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CURRENT AND FUTURE TRENDS IN THE QUALITY CONTROL OF PHARMACEUTICALS AND BIOPHARMACEUTICALS: IMPACTS ON COST OF GOODS SOLD (COGS)

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There's time and season for every purpose under heaven…(The Bible)

1. INTRODUCTION

Government and private spending in the healthcare sector has grown significantly in the past decades and continues to grow.
The contribution of the cost of pharmaceuticals to this growth is not negligible, notably due to the increased capabilities of medicine and the development of new technologies in the healthcare sector.

Whilst governments are taking steps to control the rising cost of healthcare, the pharmaceutical industry is faced with the problem of products that will lose patent protection over the next few years, fuelling the urgent need to improve its ability to innovate.
Generic manufacturers with their low cost manufacturing operations are already capitalizing on these opportunities in the pharmaceutical industries while considerable efforts are in progress to do so in the biopharmaceutical sector.
On the other hand, issues like globalization and personalized medicine are bound to radically change the playing field for companies and will force them to reconsider their strategies and question their competitive advantage.
These factors, among others is putting the industry under pressure to cut development, manufacturing and distribution costs by placing increased emphasis on quality and manufacturing efficiencies.
According to the Center for Drug Evaluation and Research (CDER), the current good manufacturing process allows about 10% waste - an error rate that would be unacceptable in many other industries.

Data compiled by PricewaterhouseCoopers (PwC) argues that the pharmaceutical industry often runs plants at 15 per cent or less capacity, accepts that between 5 and 10 per cent of production will need to be scrapped or reworked, and that quality control takes up more than 20 per cent of total production costs[1,2].

Another study revealed that when compared to other manufacturing sectors, internal production efficiency in the pharmaceutical industry is not high, with significant batch rejection rates up to 30% due in part to a lack of true process understanding and inappropriate approach to quality control.

A report presented by Xcellerex during the IFPAC conference in 2005 estimated a total of US$3.6B spent on manufacturing out of specification drugs[3].

Effective and efficient approach to Quality Control and Assurance of pharmaceuticals will go a long way to reduce cost due to waste and batch rejection with significant consequences on the COGS.

COGS were estimated to be $145 billion based on the assumption that COGS is equal to 27% sales for brand name pharmaceuticals. (The estimate of global pharmaceutical sales in 2005 is $602 billion according to the IMS Health Prescription drugs Report 2006).

Today, there is an urgent need for industries to use their existing resources to address the fundamental challenges facing it by investing in innovative development and manufacturing processes to guarantee their continued existence.

The aim of this project is to explore the impacts of new approaches to quality control and management in the pharmaceutical and biopharmaceutical industries and their impacts on the manufacturing costs.

COGS reduction will have significant impact on the cost of pharmaceutical products and contribute to the overall reduction in the rising cost of healthcare and improve drug availability by :

1. Directly impacting the market price of pharmaceuticals
2. Increased availability of funds that could be diverted to drug research and development

Future approaches to routine Quality Control and management of pharmaceuticals will include:

1. Risk assessment based on comprehensive understanding of the manufacturing process in order to identify the points with critical impacts on the quality of the product.
2. The exploration and implementation of new sensing and control technologies that will allow critical product and process variables to be monitored continuously and controlled automatically.

These approaches coupled with others to be discussed in details in chapter five of this study will dramatically reduce the current industries' wasteful reliance on quality control via end of production testing and off-specification rejection.

1.1 OBJECTIVES

1. Identify the burden of routine Quality Control of pharmaceutical and biopharmaceutical products on COGS.
2. Evaluate the impacts of the current QC approach on COGS.
3. Evaluate how the implementation of new approaches to Quality Control and management could influence the COGS.

1.2 SCOPE

1. Routine quality control of marketed pharmaceutical and biopharmaceutical products.
2. Validation and stability studies are not included in this study.

2. ROLES OF QUALITY CONTROL IN THE PHARMACEUTICAL AND BIOPHARMACEUTICAL INDUSTRIES

Quality Control is a process employed to ensure a certain level of quality in a product or service.

The concept of quality control has been applied since the middle ages and it has greatly evolved during the industrial revolution period and during the two world wars to its modern day concept.

To a pharmaceutical manufacturer it implies a detailed system of inspection and control covering the evaluation, production and distribution of every drug, with the objectives to produce medications of superior efficacy and safety and to provide assurance to the physician, the pharmacist and the consumer that a given product performs uniformly and in a satisfactory manner for the purpose for which it is recommended.[4]

The pharmaceutical quality control laboratory serves one of the most important functions in pharmaceutical evaluation, production and distribution[5].

The EU GMP guidelines requires that each holder of a manufacturing authorization should have a Quality Control Department which should be independent from other departments, and under the authority of a person with appropriate qualifications and experience, who has one or several control laboratories at his disposal, in addition adequate resources must be made available to ensure that all the Quality Control arrangements are effectively and reliably carried out.
A significant portion of the FDA's 21 CFR part 211 pertain to the quality control laboratory, its organization, legal responsibilities and product testing.[6]

Some of these responsibilities are clearly detailed in the subpart B 211.22 as follows :

- ✓ Approve or reject all components, drug product containers, in-process materials, packaging material, labeling and drug products.
- ✓ Authority to review production records to assure no errors have occurred, or if have occurred, have been fully investigated.
- ✓ Approve/reject drug products made by other company.
- ✓ Must have adequate lab facilities for testing/approval/rejection of components, drug product containers, in-process materials, packaging material, labeling and drug products.
- ✓ Approve or reject all procedures or specifications affecting drug product.
- ✓ Responsibilities/procedures must be in writing and must be followed.

2.1 PHARMACEUTICAL INDUSTRY

The earliest drugstores date back to the middle ages.The first known drugstore was opened by Arabian pharmacists in Baghdad in 754, and many more soon began operating throughout the medieval Islamic world and eventually medieval Europe. By the 19th century, many of the drug stores in Europe and North America had eventually developed into larger pharmaceutical companies

The modern pharmaceutical industry traces its origin to two sources: apothecaries that moved into

wholesale production of drugs such as morphine, quinine, and strychnine in the middle of the 19th century and dye and chemical companies that established research labs and discovered medical applications for their products starting in the 1880s.

Most of today's major pharmaceutical companies were founded in the late 19th and early 20th centuries. Key discoveries of the 1920s and 1930s, such as insulin and penicillin became mass-manufactured and distributed.

