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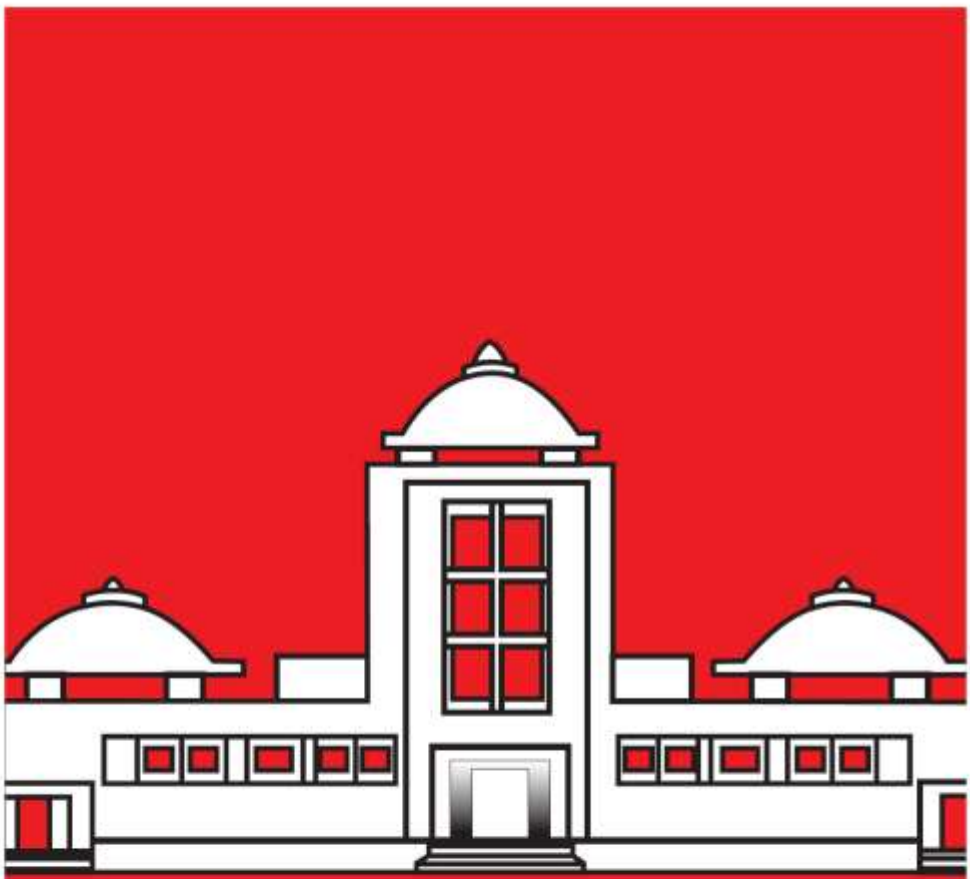

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Contents

Cost of Quality

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Abstract

Everybody is looking for high-quality products and to achieve this high quality the industry needs to invest lots of money. To manage these investments organization must know about the various parameters through which the organization can optimize the extra investments. Therefore, it is very essential to know about the various models and optimization processes. Having such data helps a company to assess the possible savings to be made through the implementation of process changes. If the cost of Quality is not monitored, then companies may face heavy loss.

Keywords: Cost, Quality, Cost Optimization, Quality Cost, Poor Quality.

Introduction

Quality cost (COQ) is portrayed as a philosophy that empowers an association to assess how much its assets are utilized for exercises that stay away from low quality, evaluate the nature of the merchandise or administrations of the association, and are the consequence of interior and outside disappointments. Having such information encourages an organization to evaluate the potential reserve funds to be made through the execution of cycle changes.

The cost of quality was defined by many scientists but the most widely accepted one is that ***Dale and Plunkett*** (1995). According to Dale and Plunkett, quality costs are **"*the costs incurred in the design, implementation, operation and maintenance of a quality management system, the cost of resources committed to continuous improvement, the costs of the system, product and service failures, and all other necessary costs and nonvalue-added activities required to achieve a quality product or service*."**

According to the American Society for Quality (ASQ), to achieve the Six Sigma approach to quality, evaluation of the quality of the products and recording the cost of quality incurred as well as the steps taken to improve the quality is very important.

For example, in 1991 a UK-based company named British Aerospace Dynamics that dealt with aerospace products found out after evaluating the prevention cost, appraisal cost, and failure taking into consideration the percentage of total manufacturing cost that they were incurring some losses. They laid down the objective to reduce the COQ by one-third in a year and were able to achieve it within the stipulated time.

The quality cost is classified into two parts based on conformance. The cost of conformance and non-conformance are further sub-divided into their subparts as defined in Figure 1.

Figure 1: Classification of Quality Cost

Materials and Method

Models of Cost of Quality

1. Feigenbaum's P-A-F Model
2. Juran's Model
3. Process Cost Model
4. Cost-benefit Model

Feigenbaum's P-A-F Model

i. Feigen Baum proposed a system of reporting which divided the cost of quality into two key categories:
   - Costs arising from quality-obtaining activities (prevention and assessment costs) and
   - Costs that result from lack of quality (costs of internal failure and costs of external failure)

ii. The foundation of the PAF strategy is that minimizing the cost of internal and external failures by investing in prevention and evaluation programs and potential expenditure in prevention would inevitably decrease the cost of the assessment.

iii. **Prevention costs** - Planning Product design, process design & review Process control Data collection, analysis & reporting.

iv. **Appraisal costs –** Inspection, testing, testing equipment maintenance costs.

Intangible costs model

i. Intangible costs are those of real or future existence, but they can only be measured and not determined (accounted). Reducing sales, Profit Company, non-conformities, and the resulting loss of potential customers may be the case.

ii. Intangible/opportunity/hidden costs are informed and viewed as a quality cost category that complements various approaches to quality costs or models of quality costs.

iii. The authors (Sandoval-Chavez and Beruvides, 1998), for **example,** have developed an updated quality cost model that includes three components of opportunity loss:

- Under-utilization of production capacity, human resource capacity, etc.
- Improper handling of materials
- Weaknesses in service delivery

Process Cost Model (Crosby Model) – it focuses on the calculation of process quality costs, which in this case, reflects the number of conformity costs and non-conformity costs associated with each process. Starting with the standard (ISO 9004-1:1994), which proposes three methods, the question of quality costs is discussed among the standards family of the International Organization for Standardization:

i. **Quality costing approach**, PAF = prevention, evaluation + internal + external defects;
ii. **Quality loss approach**, which approaches the tangible and intangibles costs, following the Intangible costs model.
iii. **Process-cost approach**, In compliance with the model of process cost.

Costs of Conformance – Cost of compliance is the cumulative cost of making sure a product is of good quality. It covers the costs of the activities of quality assurance, such as requirements, training, and processes; and the costs of the activities of quality management, such as assessments, evaluations, inspections, and examinations.
Cost of Compliance reflects the commitment of a company to the efficiency of its goods.

Costs of Non-Conformance – These covers all in-process costs arising from quality issues in particular rework costs and post-delivery costs, including additional rework, re-performance of missed work (internally used products), likely loss of the company, possible legal redress, and other future costs.

Cost-Benefit Model

i. This technique is usually correlated with programs for quality enhancement.
ii. Define all elements of expenditure & spending relevant to (as cost elements).

iii. Define and measure all elements correlated with benefits/savings, maybe in terms of Rupees.

iv. Shaping the cost-benefit ratio. Go for the change plan, when the ratio is >1.

Example: In 1963, a company located in Germany named National Cash Register dealing with precision mechanics with help of COQ models reduced the cost of Quality from 64% to 44% in 6 years.

Results

It is important to properly monitor the costs of doing a quality job, performing quality changes, and meeting targets such that the long-term impact of quality on the enterprise is a desirable one.

These costs must be a true reflection of the quality effort, which are ideally calculated based on a quality cost study. Such an overview provides a framework for evaluating the efficacy of quality control and provides a way to recognize problem areas, opportunities, savings, and goals for intervention.

Once developed, the quality cost structure can become dynamic and have a positive effect on the accomplishment of the mission, goals, and objectives of the enterprise.

Optimization of Cost of Quality

Optimization of cost of quality is performed to ultimately increase the profit cost to the organization and achieve the product quality by spending minimum cost. The optimization levels are shown in Figure 2.

