarding other than the quality issues e.g. loss or damage of the materials they should go for the insurance claim which considers the following steps:

(i) Firstly complain have to raise from the QC department

(ii) Then they usually notify the insurance company over the claim letter

(iii) Physical inspection has been made by the third party who is organized by the Insurance Company.

(iv) They have to provide the necessary documents required by the third party.

(v) In the mean time Insurance Company will arrange to send the prejudice letter.

(vi) They have to share it along with the other documents which are required by the insurance company.

(vii) Insurance company will arrange to provide Loss on Voucher and they have to send it back to the insurance company with proper signing from their authorities with retaking a copy in their file.

(viii) Finally, the cheque is received from the insurance which should share it with the accounts as well.

C & F bill Processing: This is the final step of import procedure. After receiving the C & F bill they have to prepare the bill to submit the accounts department.

File Closing: After processing the bill they have to close the file and keep it at record room.

Export Procedure of SK+F pharmaceutical products to abroad

The export procedure of Pharmaceutical products differs from the export of the other products mainly from the regulatory points. The products are to be first registered in the respective countries which may take at least two years or more. After successful negotiation with the prospective partners in the respective countries and product registration we receive the Purchase orders from the importers. We collected export permission from the DGDA and ship the goods. Unlike other consumable products Pharmaceutical products needs heavy promotions to the prescribers.

Major export destinations are Afghanistan, Myanmar, Sri Lanka, Nepal, Philippines, UAE etc. The total

exports of pharmaceutical products are shown in Table-:

Table: Total Export of Pharmaceutical Products during last five years.

Year	Export (in Million US$)	Growth Rate
2011	1.0	-
2012	1.6	60.00
2013	2.1	31.25
2014	2.6	23.81
2015	2.8	7.69
2016	2.9	8.07

Source: SK+F, Corporate Office, Dhaka

Distribution System

All medicines and medical products of Eskayef are being distributed by Transcom Distribution Company Limited (TDCL) which is also a sister concern of Transcom group. TDCL has the largest independent distribution setup in Bangladesh with full infrastructural facilities provided by a countrywide network of 30 branch offices along with one main office, warehouses and delivery vans, directly servicing over 8000 outlets throughout the whole country. TDCL is an allied business company of TRANSCOM Groups responsible for distributing multi-dimensional products across the country.

The company started its business with the distribution of quality pharmaceutical products manufactured by ESKAYEF, NOVO NORDISK, SERVIER, ALLERGAN And consumer brands like Frito Lay, Heinz, Wrigley, Mars, Energizer, Schick, L'Oreal, Garnier, ConAgra Foods, McVities and Hemas. It started its diagnostic distribution division in 1993 by distributing laboratory equipments and reagents from Hettich (Germany), TREK Diagnostics(USA) and Fortress(UK). It also distributes crude oil and oil products from Vitol. Basically TDCL has twenty six distribution divisions.

Table: Main Distribution Centers of TDCL

Division	Distribution Centers
Dhaka	Dhaka South, Dhaka North, Narayangonj, Savar, Keraniganj, Bhairab, Kishoreganj, Tangail, Gazipur, Faridpur
Chittagong	Chittagong South, Chittagong North, Camilla, Noakhali, Chandpur, Cox's Bazar, Feni
Khulna	Khulna, Jessore, Kushtia
Rajshahi	Rajshahi, Pabna, Bogra
Sylhet	Sylhet, Moulovi Bazar
Barisal	Barisal, Patuakhali
Rangpur	Rangpur, Dinajpur
Mymens	Mymensingh

Sales Department of Eskayef Pharmaceuticals Ltd

The sales department of SK+F has been functioning with the key personnel which is shown in the Table:

Table : Personnel of Sales Department

Position	Reporting Officer	umber of Persons
Director (Sales)	Managing Director	1
Zonal Head	Director (Sales)	6
Regional Head	Zonal Head	36
Field Manager/ Area Manager	Regional Head	282
Medical Services Officer	Manager/ Area Manager	2022

The key responsibilities include**:**

OPERATIONAL

- Achieve Team sales target through Prescription generation.
- Ensure implementation of marketing & sales strategies provided by H.O. / Respective Department.
- Cross check up to grass root level- the activities of Team members in order to ensure
- optimum utilization of Company resources.
- Keep up to date information & convey it to H.O about each & every territory within the region & review action plan / strategies in response to changing market environment.
- Prepare & submit Daily call reports, feedback & market reports to the concerned
- person / Department in time (following day).
- Keep good relation with all the customers & commendable relation with **"A"**
- potential customers (Sp. Doctors) throughout the assigned territory.
- Keep very good rapport with the key persons of different organizations- (BMA, BPMPA, BCDS etc) in the territory. Disseminates related information in time to next level superior, so that appropriate measures can be taken.
- Keep all information of the competitor's activities, especially Sales & marketing strategies.
- Ensure effective time management & result oriented call by all Team members.
- Penetrate 100% of your territory to know all out of the market situation & effective product positioning by your Team members.

Recommendation

- Boost capacity by reducing excessively long changeover times and cleaning cycles
- Create a culture that identifies and solves problems where and when they occur
- Avoid unnecessary capital expenditures while ensuring product availability
- Eliminate unplanned equipment downtime
- Align regulatory compliance processes with requirements
- Simplify paperwork processes prior to automation
- Reduce excessive energy costs
- Engage and empower employees to ensure ownership, reduce high turnover, and improve quality
- Rapidly and effectively integrate new acquisitions

Conclusion

Access to medicine as a human right is one of the main objectives of healthcare systems. Pharmaceutical operation and supply chain should provide medicines in the right quantity, with the acceptable quality, to the right place and customers, at the right time and with optimum cost to be consistent with health system's objectives and also it should make benefits for its stockholders. Any risks affecting the pharmaceutical supply chain, not only can waste the resources but also can threaten the patients' life by hindering access to medicines. Risk management is not only important in the pharmaceutical operations, but also is a major player in other aspects of pharmaceuticals such as prescription and uses of medicine. Assessing and implementing the strategies to manage the risks in pharmaceutical supply chain is essential in health systems. The importance of the risk management is becoming more vital because medicine is a highly regulated product which is under the controls and tight limitations of public regulatory authorities. Also production and supply of medicines as strategic goods in developing countries with much economic, social and political instability is faced with more uncertainties and vulnerabilities.

Operation and Supply chain risk management (SCRM) is a crucial and indivisible part of managements to achieve mentioned objectives. These activities attempts to minimize operation and supply chain vulnerability and uncertainties through mitigation plans. Therefore it is essential to identify, assess and prioritize all risks to reduce and control the probability and impacts of unfortunate events. It is aimed to managing the risks in a complex and dynamic supply and demand networks.

Various works have been reported regarding different aspects of operation and supply chain risks and risks management in the manufacturing sectors. In pharmaceutical sector, although there are some review studies in operation and supply chain risk management with focus on counterfeit, production and supply chain logistics, quality assurance and enterprise risk management but there is not any systematic review on the pharmaceutical risk management with perspective of manufacturers' risks; meanwhile, there are some systematic reviews on in other industries.

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