The industry in Europe is one of the world's biggest producer of pharmaceutical products, second only to the US. Between 1970 to 2000, the industry in Europe accounted for more than 30% of the worlds production in pharmaceuticals. Between 1986 and 1990 the major European countries in pharmaceuticals (Germany, UK, France, Switzerland and Italy) demonstrated the most dramatic production growth rates (a total increase of 45%) ahead of the US and Japan with 19 and 31% respectively. During the late 1990s, Europe lost its lead as the world largest producer of pharmaceuticals to the US.[7]

With an output of Euro121.3 billion in 2000, the US has taken over the top position followed by Europe Euro112 billion and Japan Euro62 billion. Data from 2001 indicates that France is the largest producer of pharmaceuticals in Europe with approximately 19% of the European pharmaceutical output followed by the UK at 15% while Germany and Switzerland accounts for 14% each.[7,8]. Today, the seven main European markets represent a marketplace for pharmaceutical products worth US$162 billion a year and its expected to grow by US$47 billion over the next five years.

There are now more than 200 major pharmaceutical companies, jointly said to be more profitable than almost any other industry, and employing more political lobbyists than any other industry. Advances in biotechnology and the human genome project promise even more sophisticated, and possibly more individualized medications.

2.2 BIOPHARMACEUTICAL INDUSTRY

The discovery of recombinant DNA and monoclonal antibody technologies in the 1970s marked the birth of the biopharmaceutical industry. Unlike chemically synthesized small molecule drugs that have long dominated the traditional pharmaceutical industry, biopharmaceuticals are complex macromolecules created through the genetic manipulation of living organisms using gene cloning, recombinant DNA (gene splicing), or cell fusion technologies.

The molecular weight usually varies from about 10,000 to 1,000,000 Daltons while their potency may depend on their primary, secondary, tertiary and quaternary structure; glycosylation or disulfide bridges between chains or conjugation to small molecule.

In terms of product type, these may include recombinant proteins, recombinant antigen vaccines and vaccines crafted from genetic material such as DNA, therapeutic monoclonal antibodies and Oligonucleotides (short sequences of DNA or RNA) such as antisense molecules which interrupt the production of disease causing proteins by inhibiting gene function and gene therapy and can enhance the production of a missing protein through the addition of a synthetic gene.[9,10]

Biopharmaceuticals are usually administered by subcutaneous, intravenous, or intramuscular injection.

The biopharmaceutical category also often includes drugs derived from plants, fungi or marine organisms, but these are more in the realm of traditional medicinal chemistry research based on the random screening of natural compounds.

Biologics is an area that consists of blood derived polyclonal antibodies and clotting factors, antibiotics, and classical vaccines based on live or killed viruses, they are frequently classified as biopharmaceuticals, but these products predate the emergence of recombinant DNA and monoclonal antibodies. Insulin, for example, was originally obtained from porcine or bovine pancreas while human growth hormone was extracted from the pituitary glands of cadavers.

2.3 POLICY AND REGULATORY

Regulation is designed mainly to protect the health and safety of the population. It is aimed at ensuring the safety, quality, and efficacy of the pharmaceutical products which are covered under the scope of the regulation.

The major roles of regulatory agencies in the pharmaceutical industries include but not limited to the following :

- ✓ Inspection of facilities, process and product in order to ensure patient or consumer safety.
- ✓ Ensure compliance to applicable regulations.
- ✓ Approve product for marketing.
- ✓ License facility or product.
- ✓ Remove product from the market in case of established risks to patients
- ✓ Remove product license(s).
- ✓ Institute serious regulatory actions or sanctions.

Major international regulatory instances that governs the pharmaceutical and Biotechnology industries are the US Food and Drug Administration FDA, the European Agency for the Evaluation of Medical Products EMEA, the Japanese Ministry of Health Labor and Welfare MHLW, the Swiss Agency for Therapeutic Products Swissmedic and the International Conference on Harmonization ICH.

2.3.1 The US Food and Drug Administration (FDA)

Some milestones in the history of the development of pharmaceutical regulations include the 1937 requirement to establish drug safety before marketing following cases of deaths from elixir of sulphonamide containing ethylene glycol; this act is still the basis for regulation of pharmaceutical products in the US and most developed countries.

In 1962 the Kefauver-Harris drug amendment for better drug efficacy and safety were passed; manufacturers are required to prove to the FDA the effectiveness of their products before marketing, consequence of the thalidomide tragedy in which the use of new tranquillizer in pregnant women caused severe birth defects[11].

Legislation was enacted to test and approve drugs and to require appropriate labeling. Prescription and nonprescription drugs became legally distinguished from one another as the pharmaceutical industry matured.

In 1964, the World Medical Association issued its Declaration of Helsinki, which set standards for clinical research and demanded that subjects give their informed consent before enrolling in an experiment. It became a requirement for Pharmaceutical companies to prove efficacy in clinical trials before marketing drugs.

2.3.2 The European Medicine Agency (EMEA)

In Europe, the EMEA was created in 1985 with the following major roles :

- ✓ Provide independent, science-based recommendations on the quality, safety and efficacy of medicines, and on more general issues relevant to public and animal health that involve medicines.

- ✓ Apply efficient and transparent evaluation procedures to help bring new medicines to the market by means of a single, EU-wide marketing authorisation granted by the European Commission.

- ✓ Implement measures for continuously supervising the quality, safety and efficacy of authorised medicines to ensure that their benefits outweigh their risks.
- ✓ Provide scientific advice and incentives to stimulate the development and improve the availability of innovative new medicines.
- ✓ Recommend safe limits for residues of veterinary medicines used in food-producing animals, for the establishment of maximum residue limits by the European Commission
- ✓ Involve representatives of patients, healthcare professionals and other stakeholders in its work, to facilitate dialogue on issues of common interest.
- ✓ Publish impartial and comprehensible information about medicines and their use.
- ✓ Develop best practice for medicines evaluation and supervision in Europe, and contributes alongside the Member States and the European Commission to the harmonisation of regulatory standards at the international level.[12]

2.3.3 The Japanese Ministry of Work, Labor and Welfare (MHLW)

The Japanese Ministry of Work, Labor and Welfare MHLW was established in January 1938 as a new ministry to supervise health, social welfare/insurance and labor administration.

An advisory organ to the Ministry of Health and Welfare; the Central Pharmaceutical Affairs Council is composed of experts in the fields of medical science, pharmaceutical science, veterinary science and statistical science which deliberates on available basic and clinical studies data and make propositions for drug approval to the Minister of health and Welfare who makes the final decisions on the approvals of new drugs

Good Laboratory Practices (GLP) for the implementation of animal testing (against toxicity) during non-clinical tests and Good Clinical Practices (GCP) for the implementation of clinical tests are set forth. Each test is regulated by GLP and GCP so that it is conducted appropriately[13].

The major roles of the MHLW in the drug regulatory is as follows :

- ✓ Examinations for the Approval of New Drugs
- ✓ Licenses for the Manufacturing (Import and Sales) of Drugs, etc.
- ✓ Ensure compliance with manufacturing quality control methods
- ✓ Examination of the approval of products other than new drugs

2.3.4 The Swiss Agency for Therapeutic Products (Swissmedic)

The Swiss agency for therapeutic products Swissmedic is a Swiss based regulatory organ established in 2002 and responsible for the control of pharmaceutical products and medical devices in Switzerland.