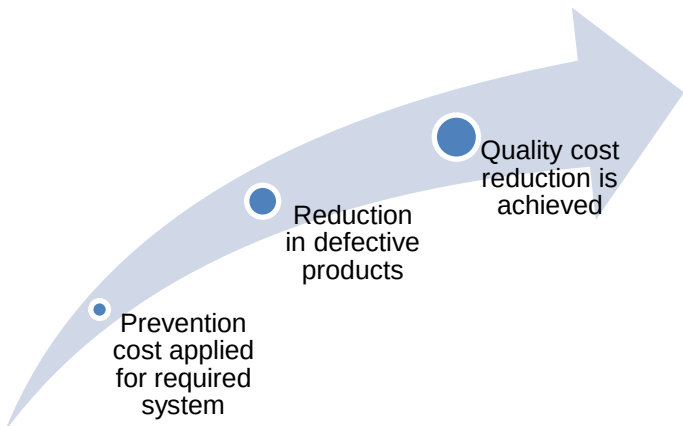

Figure 2: Steps in Optimization of CoQ

Preventing Cost of Quality

Mitigation costs are paid to decrease or mitigate quality problems. The layout, upgrade, and operation of the quality control system are aligned with these costs. They are planned and expended before actual service. The fields where CoQ is used are mentioned in Figure 3.

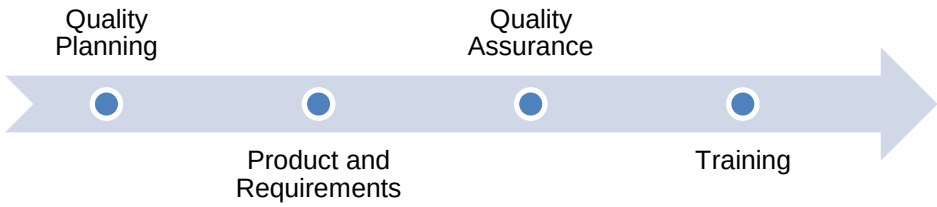

Figure 3: Use of Cost of Quality

Discussion

Many research papers are available discussing cost models, processes, and efficiency methods but a literature review on the realistic usage of CoQ suggests that although consistency is an important aspect of an organization yet there are only a few organizations that understand the CoQ solutions provided and only a fraction of them use a systematic system of quality costs.

The examples of best practices published show that firms using CoQ systems have been very effective in minimizing CoQ and enhancing consumer service. The classical P-A-F method is the paradigm most widely applied in practice; however other categorizations of quality costs are recorded as being used with success. While the P-A-F categorization serves as a foundational term, the various costing structures also vary greatly from business to business. Each model is typically tailored according to the needs of the organization, which results in the different frameworks of CoQ. Several elements are either used or found to be unimportant and left out of the equations. Also, the chosen bases for the measurement of CoQ often differ, creating uncertainty in the estimates of quality costs and making it much more difficult to equate the effects of the CoQ systems between firms. However, the fundamental values of the P-A-F method remain largely intact in the businesses examined.

It is important to conduct more studies on how good firms make decisions concerning quality management and how they reduce quality costs. In particular, more rigorous surveys on the selection and evaluation of quality costs in realistic environments could provide valuable insights on best practices of CoQ, enable businesses to submit Quality cost information, and allow them to incorporate robust cost structures of quality.

CoQ assessment should be a feature of every curriculum for quality control. The technique is not difficult and is well known. CoQ systems provide a good tool for quality cost detection and assessment and thus allow targeted action to minimize CoQ. To truly realize the advantages of the methodology, to improve their ability to adopt a CoQ calculation method, and to save resources, more education at the realistic level is required for managers to better understand the CoQ principle.

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Indian History of Pharmacy Profession and Pharmaceutical Technology with Reference to Their Global Evolution

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Abstract

India made appreciable development in the post-Independence era in its pharmaceutical competence and pharmaceutical production. Pharmaceutical production has touched $30 billion from almost zero in this period. Regarding the availability of services of pharmacists to Indian citizens, the status remains the same. It jeopardises adequate health care to the people of India, which they have fundamentally guaranteed right under the Constitution of India.

Keywords: Charak Samhita, Vaidya, Pharmaceutical Technology, Pharmacy Profession, Medical Profession, Registered Pharmacist, German Empire Frederick II 1200 AD, United States of America, Pharmacy Act 1852, Drugs Enquiry Committee Report 1931, Drugs Act 1940 and Rules 1945, Pharmacy Act 1948.

Introduction

It is an accepted fact that Indian civilization is one of the oldest civilizations in the world. Knowledge of astronomy, spiritual concept, knowledge of disease (ROG), its diagnosis (NIDANAM), treatment (Saman), Materia Medica (Pharmacopoeia of Herbs), and knowledge of preparation of dosage forms is the oldest in the world. Indians' heads are high with the achievements in the field of pharmaceutical technology and production of pharmaceuticals in India. India is the foremost global player in the world trade of pharmaceuticals. India possesses excellency in the technology of manufacturing quality and cost-effective pharmaceuticals. It is an accepted fact that wrong prescription, bad medication, and self-medication have a great contribution to the mortality rate. Even in developed countries, reports of wrong prescription and bad medication are fairly high. In India, outcome of the wrong prescription, bad medication, or self -medication has not been taken seriously yet. Neither government nor private agency exists to survey these menaces. So, the causality resulted due to these menaces can only be guessed. Question to ponder whether services of pharmacists to the people will be helpful in reducing the damage being caused by these menaces? The disparity in recognition of services, emoluments, or social status of pharmacists working in India and developed countries is big. Such a big disparity is not seen in any other profession. Does it cost heavily to the health and welfare of

Indian citizens? These things must be discussed on public platforms.

Oxford and Cambridge dictionaries define a “Profession” as, “A type of job that needs special training or skill especially one that needs a high level of education.” The profession is a specific type of service which is being rendered to society for their benefit or comfort or wellness.

The widely accepted definition of the **medical profession** is “The practice of the diagnosis, treatment, and prevention of disease.”

Pharmacy Professionals are “Healthcare professionals with specialised education and training to ensure the appropriate use of medications and services to achieve an optimal therapeutic outcome.”

Pharmaceutics is “A discipline of pharmacy that deals with the process of turning a new chemical entity or old drugs into a medication to be used safely and effectively by patients.”

Pharmaceutical Technology is defined as, “The science and technology which deals with research, development, manufacturing, application, and repair of the different types of machinery in pharmaceutical industries.”

After deliberation on the above definitions, it can be concluded that the profession of pharmacy and the profession of medicine can both provide optimal health care to humans and animals. It is also evident that there is a very fine lining of separation between these two professions, sometimes it is difficult to segregate these two professions. Both professions have a common object and objective.

If the history of civilization is to be discussed, one must go long back where there are no told, or written documents are available.

It is a matter of hypothesis to decode the evolution of civilization. When the human race would have started living together that is the commencement of community life, they must have thought for food first. So, the activities of farming and agriculture had come into existence. After getting rid of hunger, their main concern and priority would have been to alleviate the pain and physical sufferings that are, wound, fever, abdominal discomforts, and so on. Thus, the next challenge they had undertaken would have been the search for some herbs, minerals, and organs of animals that could help alleviate the pain and physical suffering. Many persons must have learned the expertise to identify those herbs and minerals which could mitigate the suffering. It is believed that it was some leaves that had been first identified as clotting agents, anti-infective agents, carminatives, etc.

Identification of herbs having property to mitigate suffering must have been first research. **It was the beginning of the Pharmacy profession.**

Much after that, the pharmacy professionals had developed expertise regarding the identification of the reasons for pain, fever, and other sufferings. The same professionals had distinguished the different types of pain, fever, and other sufferings. Finally, expertise for diagnosis, treatment, and selection of herbs for mitigation of sufferings came into the picture. **It would have been the beginning of the Medical Science and Medical Profession.**

The aforesaid statement may be concluded as Pharmacy profession is older than the medical profession. Of course, at that time, the same person was practicing both as a pharmacist and physician. In India they were designated as VAIDYA. In Europe they were called APOTHECARY.

The pharmacy and medical profession in India were never commercialised since its beginning till the advent of the British in India.

This profession was treated as a service to humanity. Charak Samhita verse No. 13 states:

"It is better to die by eating poison or by eating boiling copper sulphate solution or by eating red hot iron ball than to extort money from patient." [1]

The Vaidya's were entitled only to get honorarium from patients to sustain their families. The profession of pharmacy and medicine in India remained integrated till the enforcement of **the Pharmacy Act, 1948.**

In Europe, the United States of America was not in the picture in long back history. The USA was ruled by the British. Status of pharmacy may be evaluated by:

"Pharmacy remained a function of medicine until the increasing variety of drugs and the growing complexity of compounding demanded specialists who could devote full attention to the art. The pharmacy was officially separated from medicine for the first time in **1240 AD when a decree of the German Empire Frederick II** regulated the practice of pharmacy within the part of his kingdom called the two Sicilies" [2.] **The United States of America enacted Pharmacy Act as early as 1852**.