It is a public institution whose core activities cover the following :

- ✓ Licensing medicines
- ✓ Granting authorizations to manufacture and distribute wholesale, and inspecting facilities
- ✓ Monitoring medicines and medical devices already on the market
- ✓ Controlling the traffic of narcotics

- ✓ Laboratory testing of medicine quality
- ✓ Drafting laws and standards

It is independent of other regulatory institutions but works in close collaboration with international organizations and governments, it has maintained a good working relation with the Council of Europe to draft internationally binding quality standards for medicines. It ensures the application European Pharmacopoeia in Switzerland and publish the Swiss Pharmacopoeia[14].

2.3.5 The International Conference on Harmonization (ICH)

The International Conference on Harmonization (ICH) is not a regulatory body but an organization established with the objective of promoting international harmonization of guidelines and requirements for product registration.

This objective is pursued by bringing together representatives of the Pharmaceutical Industry and regulatory bodies from the EU, Japan and the USA to discuss, establish and recommend common guidelines.

The organization was set up in April 1990 and consist of the following parties :

- ✓ Europe : The European Union (EU) and the European Federation of Pharmaceutical Industries and Associations (EFPIA).
- ✓ Japan : Ministry of Health, Labor and Welfare (MHLW), and the Japan Pharmaceutical Manufacturers Association (JPMA).
- ✓ United States of America : Food and Drug Administration (FDA) and the Pharmaceutical Research and Manufacturers of America (PhRMA).

Additional members include observers from the World Health Organization (WHO), European Free Trade Association (EFTA), and Canada. The observers represent non-ICH countries and regions.

Through the steering committee, the ICH make recommendations on ways to achieve harmonization in the interpretation and application of technical guidelines and requirements for product registration in order to reduce the need to duplicate the testing carried out during the research and development of new medicines.

The ultimate goal is to encourage economical use of human, animal and material resources, and the elimination of unnecessary delay in the global development and availability of new medicines whilst maintaining safeguards on quality, safety and efficacy, and regulatory obligations to protect public health.

Since the beginning of the process, more than 50 technical guidelines have been harmonized in the field of quality, safety and efficacy of pharmaceutical products[15].

3. TYPES OF TESTINGS

Pharmaceutical and Biopharmaceutical products are tested during the production process in order to ensure that the intermediate or active pharmaceutical ingredient (API) conforms to its specification (in-process controls).

Active Pharmaceutical Ingredient (API) is generally referred to as any substance or mixture of substances to be used in the manufacture of a drug product and that when used in the production of a drug, becomes an active ingredient of the drug product

Tests are also carried out at the end of the production process (release tests) to verify that the final product conforms to the specification required by the applicable pharmacopoeia monograph.

Most release testing focuses on the physicochemical properties, the identity, the potency, the purity and microbiological state of the final drug product.

3.1 MICROBIOLOGICAL PURITY TESTS

Microbiological purity tests of pharmaceutical and biopharmaceutical products are conducted in order to establish that the intermediate and the final drug products does not contain any foreign substance or microorganisms from the process or the manufacturing environment that could potentially harm the patient when the product is used under the prescribed conditions.

- ✓ Bioburden
- ✓ Sterility
- ✓ Endotoxin
- ✓ Mycoplasma*
- ✓ Virus testing*

*Mycoplamsa and virus testing are carried out on biopharmaceutical products.

3.2 PHYSICOCHEMICAL TESTS

These are series of tests designed to determine and characterize the physical and chemical properties of the intermediates substances and the final drug product.

Results are often compared to specifications established in the pharmacopoeia monographs; most of the tests are listed below :

- ✓ Identity
- ✓ Purity
- ✓ Potency assay
- ✓ Pharmaceutical tests
- ✓ Sub-visible particle count

3.3 CRITICAL TO QUALITY STEPS

The Microbiological and Physicochemical tests outlined above are usually carried out in the following steps of the manufacturing process:

3.3.1 API starting materials and Excipients

API starting materials are raw materials, intermediates or an API used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API.[8]

As clearly established in the annex 8 of EU GMP, raw material analysis is an essential process in any pharmaceutical manufacturing laboratory.

"The identity of a complete batch of starting materials can normally only be ensured if individual samples are taken from all the containers and an identity test performed on each sample. It is permissible to sample only a proportion of the containers where a validated procedure has been established to ensure that no single container of starting material has been incorrectly labeled"[16]

Raw materials testing ensures that the starting materials and components used in pharmaceutical products are suitable for their intended use. Conducting raw materials analysis using appropriate test methods and successfully meeting the challenges of such testing can prevent costly production problems and delays.

Methods, specifications and guidelines for testing raw materials are usually specified in the major compendia notably the United States Pharmacopoeia/NF, European Pharmacopoeia, Japanese Pharmacopoeia, and other regional and international regulatory documents.

A typical manufacturing process for the production of a liquid drug product use as much as 10 different excipients whose specifications must conform to those described in the monographs of European Pharmacopoeia, US Pharmacopoeia, and the British Pharmacopoeia.

The EU GMP guidelines allow the use of supplier's Certificate of Analysis in the place of performing tests other than identity test, under the condition that the manufacturer has a system in place to evaluate suppliers.

The identity test could be skipped in the presence of supplier's Certificate of Analysis for hazardous and highly toxic and dangerous raw materials.[16,17]

3.3.2 Intermediates

These are materials produced during steps of the processing of an API that undergoes further molecular change or purification before it becomes an API.[8]

These tests are established to monitor the progress and control the performance of processing steps that cause variability in the quality characteristics of APIs[18]. In-process controls play a specially important role in ensuring the consistency of the quality of intermediates products and eventually the conformity of the final product.

The EU GMP guideline stipulates that In-process controls and their acceptance criteria should be defined based on the information gained during the development stage or historical data.

The acceptance criteria, the type and extent of testing will depend on the nature of the intermediate or API being manufactured, the reaction or process step being conducted, and the degree to which the process introduces variability in the product's quality.

Less stringent in-process controls may be appropriate in early processing steps, whereas tighter controls may be appropriate for later processing steps such as isolation or purification[19].

In-process controls can be performed by qualified production department personnel and the process adjusted without prior quality unit's approval if the adjustments are made within pre-established limits approved by the quality control department.

3.3.3 APIs (drug substances) and Final drug product

Active Pharmaceutical Ingredient or drug substance is any substance or mixture of substances to be used in the manufacture of a drug product and that when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.[8]

Each batch of finished active pharmaceutical ingredient must meet established specifications for quality, purity, identity, and potency, including, where applicable, specifications for tests and limits for residues of solvents and other reactants.

Drug substances and each lot of finished drug products are also required to be sterile before release for manufacturing process or human use respectively.

Sterility test is carried out according to USP chapter 71 which is harmonized with the equivalent chapters in the EP and JP.

3.3.4 Primary and Secondary packaging materials for drug products

FDA's Center for Drug Evaluation and Research has issued several guidance documents specifically listing appropriate material and container requirements and testing necessary to demonstrate drug safety.

These requirements are laid out in CDER's Guidance for Industry — Container Closure Systems for Packaging Human Drugs and Biologics, May 1999.[20]

The secondary components of the packaged drugs are also controlled for the types of packaging material, the dimension , inserts, printed materials and pack integrity.

4. MANUFACTURING COST AND QUALITY CONTROL

Cost of goods sold COGS also referred to as materials and production cost includes all expenses directly associated with the production of goods or services a company sells. It includes items such as materials, labor and overheads and exclude depreciation, depletion and amortization.

COGS is subtracted from sales to determine the gross profit on an income statement. The exact costs included in the COGS calculation will differ from one type of business to another.

In the pharmaceutical and biopharmaceutical industries, cost attributed to manufacturing are a major part of a company's total expenses and it includes all costs incurred in producing the goods including write-offs from plant, property and equipment, raw materials, inventory, etc.[21]

The manufacturing process of a pharmaceutical product include all activities and operations related to the receipt of materials, production, packaging, repackaging, labeling, re-labeling, quality control, release, storage and distribution.[8]

Manufacturing cost account for a substantial part of the total cost structure and according to some estimates, the average figure for a manufacturer of brand-name pharmaceuticals is 26%, manufacturer of generics could have as high as 52% while the average in the biotech industry is 14%.[21,22] .The higher value as a percentage of sales for generics is most probably a reflection of lower expenditure on R&D and sales and marketing in this sector of the industry.

In 2008, COGS is estimated in absolute terms to be as much as US$200 billion for all pharmaceutical products, this estimate is based on the assumption that COGS represent 27% of a projected total pharmaceutical sales of US$735 billion in 2008.[23]

The high COGS of pharmaceuticals is in part a direct consequence of the necessity to comply with local, regional and de facto global regulatory guidelines and government legislations for save and efficacious medicines and the methods put in place by the manufacturers to deliver the required excellence in terms of quality.

In the current global environment where investments for new and efficient therapies are becoming scarce and the prices of available pharmaceuticals are in constant increase, building quality into pharmaceutical and biopharmaceutical process and products could help to increase manufacturing efficiency and reduce manufacturing cost.

The reduction in the manufacturing cost would either translate to availability of capital for investment in R&D or lower the market prices for pharmaceutical products. Recent studies has suggested the existence of strong correlations between COGS reduction and increase in R&D expenditure, drug prices and public health.[24]

The following pharmaceutical and biopharmaceutical manufacturers were contacted for data on COGS and costs attributable to batch failures, reworks, re-processing and re-labeling.

Table 4.1 : Manufacturers contacted for COGS data

NAME	MEANS OF CONTACT	RESPONSE\RESULT
ACTELION	E-MAIL THROUGH COMPANY WEBSITE	MANUFACTURING ACTIVITIES ARE OUTSOURCED
DEBIOPHARM LAUSANNE	E-MAIL, TELEPHONE, SITE VISIT	MANUFACTURING ACTIVITIES ARE OUTSOURCED
MERCKSERONO AUBONNE	E-MAIL, TELEPHONE, FACE TO FACE DISCUSSION WITH THE SITE FINANCE MANAGER	DATA ON COGS, NO DATA ON BATCH FAILURE OR OTHERS.
MERCK ETHICALS DARMSTADT	E-MAIL	DATA CANNOT BE PROVIDED FOR CONFIDENTIAL REASONS
NOVARTIS BASEL	E-MAIL, TELEPHONE	DATA ON COGS, NO DATA ON BATCH FAILURE OR OTHERS
NOVARTIS NYON	E-MAIL	DATA CANNOT BE PROVIDED FOR CONFIDENTIAL REASONS
OM PHARMA GENEVA	E-MAIL, TELEPHONE	NO REPLY TILL DATE
BAXTER CORPORATION, US	E-MAIL	NO REPLY TILL DATE
BRISTOL MEYER SQUIBB, IRELAND	TELEPHONE DISCUSSION WITH CONTACT	SUCH DATA ARE CONSIDERED TO BE CONFIDENTIAL
GLAXOWELLCOME, UK	PERSONAL CONTACT	NO DATA COULD BE PROVIDED FOR CONFIDENTIAL REASONS

4.1.1 Pharmaceutical manufacturing cost breakdown

Table 4.1 below show the cost breakdown data for pharmaceutical production process simulation for company A involved in the production of an active pharmaceutical ingredient (API). The process is programmed to produce 171kg of the compound per batch in a 12 step procedure at about US$257/kg.

Labor is its most important component accounting for 35% of the overall cost, it is estimated that 16 operators are required to run the plant around the clock supported by four QC/QA scientists. The facility-dependent cost, which is essentially composed of depreciation and maintenance of the plant, is in the second position at 25%, while raw materials accounts for 24%.

The percent of the production cost attributed to Quality activities (quality control and assurance) is 5.3%, however the cost of failed batches or out-of specification result detected at the end of production would result in considerable waste in terms of raw materials, labor and efforts deployed for investigation, rework and re-processing.

Company B manufacturing activities involve the conversion of the active pharmaceutical ingredient into the final drug product.

Raw material therefore accounts for the most important part of the production process (80%), while facility-dependent and labor-related items account respectively for 9 and 8%.

QC/QA cost contribution to the production process is 3%, no detail could be obtained concerning the cost structure and the degree of automation of the manufacturing process.

The relative importance of continuous monitoring of critical-to-quality parameters during the production process cannot be overemphasized. The risk of dependence on end-of-production testing or any other approach, other than on-line or at-line monitoring is very high considering the cost of the raw materials alone.

Table 4.2 : Cost breakdown for pharmaceutical manufacturing

ITEM	COMPANY A%[21]	COMPANY B %
FACILITY-DEPENDENT	25.1	9
RAW MATERIALS	24.2	80
LABOR-DEPENDENT	35.4	8
QC/QA	5.3	3
WASTE TREATMENT/DISPOSAL	10.0	0
TOTAL	100	100

Table 4.3 : QC Cost breakdown Company A

ITEM	%
PERSONNEL	70
SUPPLIES	22
MAINTENANCE	6
EXTERNAL ANALYSIS	1
TRAINING	1
TOTAL	100

As shown in table 4.2, the burden of the QC cost in the overall manufacturing cost structure cannot be considered to be a major cost driver.

Typical QC Laboratory in a pharmaceutical set-up will present a cost structure similar to the one presented in table 4.3.