Drug Enquiry Committee Report 1931, (Chopra Committee) was the first Indian document where the word "**Pharmacy Profession"** made its appearance. It stated that:

"As regards to the profession of pharmacy, there are practically no restrictive laws of general application except certain provisions in Municipal Acts of some provinces…." [3]

"A close study of conclusions arrived at previous chapters of this part irresistible points to the pressing need for immediate improvement of the situation regarding the profession of pharmacy in India…." [4]

Ironically, the term "pharmacist" found no space either in Drugs Act 1940 or Drugs Rules 1945. It is only in 1994 vide GSR676(E) dated 6-9-1994 where for the first-time term, "registered pharmacist" was mentioned in Rule 65 of Drugs and Cosmetics Rules 1945 by Amendment.

Still, there is no definition of Pharmacist or Registered Pharmacist in both Drugs and Cosmetics Act 1940 or Rules thereunder whereas, the term Registered Medical Practioner has been well defined.

"Registered Pharmacist" had been defined for the first time in Pharmacy Act 1948, Section 2(i). It was only in 1981 that services of Registered Pharmacists were made mandatory in India for of compounding and dispensing vides amendment in Drugs and Cosmetics Rules 1945 in 1976.

So far as the development of Pharmaceutical Technology and Pharmaceutical Industries in India is concerned, today it can be told confidently that India stood second to none in the globe. Volume-wise India is the largest manufacturer and exporter of pharmaceuticals. It is truly said that

India is a pharmacy for Europe, Africa, and the USA. Recently the world has recognised the pharmaceutical potency of India when hydroxyquinoline and other emergency medicines were required by the whole world. India has shown their pharmaceutical technology competency by becoming one of the first a few countries to develop, design, and manufacturing quality COVID vaccines at low cost. This vaccine has a special feature of storage that can be stored at temperature ranging from 2-8 degrees Celsius, which shoots India or other countries of Asia and Africa continents. The modern medicines in India are still known as English Medicine. At the time of independence, we were totally dependent on Europe for the supply of modern medicines. Approximately 95% of medicines required were procured by import from Europe. Today 95% of our medicine need is met by indigenous industries. Today we are manufacturing pharmaceuticals and drug devices worth approximately $30 billion out of which, more than 50% is exported. Still, one bottleneck that the pharmaceutical industries of India are facing is the lack of adequate research and development facilities.

Conclusion

Concluding the discussion, it is evident that India has progressed beyond our expectations in the field of pharmaceutical technology and pharmaceutical production. We have emerged as silver lining hope for the world, in the present post COVID era, to meet the need for pharmaceuticals and vaccines. Contrary to this where the Europe and USA recognised the necessity of pharmacy professionals for adequate medical care as early as 1240 AD and 1852 respectively; India is still to acknowledge the need for pharmacists in ensuring good medical care to their citizens.

Acknowledgement

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Analytical Method Development and Validation

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Abstract

Analytical method development, approval, and move are key components of any drug development program. Successful method development guarantees that research center assets are streamlined, while methods meet the goals needed at each phase of medication development. Processes are created to help drug test according to the specifications during assembling and quality delivery activities, just like during long-haul steadiness contemplates. The act of approval verifies that a given method quantifies a boundary as proposed and builds up the exhibition furthest reaches of the estimation. The time and exertion that are placed into growing scientifically-stable, vigorous, and analytical methods that are transferrable must be lined up with the development stage of medications. The assets which are exhausted on process approval should be continually offset according to administrative necessities and the likelihood for item commercialization.

Keywords: Analytical Method Development, Analytical Method Validation

Introduction

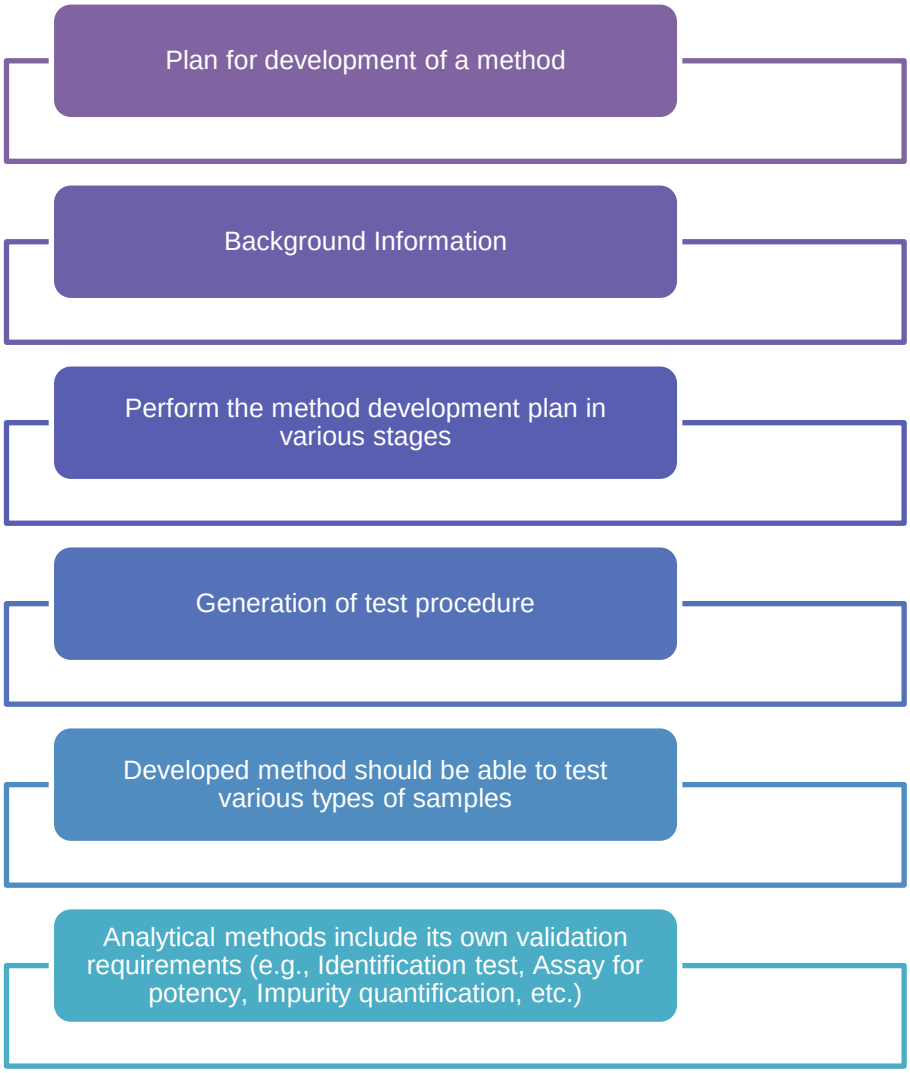
The counts for medicines are increasing in the pharmaceutical market with every passing year, so as a result various modifications of structures to the existing one or else a new entity is introduced into the market. Regularly a delay comes from the time the medication was introduced into the market till the day it is incorporated in the pharmacopeia. This occurs because of the potential vulnerabilities in the regular and more extensive use of medications, results of initial levels of toxicity (bringing about their takeaway from the market), improvement of patient opposition, and presentation of improved medications by contenders. In these circumstances, norms and analytical methodology for these medications may not be accessible in the pharmacopeias. Therefore, importance is given to creating more current analytical techniques in those medications.

The development of any analytical method its approval and move become key components of the various drug development program. Successful development of method guarantees in a way that research center assets seem streamlined, while goals are met by various methods needed at the individual phase of medication development. Method approval, as needed by administrative organizations at specific phases of the medication endorsement measure, is defined as the "cycle of exhibiting those analytical methodologies are reasonable for their

expected use".

Analytical method development and approval are ceaseless and interconnected exercises led all through the medication development measure.

Steps for development and validation of a method



Analytical method validation

Fruitful acknowledgment of the validation boundaries and execution standards, by all gatherings included, requires the agreeable endeavors of a few divisions, including analytical development, QC, regulatory affairs, and the people requiring analytical information. The working methodology or the Validation Master Plan (VMP) ought to characterize the jobs and duties of every office engaged with the validation of analytical strategies.

Materials and Method

Validation Parameters – the validation parameters if performed according to the mentioned guidelines will bring an effective change in the pharmaceutical industry which will increase the productivity and robustness of the method applied.

- Specificity – examination must be carried out with the ID tests validation, the amount, and assurance of impurities. The technique utilized for showing explicitness depends upon the aim of the analytical strategy.
  - Identification – reasonable distinguishing proof tests must contain an option for separating the mixtures of structures that are relatable and which are probably available. The segregation for any methodology might get affirmed by getting positive outcomes (maybe by examination using a reference material which is regarded) from tests possessing the analyte, combined with outcomes that are negative with tests that don't contain the analyte.
  - Test for assay and impurity– for chromatographic methodology, delegate chromatograms should be utilized to show explicitness & individual parts should be properly named. Comparative contemplations should be given to other partition procedures. Basic detachments in chromatography should be explored at a proper level. For basic detachments, explicitness should be exhibited with the goal of both the segments which elute nearest from one another.