Labor or personnel related (wages and all other forms of compensation) cost account for 71% if training is included, materials and reagents account for 27%, while calibration and maintenance of equipment account for 6%.

This cost structure is coherent with what is obtainable in pharmaceutical quality control laboratories under the present labor-intensive approach to quality control and management.

4.1.2 Biopharmaceutical manufacturing cost breakdown

Table 4.4 below showed cost breakdown for manufacturing site of a biopharmaceutical company whose activities covers fermentation/cell culture, recovery and purification in addition to formulation, aseptic filling and packaging of freeze-dried and liquid injectable products.

Table 4.4 : Cost breakdown for Biopharmaceutical manufacturing

ITEM	%
FACILITY-DEPENDENT	25
MATERIALS AND OTHERS	29
LABOR-DEPENDENT	24
QC/QA	14
OVERHEADS	8
TOTAL	100

Table 4.5 : Manufacturing Cost breakdown

ITEM	BIOTECH	SYRINGES	FD	PACK 1	PACK 2
FACILITY-DEPENDENT	17	18	40	22	19
MATERIALS AND OTHERS	37	25	20	34	34
LABOR-DEPENDENT	28	24	19	27	26
QC/QA	10	25	14	10	15
OVERHEADS	8	8	7	7	6
TOTAL	100	100	100	100	100

Table 4.6 : QC Cost breakdown for Biotech, FDF syringes and FD

ITEM	%
PERSONNEL	72.6
SUPPLIES	21
MAINTENANCE	2
EXTERNAL ANALYSIS	3
TRAINING	1.4
TOTAL	100

Table 4.7 : QC test distribution

COST ITEM	%
DEVELOPMENT	15
BIOTECH PRODUCTION	21
FINAL DOSAGE FORMS FREEZE DRIED	26
FINAL DOSAGE FORMS SYRINGES	33
PACKAGING	5
TOTAL	100

The QC/QA activities accounted for about 14% of the manufacturing cost in the example of the biopharmaceutical industry given above as against an upper limit of 5% in the examples of pharmaceutical industries studied. This can probably be explained by the fact that the quantity/type and cost of tests required to establish compliance to regulatory requirements for biotech products is significantly higher compared to pharmaceutical products.

It was impossible to obtain additional and similar data from other pharmaceutical and biopharmaceutical companies contacted, no trend could therefore be established based on the data obtained. However, this data appears to be coherent with generally accepted and published figures in industry-related literatures.

QC/QA cost per see cannot be considered as a major cost driver in the manufacturing of pharmaceuticals and biopharmaceuticals apart from the isolated 25% seen in the FDF syringes sector, however the impacts of batch failure or out of specification results will be significant, considering the high volume and value of these products.

The QC Laboratory cost breakdown in table 4.6 is similar to the one presented in table 4.3, with labor accounting for a significant portion of the cost, with a slight difference in the cost attributed to external analysis.

External analysis are tests carried out by specialized external laboratories on process samples most especially during the cell bank characterization and virus testing of cell culture intermediates of Biotech process.

Table 4.7 shows a progressive increase in QC activities (testing) from 21% in the cell culture (Biotech) phase to 33% in the final dosage forms phase of the manufacturing process.

This is also a confirmation of the industries' traditional reliance on finished product testing to assess the quality of their product, a behavior that encourages less scrutiny on minor variations of the process on the way to the final product.

4.2 BATCH FAILURE / REJECTION/REWORK/RECALLS

It was impossible to obtain data related to batch failure, rejection or rework rates in the pharmaceutical and biopharmaceutical industries, all the companies contacted declined to give information concerning the subject. Information related to the subject were considered confidential and are thus not released to the public or for academic purposes.

Based on the rejection rates between 5 to 10% reported in industry-related articles and literatures for the traditional pharmaceutical [25,26] product, a significant loss due to process inefficiency and reliance on end-of-process control is and will continue to be a costly venture for the industry under the current approach to quality control and quality management.

Using the reported US$90 billion/year spent on manufacturing, the cost for the industry will be between US$ 4.5 billion and US$ 9 billion per year.[21,22,23]

It is also interesting to consider that the number of drug recalls has risen sharply in recent years, three-quarters of which are attributed to manufacturing defects.

The top ten reasons for FDA recalls in the fiscal year 2005 presented below confirmed the fact that a large proportion of product recalls are connected to manufacturing and quality-related defects.[11]

Table 4.6 : Top 10 reasons for FDA recalls in the fiscal year 2005

TYPE	NUMBER	%
cGMP DEVIATIONS	144	40.6
FAILED USP DISSOLUTION TEST REQUIREMENTS	55	15.5
MICROBIAL CONTAMINATION OF NON-STERILE PRODUCTS	30	8.5
LACK OF EFFICACY	25	7.0
LABELLING ERROR	24	6.8
IMPURITIES/DEGRADATIONS	18	5.1
LACK OF ASSURANCE OF STERILITY	17	4.8
LACK OF PRODUCT STABILITY	16	4.5
MISBRANDED	13	3.7
SUBPOTENT	12	3.4
TOTAL	354	100

The European Medicine Agency, EMEA also released a statement on batch recalls for quality defects covering the same period (2005). 65 product defects were registered out of which 20 (30%) were recalled.[12]

A summary of recalls and their classification is presented in the table below:

Table 4.7 : EMEA classification of batch recalls for quality defects

TYPE OF RECALL	NUMBER	INCIDENCE
CLASS I: DEFECTS WHICH ARE POTENTIALLY LIFE THREATENING OR COULD CAUSE SERIOUS RISK TO HEALTH	2	10
CLASS 2 : DEFECTS WHICH COULD CAUSE ILLNESS OR MISTREATMENT BUT ARE NOT CLASS ONE	4	20
CLASS 3 : DEFECTS WHICH MAY NOT POSE A SIGNIFICANT HAZARD TO HEALTH BUT WHERE A RECALL HAS BEEN INITIATED FOR OTHER REASON BUT NOT CLASS 1 OR 2	14	70

The top 10 reasons for the defects and their incidence are summarized in the table below :

Table 4.8 : Top 10 reasons for 65 product quality defects registered in the EMEA centralized procedure in 2005.[12]

TYPE	NUMBER	INCIDENCE
PRODUCT INFORMATION LITERATURE	14	23.1
DEVIATION FROM MARKET AUTHORIZATION	10	15.4
ANCILLARY MATERIALS	9	13.8
OOS	8	12.3
GMP INSPECTION FINDINGS	4	6.2
CORING PROBLEMS	4	6.2
PARALELL DISTRIBUTION	3	4.6
CHEMICAL CROSS CONTAMINATION	2	3.1
DISSOLUTION TEST	2	3.1
OMCL OOS	2	3.1

Single events were registered each for microbiological contamination, sterility assurance and stability testing. The microbiological cross-contamination case in addition to another serious GMP inspection finding not mentioned in the report were the 2 cases in class 1 recall category.