    In the situations in which vague measure is utilized, various analytical systems should be utilized to exhibit by and large explicitness. For instance, where titration is embraced to measure the dynamic substance for discharge, the blend of the examination and an appropriate test for contaminations can be utilized. The methodology is comparative for both test and pollutant tests.
  - Analyte discrimination with available impurities – for the test, this ought to include a show of the separation of the analyte within the sight of pollutants as well as excipients; for all intents and purposes, this should be possible by spiking unadulterated substances (dynamic substance or item) with suitable degrees of debasements or potentially excipients and exhibiting the test result is unaffected with the consisting materials (examination with the measurement result acquired on unspiked tests). Testing of the impurity, segregation might be set up by spiking dynamic substances/items including suitable degree pollutants and showing the division of these debasements independently as well as from different segments in the example network.
  - Analyte discrimination with impurities unavailable – on the off chance that debasement or corruption item principles are inaccessible, particularity might

be shown by contrasting the test after-effects of tests containing pollutions or corruption items to a subsequent all-around described methodology e.g.: pharmacopeial strategy or other approved analytical technique (free system). As fitting, this ought to incorporate examples put away under significant pressure conditions: light, heat, moistness, corrosive/base hydrolysis, and oxidation.

- Linearity – a linear relationship must be assessed over an analytical technique range. These could have been shown straightforwardly into the dynamic substance as well as on independent weighing of engineered combinations of the item parts, utilizing the proposed technique. The last viewpoint can be concentrated during examining the range. Assessment of linearity can be done by visually examining the plot of signs to be an element for detection of the analyte. A linear relationship is assessed in the event. There should be proper measurable techniques for the test results, for instance, the least-squares method for determining the regression. To determine the level of linearity regression might be useful to give numerical assessments. The coefficient of correlation, the slope for the line of regression, etc. must be submitted. A graphical representation of the information should be included. Linearity foundation suggests at least 5 fixations. Several methodologies must also be supported.
- Range – the predefined range is generally obtained from examining the linearity and relies upon expected utilizing the technique. Set up is done by affirming any analytical experiment gives an adequate level of linearity, precision, and accuracy and when applied to tests having measures of the sample inside or into the boundaries of the predetermined scope of the technique.
- Accuracy – accuracy must be determined in every mentioned concentration of analytical method.
    - Assay
        - ✓ Active substances – a few techniques for deciding accuracy are accessible:
            - Use of an analytical strategy to a known purity analyte (e.g., reference material).
            - Examination of consequences of the proposed analytical method concerning subsequent very much portrayed system, the accuracy of which is expressed and additionally characterized.
            - Accuracy can be surmised after exactness, specificity and linearity have been set up.
        - ✓ API – to determine accuracy a variety of techniques are available:
            - Analytical techniques are applied to synthetic items and to

the segments where regarded quantity of compound is added for analysis.

- At every condition in which there is difficulty in acquiring tests for every item part, they might be adequate for adding a known quantity of the compound into the item or else thinking about results obtained from another all-around described strategy, the accuracy of which is expressed as well as characterized.
- Accuracy might be done once exactness, specificity as well as linearity is set up.

- Quantitation of impurities – accuracy should be evaluated on examples (substance/item) spiked known measures of impurities. The situation which finds difficulty in getting tested of specific potentially degradants or impurity items; viewed as worthy to look at results got with the autonomous system. The reaction factor of the medication substance can be utilized. It must be understandable in which way the single or complete impurities are to be resolved e.g., w/w or zone percentage, in various cases concerning the analyte which is of concern.
- Data recommended – accuracy must be evaluated utilizing at least 9 conclusions over at last 3 focus levels covering the predetermined reach (for example 3 focuses/3 duplicates each absolute analytical technique). Accuracy needs to be accounted for as amount recovered by assay of known added measure of the substance in an example as the contrast in-between the average and the acknowledged genuine worth along with the certainty spans.

- Precision – essay test approval and impurities quantitative assurance are incorporated examining accuracy.
  - Repeatability – it can be examined by –
    - ✓ At least 9 determinations will cover a specified range for the process (3 determinations each).
    - ✓ Six readings for test concentration which are at a level of 100%.
  - Intermediate precision – the degree up to which this value must be set up relies upon the conditions under which the strategy is proposed to be utilized. The candidate ought to build up the impacts of arbitrary occasions of analytical strategy precision.

    General varieties to be contemplated incorporate days, analysts, gear and so on it isn't viewed as necessary to study these impacts individually. The utilization of a trial plan (grid) is energized.

- Reproducibility – reproducibility is surveyed by methods for a between laboratory preliminary. It ought to be considered in the event of normalization of the analytical system, like in the case of the incorporation of methods in the pharmacopeias. This information isn't important for the showcasing authorization dossier.
- Data recommended – SD and RSD (CV) and certainty span must be accounted for every research precision.

- Limit of detection – a few methodologies for deciding as far as possible are visiting be conceivable, contingent upon whether the methodology is non-instrumental or instrumental. Approaches other than those recorded underneath may be satisfactory.
  - Based on visual evaluation
  - Based on the signal-to-noise ratio – it ought to be applied to analytical systems which display baseline noise. Assurance of S/N is conducted by contrasting estimated signals from both test and known concentrations of analyte with those of clear examples and builds up underside concentration at which analyte may be reliably identified. A ratio between 3 or 2:1 is usually considered appropriate.
  - Based on response SD and slope – the DL is regarded as:

    Detection limit = $\frac{3.3\,\sigma}{s}$

    Here, σ = Standard deviation; s = calibration curve slope
    - ✓ Depending on SD of blank – estimation of the greatness of analytical foundation reaction is conducted by analyzing a fitting number of clear examples and ascertaining their SD.
    - ✓ Based on the calibration curve – a particular calibration bend ought to be considered utilizing tests consisting of analytes within the scope of the Detection limit. The remaining SD of the regression curve or the SD of y-intercepts of regression lines is additionally utilized.
  - Recommended data – the detection limit and strategy utilized for deciding detection limit ought to be introduced. Within the event that DL is resolved keen about visual assessment or obsessed with the signal to noise ratio, the introduction of important chromatograms is considered satisfactory for an avocation.
- Quantitation limit– various techniques are accustomed to determining the limit of quantitation is offered, relied on which a process is often considered instrumental/non-instrumental.
  - Based on visual evaluation – the visual assessment is also utilized for

non-instrumental strategies however it can likewise be utilized with instrumental techniques.

Limit of Quantitation is usually dictated by analysis of tests concerning a known concentration of analyte and by building up bottom limit at which analyte may be evaluated via adequate accuracy & precision.

- Based on the signal-to-noise ratio – this methodology must be applied to analytical strategies that display baseline noise. Assurance of S/N ratio is conducted by contrasting estimated signals from tests & known concentration of analyte with those of clear examples & by putting in bottom concentration at which analyte will be reliably evaluated. A typical signal-to-noise ratio is 10:1.
- Based on the SD of the curve and slope – the QL can be regarded as:

  Quantitation limit = $\frac{10\,\sigma}{s}$

  Here, σ = SD of the curve; s = calibration curve slope

  - ✓ Based on the blank's SD – estimation of the greatness of analytical foundation reaction is performed by analyzing a fitting number of clear examples & ascertaining the SD of those reactions.
  - ✓ Based on the curve of calibration – a specific calibration bend should be considered utilizing tests containing an analyte within the scope of DL. The remaining SD of a curve or the SD of y-intercepts of regression lines could also be utilized as the SD.
- Data recommended – the limit of quantitation & also the method used for determining it should be presented.

- Robustness – assessment of robustness should be considered during the advancement stage & relies upon the kind of technique under study. It should show the reliability of analysis regarding purposeful varieties in technique boundaries. The analytical conditions should be suitably controlled, or a precautionary proclamation should be remembered for the methodology if the analyst cannot conduct variation in analytical conditions. One outcome of the study of robustness should be that a progression of system suitability boundaries is about to ensure that the validity of analytical methodology is preserved at whatever point utilized.
- Testing stability of the system – testing the suitability of the system could be a vital piece of the many analytical methods. The tests rely upon the thought in which gear, instruments, analytical operations, and tests to be analyzed establish a necessary system that may be examined all things considered. System suitability test boundaries to be founded for a selected method rely upon the type of technique being approved.

Results

Importance and significance

- It assures a high quality of the method & procedure.
- The time-bound may be a matter of concern.
- Qualitative costs are reduced.
- Minimum rejection occurs.
- There is a reduced amount of batch failures which successively increases the efficiency still as production.
- A minimal number of mix-ups.
- There is proper method optimization.
- There is an increasing number of results.
- Equipment maintenance is comparatively feasible.
- In process pharmaceuticals as well as in finished pharmaceuticals is a smaller amount.
- Automation is fast.
- Improvement within the awareness of the method.

Application / benefits for method validation

A strategy should be approved when it is important to check that its presentation boundaries are sufficient for use for a specific analytical issue. E.g. –

- A currently developed method.
- A new issue in the revised/established method.
- At the point when an audit of QC shows a setup strategy is changing with time.
- At the point when a setup strategy is utilized in an alternate research center, with various investigators or with various equipment.
- Exhibition of the proportionality between two techniques, for example, another strategy furthermore, a Standard. Certain regions of analytical practices, such as in clinical chemistry will determine Validation necessities pertinent to the strategy.
- It is needed for new molecules, processes and reactions, estimation of herbal products.
- Impurity profiling
- It provides us the required data for a given analytical problem.
- It provides the required sensitivity.
- It gives the required accuracy.
- It gives the required range of analysis.

Discussion

The development of any analytical method and its validation becomes interconnected and is directed all through the medication and development measures. The validation checks training assures that a method is quantified according to the expectations, and it builds up estimation limits.

Contradictorily, approved procedures demonstrate results. They play a vital role in ongoing the development of the drug as characterization of information which is raised based on supporting item. A growing, stable, as well as transferrable methods for analytical purposes, must be lined up following the stage of development of medicine. The assets utilized in the validation of any method must be following the prerequisites of the regulatory perspective and for commercialization.

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A Review on MicroRNA – The New Frontier in Cancer Theranostics

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Abstract

Micro RNAs (miRNAs) are very small units of RNA that do not code for proteins but regulate gene expression during translation. They regulate biological processes like development, cellular proliferation, and apoptosis. They also regulate the process of carcinogenesis. Regulation mainly occurs via translational repression in mammals. The dysregulation of miRNAs is an evolving symbol of cancer. Dysregulated miRNAs can lead to the development of tumors either by inhibiting the tumor-suppressive genes or enhancing the oncogenes. Tumor cells have specific profiling of miRNA expression where they may participate in the initiation and progression of different tumors functionally. Tumor cell growth may be promoted by suppressing the tumor suppressor genes controlling cellular differentiation and apoptosis. In contrast, cancer suppression may be attained through miRNA-mediated inhibition of the genes preventing cellular differentiation and apoptosis (oncogenes). miRNA profiles of any cell may be useful for the early detection, classification, and as analytical and prognostic biomarkers. A more detailed investigation on the function of miRNAs in tumor development and a better understanding of miRNA-modulating particles can give a new incentive to miRNA-mediated therapy for cancer.

Keywords: miRNA, Gene silencing, Apoptotic signaling, Cancer therapy, Cancer Diagnosis

Introduction

MicroRNAs (miRNA) are small RNA units, typically made up of 19-30 nucleotide sequences. miRNAs originate from RNAs and are highly conserved in the genome of eukaryotes and viruses. miRNA was first discovered in 1993, in *Caenorhabditis Elegans (C. Elegans)* as a small non-protein-coding RNA that affects the development through the regulation of lin-14 protein expression. Subsequently, miRNAs were found to be ample in both vertebrates as well as invertebrates which are highly conserved. The literature reports reveal that miRNA-mediated regulation at the post-transcriptional level is an overall monitoring function in various species[1].

The uninhibited growth of undifferentiated cells in the body is known as cancer which develops due to a failure in the cell's growth control mechanism. MicroRNAs have found their applications in cancer therapy as well as diagnosis. The challenge in the current scenario is to identify the targets of transcription along with the pathways that are regulated by miRNAs. miRNAs control the expression of a huge number of messengers RNAs in humans and alterations in the expression of these microRNAs may result in various diseases.

Depending upon the genomic locations, miRNAs are classified as:

- Intronic and Exonic miRNAs in coding transcription units
- Intronic and Exonic miRNAs in non-coding transcription units (Figure 1).

It has been identified that miRNA expression and function are of specific significance in cancer inception and progression as well as the development of other diseases[2].

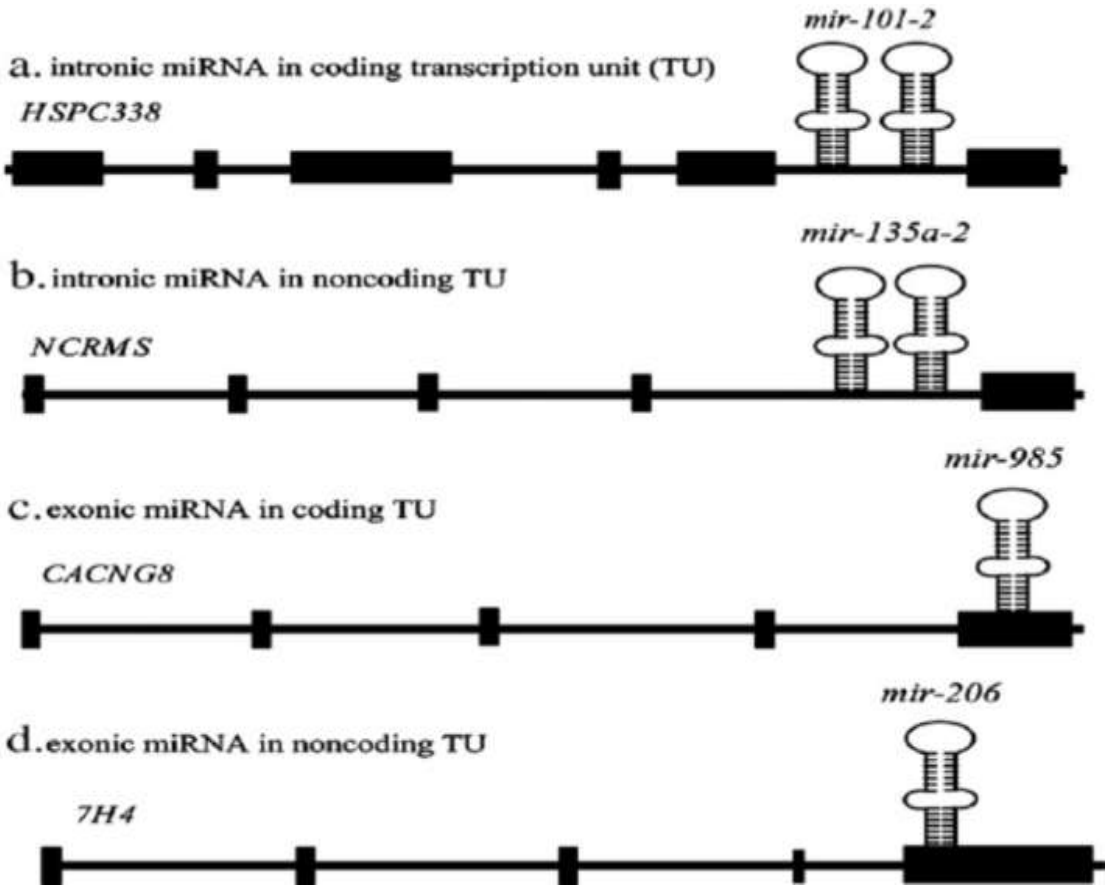

Figure 1: Types of micro-RNA based upon their genomic locations

Biosynthetic Pathway and Mechanism of Silencing

The biosynthesis of miRNA from longer precursors is a multistep pathway that includes multiple RNA cleaving steps. During transcription, first, the primary transcript (pri-miRNA) is synthesized by RNA Polymerase II. This is then cleaved into a shorter hairpin-like structure called the precursor microRNA (pre-miRNA) by the nuclear RNase 'Drosha'. This pre-miRNA is carried from the nucleus to the cytosol by the Exportin- 5 / Ran-GTP complex. RNase 'Dicer' present in the cytosol further cleaves the pre-miRNA into mature microRNA (22 nucleotides). This mature miRNA binds with Argonaute proteins (effector proteins) and is integrated into an RNA Induced Silencing Complex (RISC) (Figure 2).