From tables 4.6 and 4.8 above, significant percent of product defects are directly related to quality issues, this shows that the current approach to routine quality control and management of pharmaceutical and biopharmaceutical products encourage considerable wastes in terms of resources and time and contribute significantly to the operational/manufacturing and compliance

costs with direct consequences on the market price and drug availability.

Manufacturers as a matter of urgency must seek innovative means of implementing the available tools for continuous process monitoring in order to obtain the desired increase in efficiency and reduction in manufacturing costs.

An integrated approach that takes into consideration the implementation of long term measures rather than quick fixes should be favored and encouraged.

5. FUTURE TRENDS IN THE QUALITY CONTROL OF PHARMACEUTICALS AND BIOPHARMACEUTICALS

"Even as it invents futuristic new drugs, its manufacturing techniques lag far behind those of potato-chip and laundry-soap makers" commented a journalist in the Wall Street Journal of September 2003 concerning the manufacturing and quality control approaches in the pharmaceutical industry.

The current quality control approach in the pharmaceutical and biopharmaceutical industries focuses on end product only, it is reactive rather than proactive to compliance and as a result is accompanied with a significant rate of rework-recalls-rejects-retesting and redoing which usually translates to increased production costs directly impacting the market prices of drugs and drug availability.

The pharmaceutical and biopharmaceutical manufacturers must as question of necessity start to consider the implementation of manufacturing approaches that will employ parametric control on a real time basis, therefore assuring 100% inspection and compliance with release specifications.

This will allow the drug industry to dramatically reduce the current wasteful and cost-intensive reliance on quality control via end-product testing and out of specification rejection.

The impact on cost of manufacturing will be considerable and its social benefits will be felt in terms of increased drug availability and consumer surplus.

The implementation of some of the tools enumerated in this chapter in an integrated way will pave the road to a better and efficient routine quality control and management in the pharmaceutical and biopharmaceutical manufacturing.

5.1 RAPID AND REAL TIME TESTING

Many new technologies are currently available that provide rapid and continuous information on physical, chemical, and microbiological characteristics of pharmaceutical and biopharmaceutical raw materials and finished products to improve process understanding and to measure, control and/or predict product quality and performance in real time.[27,28,29]

5.1.1 Physico-chemical testing

An overview of some of technologies available to the pharmaceutical and biopharmaceutical manufacturers for physico-chemical testing are given below :

Table 5.1 : Physico-chemical testing

METHOD	DESCRIPTION
HIGH RESOLUTION ULTRASONIC SPECTROSCOPY	NON-DESTRUCTIVE ANALYTICAL TOOL BASED ON MEASUREMENT OF THE VELOCITY AND ATTENUATION OF ACOUSTICAL WAVES AT HIGH FREQUENCY, ALLOWS FAST AND ON-LINE ANALYSIS OF COMPOSITION, AGGREGATION, GELATION, DISSOLUTION, MICELLE FORMATION, CRYSTALLIZATION ETC.

RAMAN SPECTROSCOPY	RAMAN SCATERRING IS USED TO DIAGONISE THE INTERNAL STRUCTURE OF MOLECULES AND CRYSTALS. LIGHT OF A KNOWN FREQUENCY AND POLARIZATION IS SCATTERED FROM A SAMPLE, THEN ANALYZED FOR FREQUENCY AND POLARIZATION IT MEASURES VIBRATIONS IN APPROXIMATELY THE SAME INFOR-MATION RICH ENERGY RANGE AS MID-IR

27, 28 & 29

5.1.2 Rapid microbiology methods

New methods can reduce the time to results significantly from several days to a few hours, thereby allowing manufacturers to detect adverse trends early and make corrections before they endanger products or processes.

The table below describe some of the rapid microbiology methods currently available:

Table 5.2 : Rapid microbiology methods

METHODS	EQUIPMENTS AND MANUFACTURERS
GROWTH BASED TECHNOLOGY : BIOCHEMICAL AND PHYSIOLO GICAL PARAMETERS THAT REFLECT THE GROWTH OF MICRO-ORGANISMS AFTER FEW HOURS	BIOMERIEUX VITEK 2 AND BACTOMETER SYSTEMS BIOLOG OMNILOG MILLIPORE'S MILLIFLEX SYSTEM CELSIS ADVANCE LUMIMOMETER PALL'S PALLCHECK MICRO SYSTEM
VIABILITY BASED TECHNOLOGY: VIABILITY STAINS OR CELL MARKERS TO DETECT AND QUANTIFY ORGANISMS WITHOUT NEED FOR GROWTH	CHEMUNEX SCAN RDI SOLID PHASE CYROMETRY CHEMUNEX D-COUNT CHEMUNEX BACTIFLOW ADVANCED ANALYTICAL TECH, RBD 3000
ARTIFACT-BASED TECHNOLOGY : BASED ON THE ANALYSIS OF CELLULAR COMPONENTS OR THE USE OF PROBES THAT ARE SPECIFIC FOR MICROBIAL TARGET SITES OF INTEREST	MIDI SHERLOCK MICROBIAL ID SYSTEM WATERS MICROBELYNX SYSTEM CHARLES RIVER ENDOSAFE PTS SYSTEM CAMBREX PYROSENSE
NUCLEIC ACID BASED TECHNOLOGY : BASED ON PCR DNA AMPLIFICATION	DUPONT QUALICON RIBOPRINTER APPLIED BIOSYSTEM MICROSEQ SEQUENOMS MASSARRAY PLATFORM BACTERIAL BAR CODE DIVERSILAB IBIS PCR MASS SPECTROMETRY TIGER SYSTEM

27, 28 & 29

Table 5.3 : Other tools for process quality management

DESCRIPTION/OBJECTIVES	TOOLS
PROCESS ANALYTICAL TECHNOLOGY PAT:	MULTIVARIATE DATA AQQUISITION AND ANALYSIS
ENHANCE PROCESS UNDERSTANDING CHEMISTRY	PROCESS ANALYZERS AND ANALYTICAL
MONITOR PROCESS PARAMETERS	PROCESS AND ENDPOINT MONITORING \ CONTROL
ENCOURAGE CONTINUOS IMPROVEMENT	CONTINOUS IMPROVEMENT AND KNOWLEDGE MANAGEMENT
ICH PHARMACEUTICAL QUALITY SYSTEM Q10:	SCIENTIFIC KNWOLEDGE MANAGEMENT TOOLS
FACILITATE INNOVATION	QUALITY RISK MANAGEMENT TOOLS
ENCOURAGE CONTINOUS IMPROVEMENT	
STRENGHTEN LINK BETWEEN PHARMACEUTICAL DEVELOPMENT AND MANUFACTURING	
OBTAIN CONSISTENCY IN PRODUCT QUALITY	
PARAMETRIC RELEASE:	DATA ACQUISITION AND ANALYSIS TOOLS
ELIMINATION OF SPECIFIC OR ALL TESTS OF API OR ISOLATED INTERMEDIATES.	PROCESS ANALYTICAL CHEMISTRY TOOLS
	IN-PROCESS MONITORING TOOLS
LEAN SIX SIGMA:	RIGHT FIRST TIME USED BY PFIZER
ELIMINATION OF WASTE	JUST-IN-TIME BY BAXTER CORPORATION
REDUCTION OF PROCESS VARIABILITY	SIX SIGMA STANDARDIZED STATISTICAL TOOLS
QC STATISTICAL PROCESS CONTROL:	CONTROL CHARTS
PROCESS MONITORING	STATISTICAL TOOLS
IDENTIFICATION OF REAL PROCESS VARIATION	
EARLY DETECTION AND CORRECTION OF PRODUCT-RELATED QUALITY ATTRIBUTES	