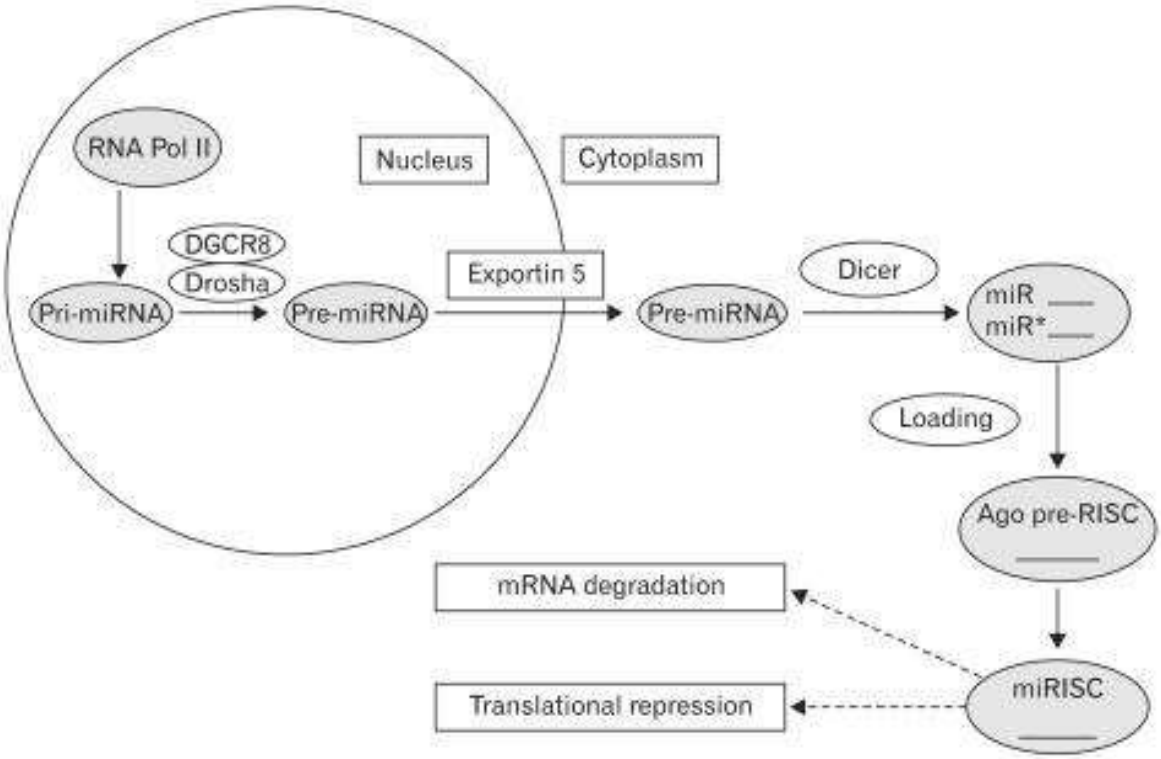

Figure 2: Biogenesis of micro-RNA

Argonaute proteins consist of the following domains: PAZ domain (binds the guide strand at 3′ end); PIWI domain (performs RNase H like activity and can catalyze the initial cleavage of a miRNA base-paired target); the MID-domain (accountable for attaching the 5′ end of the main strand) and the N-domain. The precise identification and suppression of target mRNAs by RISC is assisted by miRNA.

The selection of the transcript of interest is determined by sequence complementarity among the nucleotide sequence at the 5′ end of miRNAs and the mRNA target sites. The base pairing to the nucleotide sequence present at the 3′ end of miRNA does not play a significant role in target identification; it may be involved in the selection of target when sites have feebler miRNA matching. More commonly, the miRNA binding sites are present in multiple copies at the 3′ end of target transcripts. Current findings have shown that miRNA is capable of regulating target gene expression by binding at the 5′ end of the gene as well as within its coding sequence. The translational process is suppressed or mRNA decays due to the binding of miRNA to the target mRNA. The regulatory mechanism is decided by the extent of miRNA–mRNA complementary binding. This complementary base pairing leads to the cleavage of the mRNA strand catalyzed by Argonaute. On the other hand, mismatches ignore the cleavage and encourage the repression of mRNA translation by other pathways[2].

The Gene-Regulatory Functions of miRNAs in Cancer

Recently, the research on miRNAs has increased exponentially which has established that microRNAs are major regulators of gene expression and other biological pathways. These small RNAs perform the main regulatory functions in cancer.

Tissue specificity

MicroRNA can target various genes in diverse tissues, representing tissue specificity miRNA regulators can express various target genes simultaneously in different tissue and cells. Literature reports reveal that numerous RNA-binding proteins support miRNAs processing. HnRNP A1 is a nucleo-cytoplasmic protein that can bind to pri-miR-18a specifically and initiates Drosha-mediated processing. Therefore, HnRNP A1 protein acts as a major role in the regulation of miR-18a, while messenger ribonucleoprotein complexes (mRNPs) may cause miRNA target inhibition.

miRNA and Apoptotic signaling

Apoptosis is programmed cell death which occurs usually during the process of development and aging. It is a mechanism in which the cell population in tissues is regulated, acts as a defense mechanism when cells are injured due to any disease or fatal agents. The suppression of apoptotic pathways is thought to be a major cause of carcinogenesis. The literature reports reveal that tumor cells acquire apoptotic resistance through the anti-apoptotic protein expression or mutation/down-regulation of pro-apoptotic proteins like Bcl-2 and Bax, respectively. The regulation of apoptotic pathways by miRNAs has not been determined completely. Few studies have revealed the role of miR-15 and miR-16 in the control of the Bcl-2, which is a critical regulator of the intrinsic apoptotic pathway. A few reports have suggested the significance of miRNAs in the functioning of extrinsic apoptotic pathways[3].

Role of miRNA in the regulation of senescence

Senescence, the process of withdrawal from the cell cycle irreversibly, occurs as replicative senescence and stress-induced or premature senescence. Replicative senescence occurs due to aging, while stress-induced senescence occurs due to oncogene expression, oxidative stress, or DNA damage. Outstandingly, senescence can be defined as a blockade to tumorigenesis. Micro-RNAs can regulate the signaling pathways involved in senescence, many miRNAs which regulate the cell cycle process negatively, may also induce the senescence. As miRNAs levels are not significantly changed followed by DNA damage, they may moderately encourage senescence.

Dysregulation of miRNA Expression in Human Cancer

The literature reports demonstrate that dysregulation of miRNAs is an evolving sign of cancer. Altered miRNAs regulation may contribute to tumor progression through tumor suppression or oncogenesis. Altered miRNA expression in the tumor was first recognized in chronic lymphocytic

leukemia (CLL). Two miR genes (miRNAs), mir-15a and mir-16-1 were detected that were downregulated or absent. Further, it was demonstrated that mir15a and mir-16-1 can target BCL-2 (anti-apoptotic protein), signifying a probable mechanism by which mir15a and mir-16-1 can cause leukemia. Afterward, various studies have been carried out for the characterization of the miRNA expression profile in different types of cancers. Even, the dysregulation of Dicer and Drosha expressions has also been detected in several tumors. At present, the systematic analysis of complete miRNA expression profile has been realized to be highly significant in various cancers like leukemia, thyroid papillary carcinoma, glioblastoma, breast cancer, hepatocellular carcinoma, lung cancer, pancreatic cancer, and colon cancer [2].

It has been observed that the miRNA expression profile of tumor cells in any tissue is expressively different from normal cells of the tissue. Furthermore, the expression of miRNA varies similarly within cancer cells of similar origins, signifying its role as a means for the diagnosis and prognosis of cancer.

Micro-RNA as Tumor Suppressors or Oncogenes

The expression profiles of miRNAs are discrete in tumor cells, whereby they are known to regulate cellular apoptosis, proliferation, and differentiation[4] along with the initiation and progression of malignant cells. The miRNAs possessing oncogenic activity as well as those that promote tumor expression are named "oncomir". These oncogenic miRNAs encourage the malignant phenotype of cancer cells.

In contrast to oncogenic miRNAs, tumor-suppressive miRNAs are also present in the cells whose expression is reduced in malignant cells by impeding oncogenes or genes inhibiting cell differentiation and apoptosis negatively. let-7 microRNA (tumor-suppressive miRNAs) downregulates mir-15a and mir-16-1, which regulates Bcl-2 induced by DNA damage negatively, which ultimately leads to apoptosis or cellular senescence. Thus, it can be assumed that let-7 miRNA may act as a tumor suppressor. Some of the reported miRNAs that function as crucial tumor-suppressors of various cancers have been listed in Table 1. These miRNAs have been revealed to have effective antitumorigenic properties.

Besides the tumor-suppressive miRNAs, there are also some oncogenic miRNAs. The involvement of miRNAs in the regulation of tumorigenesis may look simply, yet it is highly complex. Table 2 shows some of the examples of miRNAs that are oncogenic.

Table 1: Tumor-suppressive miRNAs

MicroRNA	Cancer type	Function
miR-29b	Acute myeloid leukemia	Enhanced expression is related to good diagnosis and impedes tumor growth.
miR-126	Breast, lung, and colon cancers	Tumor-suppressive w.r.t tumor initiation and metastasis
miR-155	Breast cancer	Downregulates and sensitizes cancer cells
miR-495	Gastric cancer	Downregulates

Table 2: Oncogenic miRNAs

MicroRNA	Cancer type	Function
miR-9	Acute myeloid leukemia	Overexpressed and promotes leukemia progression
miR-21	Breast cancer	Overexpressed and promotes the proliferation and metastasis
miR-421	Gastric cancer	Enhances the circulating tumor cells

Micro-RNA based Cancer Therapy

As miRNAs are an important part of cancer initiation as well as progression, it is a matter of concern, whether these miRNAs can be targeted or not. Although several drugs can alter miRNA expression, the drugs targeting the specific miRNAs can be more effective as well as side effects can be reduced. Recently, the research is going on to design and synthesize oncogenic miRNA inhibitors and the agonist molecules for tumor-suppressive miRNAs which may be used singularly or in combination with clinically approved drugs. For oncogenic miRNAs, the possible therapies may include microRNA sponges, anti-miRNA oligonucleotides, small molecule inhibitors, and miRNA masking, while for tumor-suppressive miRNAs, restoration of these suppressor miRNAs can be an appreciated method[5–8].