3,30,31,32,33,34 & 35

6. SUMMARY AND DISCUSSION

Historically, pharmaceutical companies have relied on a problematic end of production quality-by-testing approach with a primary objective of meeting regulatory requirements by performing excessive quality control.

In spite of this approach to quality management, there are indications that the QC per see is not a major cost driver under the current system as far as the cases examined in chapter four are concerned.

The information obtained from the data is a confirmation of the current situation in the pharmaceutical and biopharmaceutical industries, the data is however not statistically valid for the establishment of a definite trend. Additional data would be required to establish a statistically valuable trend.

Apart from the estimated burden of QC on manufacturing costs, the financial impact of rejected batches due to out of specification results detected at the end of the production process would be considerable.

The implementation of some or the combinations of the approaches described in chapter five is still considerably low, although some industries are now beginning to embrace the application of these tools to manage quality in their manufacturing processes. A recent study conducted by Millipore Corporation indicated that more than 70% of companies in the market have become aware of PAT within the last few years but less than 40% already have a related program.

While it is possible to obtain information on the gains in efficiency and COGS savings from the implementation of these tools, there are however no clear indications if and in what ways these gains are been translated to consumer benefits.

Vernon et al proposed 2 economic models where they predicted that a 30% reduction in manufacturing cost will generate between $1.0 and $12.3 trillion in social value to the United States. Based on several assumptions, the proposed benefits in terms of consumer surplus, R&D investment and the social benefits of the accompanying R&D investments are presented in tables 6.1, 6.2 and 6.3 respectively.

Table 6.1 : Consumer Surplus Gain From Reduction In Pharmaceutical Manufacturing Costs [24]

% REDUCTION	COGS % OF SALES	CONSUMER SURPLUS 1 YR	CONSUMER SURPLUS ALL YEAR
0	27	0	0
10	24.3	$23.2 BILLION	$330.8 BILLION
20	21.6	$47.4 BILLION	$676.7 BILLION
30	18.9	$72.8 BILLION	$1.0 TRILLION
40	16.2	$99.8 BILLION	$1.4 TRILLION
50	13.5	$128.6 BILLION	$1.8 TRILLION

Table 6.2 : Effect of efficiency-induced higher profit margins on R&D Investment[24]

REDUCTION	COGS %	1 TIME INCREASE IN R&D INVST FLOW	ALL YEAR INCREASE IN R&D
0	27	0	0.0
10	24.3	$1.9 BILLION	$55.2 BILLION
20	21.6	$3.9 BILLION	$110.4 BILLION
30	18.9	$5.8 BILLION	$165.6 BILLION
40	16.2	$7.7 BILLION	$220.7 BILLION
50	13.5	$9.6 BILLION	$275.9 BILLION

Table 6.3 : Effect of efficiency-induced higher profit margins on R&D on Public Health in the United States

REDUCTION	COGS %	X	Y
0	27	0	0.0
10	24.3	$41.0 MILLION	$4.1 TRILLION
20	21.6	$82.1 MILLION	$8.2 TRILLION
30	18.9	$123.1 MILLION	$12.3 TRILLION
40	16.2	$164.1 MILLION	$16.4 TRILLION
50	13.5	$205.2 MILLION	$20.5 TRILLION

X : present value life years gained in the United States, Y : present value dollar benefits (life year=$100K) [24]

These models suggested that COGS reduction will either lead to gains in consumer surplus or increased spending on R&D of pharmaceutical companies which will also be translated to consumers' benefits.

In other words, if COGS can be reduced, the pharmaceutical companies will invest those savings into discovery of new therapies for unmet medical needs. In fact, Vernon's economic model calculates that the overall gain in consumer surplus is higher in the scenario where the gains are invested in R&D compared to when the gains are translated to a decrease in the market price of pharmaceuticals as presented in table 6.3.

A study conducted by IBM also claims that the top 30 pharmaceutical companies can protect up toUS$60 billion of future revenues, accelerate time to peak sales by two years and reduce Cost of Goods Sold (COGS) by up to 16% by managing risk and applying scientific and systems-based approaches throughout development and manufacturing.[3]

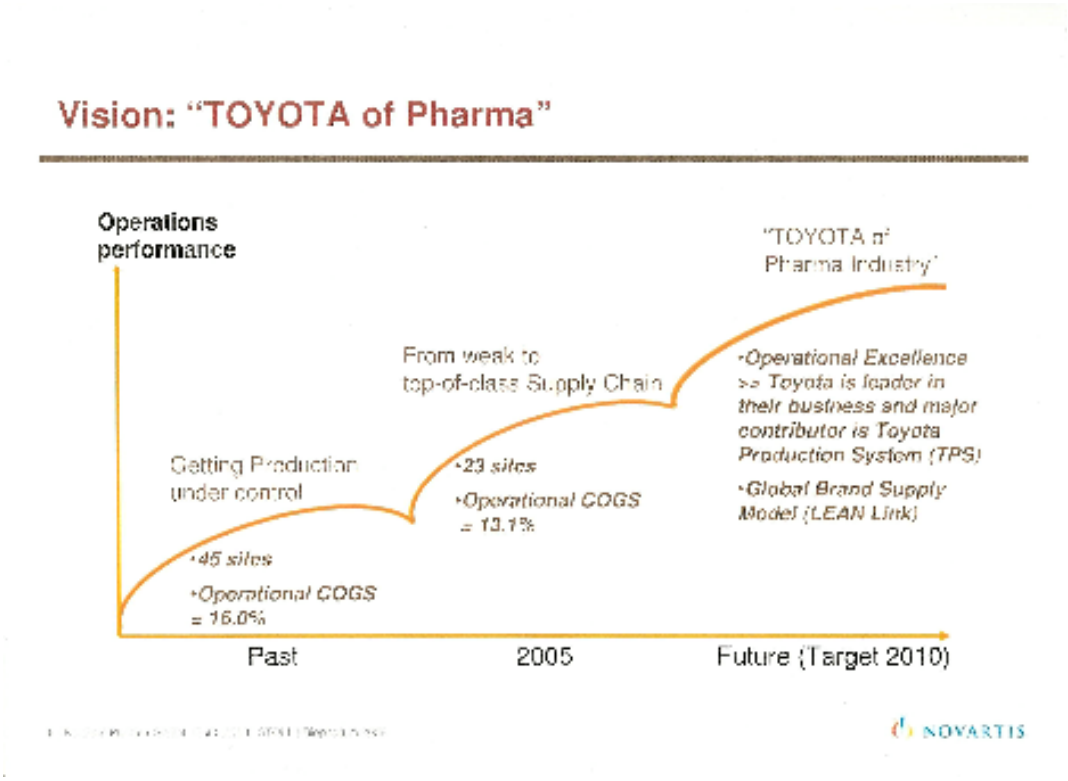
In 2003, Pfizer announced a program called Right First Time (RFT) to migrate its manufacturing towards a more predictive approach and quality control. The premise behind RFT was to improve Pfizer's scientific understanding of its process steps, identify the critical variables to quality and monitor them with the idea of eventually replacing traditional quality assurance methods with real-time monitoring.

Baxter Corporation in the United States also uses Lean principles in its North Carolina plant, the just-in-time (JIT) principle used for the manufacturing of intravenous solutions has witnessed a 74% reduction in the time between production and release.

MerckSerono Biopharmaceuticals is currently applying the Lean Six Sigma and overall equipment efficiency OEE methodologies to the major components of its manufacturing process, support activities and equipments.

The 2 processes are in their early stages and results are not yet available to evaluate their impacts on the efficiency on the different processes.

Novartis' "Toyota of Pharma vision" presented during the Biophorum 2008 conference based on Lean Six Sigma methodologies has yielded encouraging results in terms of throughput time and rate, production yield, changeover time and the Overall Asset Effectiveness with a direct impact on COGS reduction as presented below :



Apart from these examples in the pharmaceutical and Biopharmaceutical industries, technology application in other industrial sectors like Telecommunication, Petrochemicals, Automobiles, Steel and Information Technology has caused a significant price reductions; better technologies and new approaches to manufacture and quality management in pharmaceutical and biopharmaceutical production will in no doubt improve the manufacturing process , enhance product quality and help collapse costs.

The direct benefits of implementing the approaches described in chapter five in an integrated manner will include the following :

- ✓ Reduce production cycle times by using measurements and control
- ✓ Prevent rejects, scrap, and reprocessing
- ✓ Reduce cost of internal failures
- ✓ Improve process performance
- ✓ Improve efficiency and managing variability
- ✓ Improve operator safety and reduce human error

- ✓ Reduce cost of delayed implementation of improvements
- ✓ Reduce cost of preparing and reviewing post-approval submissions

Apart from behavioral and cultural modification on the part of manufacturing and QC personnel, the most visible barrier to the implementation of the methods and approaches described in chapter five of this work is capital resources, but in many cases, the long-term benefits will far outweigh the short-term costs. The success of these approaches will depend on how open manufacturers are to the idea that spending more today will save more money in the long run.

7. CONCLUSION

The inherent limitations and consequences of testing-to-compliance without adequate scientific knowledge of the process, the product or raw materials has been seen in recent years. In addition to contributing to the manufacturing costs of drugs it is also directly responsible for deaths and complications in patients, this trend is bound to continue if adequate science-based measures are not taken. Most recent examples are diethylene glycol and heparin saga which has caused several deaths and provoked life-threatening allergic reactions.

Some of the analytical advances and quality management approaches discussed in this work if and when implemented will provoke a complete shift from the current status in the industry and will certainly impact the way the pharmaceutical QC Laboratories work in the future. A change in philosophy is therefore necessary to bring about the successful implementation of the integrated approach to quality management.

Under the proposed dispensation, the concept of quality control is more deeper and covers not only product testing which will be done in most cases on a continuous/in line or at line mode, but also process optimization through data monitoring, processing and interpretation. This will involved the expertise of highly educated, more mechanically oriented personnel capable to support tasks performed throughout the process cycle.

As significant volume of data will be generated and processed, training of personnel on data management, advanced computer use and other electronic devices will become a major cost driver.

It is difficult at this stage to determine precisely to what extent the implementation of the new approaches to quality management will influence the cost structure of QC laboratory, but from the look of things, spending on personnel-related items, most especially wages and trainings will be impacted as there will be a need to engage the services of personnel whose qualifications are more adapted to the new challenge and also to update the expertise of the current employees through specialized trainings.

As most of the implementation will be categorized as capital projects by most organizations due to the important financial investment required, the QC laboratory management and leadership apart from their technical expertise must also be up to date in their knowledge of project management tools and be comfortable with the use of value added indicators like Net Present Value (NPV), Internal rate of Return (IRR) and Return On Investment (ROI).

Adequate knowledge in strategic planning and management in addition to capacities to lead change successfully will also be required of future QC laboratory management.

In terms of planning and organization of routine activities, close and continuous collaboration with the Production, Information Technology (IT) and Technical Service personnel will be one of the challenges to overcome in order to ensure the successful implementation of the system.

Slight reduction in the cost of laboratory reagents and materials like stationeries and office equipment will probably be noticed, as more emphasis will be placed on electronic data and online batch records.

The part of the QC laboratory cost spent on the maintenance and calibration of equipment will be higher compared to what obtains in most laboratory today.

New categories of cost item such as, IT materials and supplies, accessories for automated systems, Software updates for data processing and management systems will emerge.

These may initially bring about important increase in QC Laboratory expenditures, but the huge benefits that will be obtained by the pharmaceutical industry and the public health sectors far

outweigh these initial or permanent increase in QC laboratory expenditures.

Timothy Tyson in the February 2007 edition of the Journal of Pharmaceutical innovation projected that the "Factory of the Future" will employ parametric control on a real time basis assuring 100% inspection and compliance with release specifications. Patient and prescriber information will be downloaded and printed on-line along with all packaging materials. Demand information will be communicated real time to the manufacturing planning system to achieve a just in time process and reduce inventories. Capacity utilization will exceed 80% on a three shift per day, 7 days/week basis.

This will certainly cause a drastic reduction in supply outages, significant improvement in quality and regulatory compliance and result in a reduction in billions of dollars of inventory and achieve Cost of Goods below 15%.

This would result in a reduction in costs on an annual basis of greater than $30B per year for the industry or the equivalent of 30, one billion dollar per year blockbusters. It's up to us—it's about innovation—it's about time".

And for the QC laboratory to thrive under the new environment, it will have to start moving towards achieving the challenges the modern manufacturing structure will place on it as it performs its statutory roles in the delivery of safe and efficacious drugs to the world in a cost efficient manner.

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