Micro-RNA in Cancer Diagnosis

The importance of miRNAs in diverse cancers has been explained and numerous studies

demonstrate their potential as a diagnostic marker. miRNA expression profiles are used efficiently as early detection, classification, and diagnostic biomarkers. miRNAs can specify the inception of a disease as an early **detection biomarker.** As **classification biomarkers**, the miRNA's pattern of expression may recognize the cellular origin of potential cancer cells. miRNA profiles can also predict the progression of a disease as a **prognostic biomarker**. Lastly, these miRNAs can also monitor patients' response to anticancer therapy such as chemo or radiotherapy, thereby serving as a **predictive biomarker**. The alterations in miRNA profiles in the disease condition may be recognized through technologies that evaluate the alterations in miRNA content. Discovering miRNAs that can act as biomarkers for certain diseases and the development of simple and economic detection methods is a challenge to use miRNA profiles as a diagnostic biomarker. miRNA profiles can be obtained by study design; sample collection; sample analysis for miRNA detection; data processing; statistical analysis and clinical interpretation[9,10].

To obtain miRNAs with high specificity and selectivity is a challenging task due to its various essential features. Mature miRNAs are devoid of some features, like poly-A tail or 5'cap that enable their selective purification. Even, the small size of mature miRNAs unable the primers to bind with small templates. Further, miRNAs are heterogeneous in G-C content, which results in a huge interval of melting temperatures of nucleic acid and can also limit the detection of multiple miRNAs[11,12].

Conclusion

Recent studies have demonstrated the importance of miRNAs as a specific regulator of gene expression in various diseases. Numerous reports have also explained the importance of miRNAs expression during tumor initiation and progression. Thus, more systematic investigations are required to develop miRNAs as therapeutic agents for tumors. At present, the therapies against cancer include radiotherapy, chemotherapy using anticancer drugs, oncogene-specific targeting, hormonal treatment, and finally surgery for the removal of the malignant cells. It has been revealed that a better response can be obtained using combined drug therapy based on the patient's genetic profile. Thus, miRNA-mediated treatment can give a new incentive to cure cancer with a better understanding of the function of miRNAs in tumor progression and designing of miRNA-altering molecules more precisely.

During the development of miRNA-mediated therapy, two main obstacles include maintaining target specificity and obtaining high therapeutic efficiency. As miRNA targeting is sequence-specific, it is quite challenging as gene silencing needs the partial complementary binding between miRNA and protein-coding transcripts. Thus, it is significant to assess the effects of specific miRNA-mediated treatment on a proteome level to avoid undesirable gene alterations.

The therapeutic efficiency of mRNA-based treatments depends upon the number of altered genes within a cell that is responsible for the disease. Thus, target gene selection and therapeutic molecule design should be optimized. A partial therapeutic effect of miRNA has also been

observed in neurodegenerative diseases like Alzheimer's by knockdown-mediated therapy; further systematic evaluation is anticipated in cancer therapies. Another limitation is related to its delivery system. Nanoparticles should be established for the systemic delivery of miRNAs. miRNA delivery using Lipid nanoparticles is quite effective, but it induces an inflammatory response. Whereas the biodegradable polymers may induce less inflammatory responses but delivers less competently. Approaches may vary depending upon the type of tumors; further studies are required to precisely evaluate miRNA-mediated therapy in a variety of tumors as well as its diagnostic implications.

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Technology Transfer

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Abstract

The current business scenario has seen an increase in the application of the technology transfer process. Globalization, IPR rights, and liberalisation of the economy have facilitated international technology transfer. An appropriately implemented technology transfer process in the pharmaceutical industry is a very crucial step, starting from the drug development phase to manufacturing. A good technology transfer process also assures constant quality transferred. Fruitful development and commercialization of creative advances are consistently uneasy with challenges, multifaceted undertaking, and scope of advancement of techniques exist to maintain this activity. By a long shot the most famous way to deal with straightforwardly supporting effective development is through technology transfer.

Keywords: Technology, transfer, technology transfer, pharmaceutical industry, quality.

Introduction

The act of transferring logical discoveries starting with one association then onto the next for an additional turn of events, so new items, for example, instructive apparatus, electronic gadgets, etc. can open to people, in general, is known as **Technology Transfer** (TT). This process of transfer of technology is characterized as a sensible method that monitors the transfer of any cycle along with its documentation and expert skill between advancements or between make locales.

One of the most famous examples of technology transfer is the collaboration between one of the largest automobile companies, HONDA and one of the emerging domestic companies of India, HERO. HONDA had the technology; HERO had a suitable market. HONDA collaborated with HERO and transferred its technology to gain the marketplace in India.

Transfer of technology is both critical and integral for new drug development and improvement measure for new clinical items. It is the cycle by which a unique trend-setter of technology makes the technology accessible to business accomplices that will make use of technology.

Scope in Pharma-Industry

TT in the Pharmaceutical sector marks or signifies the cycle of transfer of knowledge about a drug from its pre-development phase to human trial assessment to final marketing and distribution

of the drug. It helps in developing pharmaceutical preparation in different manners as it helps to maintain productivity in cycle keeps up nature of the item, assists with accomplishing normalized measure which encourages production that is cost-effective.

In the pharma-sector, scale-up is required at every stage of production. For example, *little scope research facility advancement from 0.5 to 2 kilograms can be scaled up to 5 to 10 kilograms and afterward to 20 to 100 kg on a pilot scale. Technology transfer covers fabricating drug items in large batch sizes on bigger equipment.* The scale-up step requires technology transfer of information that has been amassed during the little scope advancement of items and cycles. It should be made understandable that great correspondence is basic for detailing and cycle transfer to be fruitful.

It is a basic tool for an analyst or a designer of technology. To make this technology accessible to someone else to abuse can be harmful. The advancement and improvement of technology can be beneficial as it can be used for implementation in various fields. Its uses may be linked to better assembling ability, advertising capacity, and business capacity. In the drug business, technology transfer that takes place by working together with different offices and different associations to market a drug item is a typical cycle.

Importance of Technology Transfer

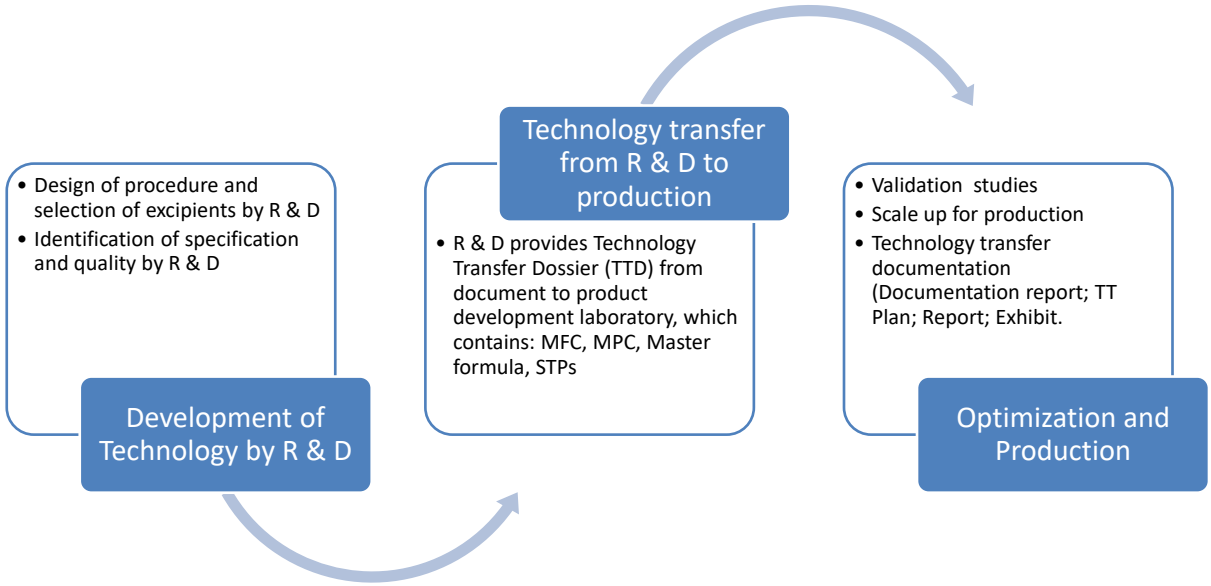
- It helps to gain a clear knowledge of all the information transferred from the R & D department to the manufacturing plant by categorizing all the information obtained.
- It simplifies certain steps and areas of concern for an easy transfer of technology.
- The developer of technology may not have the appropriate resources to market their technology. Technology transfer between developer and producer can help both to meet their targets.
- Technology transfer helps gain knowledge about the already existing process and procedures.
- A well-designed technology transfer process helps reduce the time required for the transfer of technology.
- It helps eliminate the chance of any conflict or change in opinion between the parties.
- There is a higher assurance of compliance in quality with technology transfer.
- It helps improve efficiency.

Example of TT in Pharmaceutical Industry:

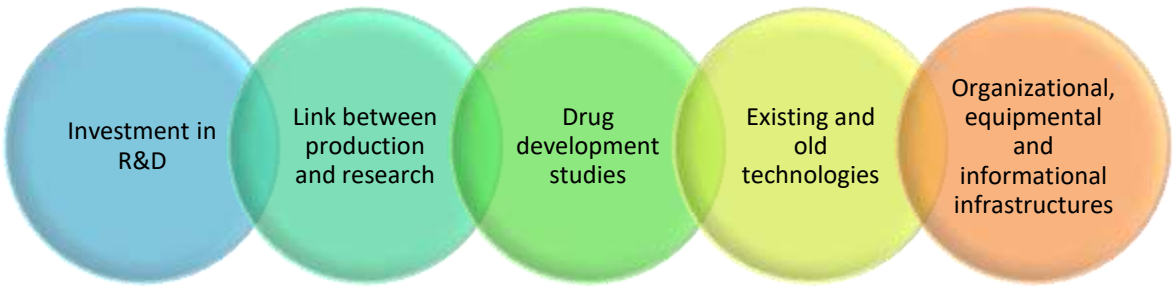
One of the most recent examples of transfer of technology in the pharmaceutical sector is between Oxford University and AstraZeneca to develop and manufacture COVID-19 vaccine AZD1222. Oxford University has the resources necessary for research and development. On the other hand, AstraZeneca, being one of the largest pharmaceutical companies, has the resource to manufacture and market the COVID-19 vaccine.

Steps in Technology Transfer

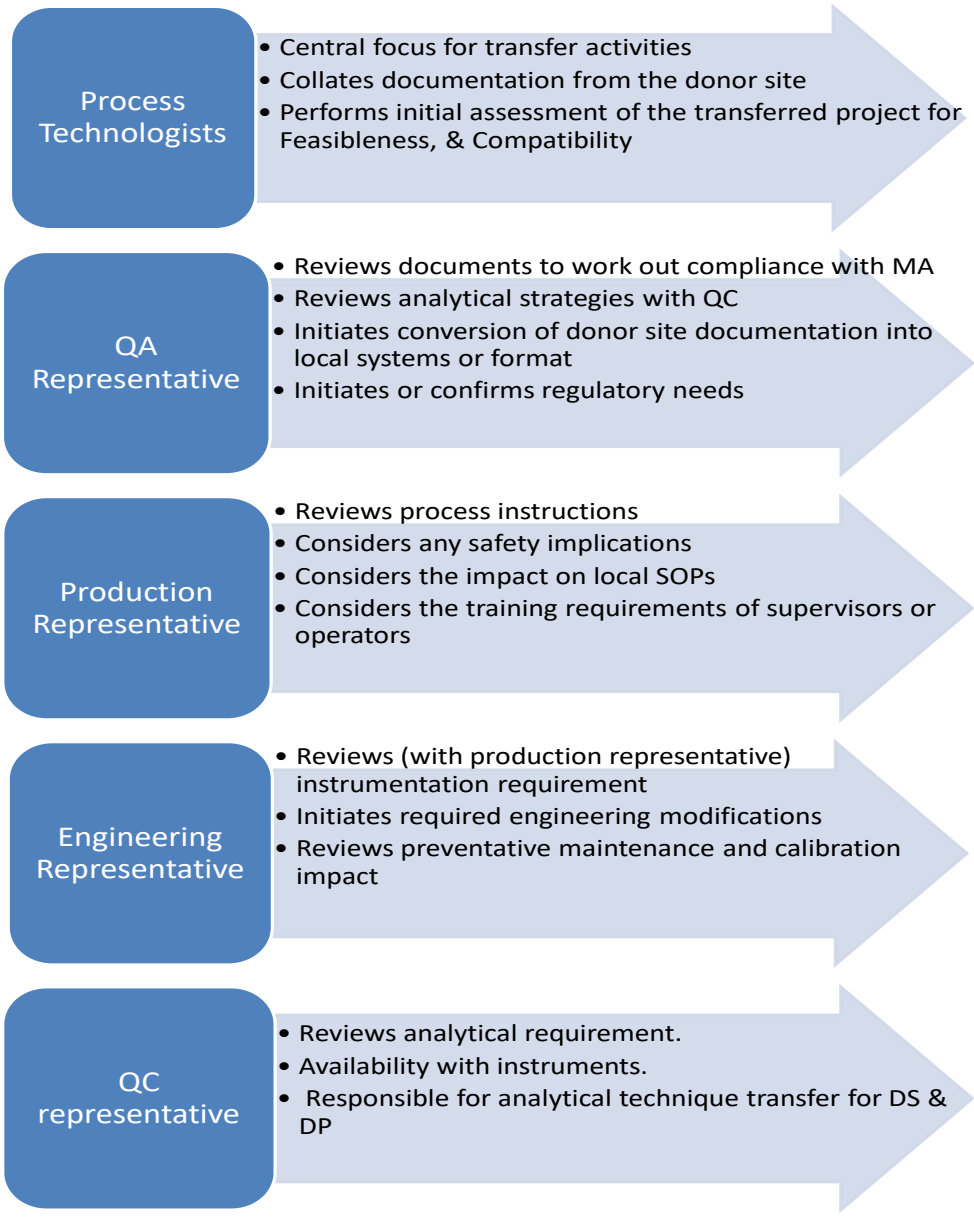
Technology Transfer is certainly not a solitary way measure. Regardless of whether it is a liquid tincture, or capsule, or transdermal fix, the change of a drug model into a fruitful formulation requires the participation from numerous people.



Factors that Affect the TT Process in the Pharma Sector



Key roles and responsibilities of different team members



Barriers of Technology Transfer

- Absence of mindfulness information and efficiency
- Local makers face huge difficulties in gathering International Quality Standards and catching basic piece of the market value.
- Restricted admittance to scientific writings coordinated to inconveniences for researchers.
- National security issues and limitations on fares of specific technologies: International

controls are intended to ensure public security and to forestall the expansion of significant innovations. Likewise, they confine the progression of advancements.

- Low subsidizing in significant regions and potential settlements: There are regions of examination of significance to the creating scene that are being financed insufficiently.
- The Pharma sector requires a large number of skilled human resources. High work turnover and non-attendance inferable from ugly states of administration is negative patron.

Success of Technology Transfer

The diverse "C" for effective technology transfer:

1. Communication: The technology transfer chain is long in most of the times, regarding both distance and time. Powerful correspondence is subsequently another fundamental fixing in the formula for an effective technology transfer. Productive and compelling two ways correspondence and company between key partners will do a lot to eliminate hindrances.

2. Certainty: Eliminating the obstructions to technology transfer regularly converts into expanded assurance, and diminished danger, for the key partners, for example, engineers, providers, and beneficiaries.

3. Challenges: There are numerous hindrances to a fruitful technology transfer. Up and down the transfer way, from the stockpile side of technology to the request side, obstacles happen at the very hub and, because of limitations on the development of data and materials, for each linkage in the technology transfer chain.

4. Capacity: Enhancing the transfer of innovations that help reasonable advancement is generally about making ideal conditions for technology transfer guaranteeing all partners can satisfy their jobs and meet their duties, speedily. Every single vital participant and partner should have the vital information and aptitudes to play out their jobs and undertakings expected of them.

5. Commitment: For an effective technology transfer there might be a decent obligation to defeat the difficulties, furnishing technology clients with the decision they merit and want, increment assurance, lessening chances, improving the correspondence between technology transfer partners, building, and reinforcing the empowering climate and accordingly the limit with respect to technology transfer

Discussion

In the Pharma sector, technology transfer implies the activity to transfer of data and advances made to acknowledge the nature of the plan of medications during assembling. There are three essential contemplations during a successful technology transfer: arrangement, human resource, and cycle. An arrangement should be formulated to sort out the staff and the cycle steps. When arranged, the arrangement should be imparted to the elaborate gatherings in an examination, at the corporate level, and the creation site.

The technology transfer doesn't mean one-time activities taken by the transferring party toward the transferred party, however, implies consistent data trade between both the gatherings to keep up the item manufacturing. For assurance of the quality of the medication produced, it is instructed to well adverse oneself why is technology transfer taking place, when and where it will take, who is the receiver and who is the transferor. Good documentation which is appropriately collected and transferred is the key to any successful technology transfer process.

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TITLE PAGE - Title page should contain title of the paper in bold face, title case (font size 14), names of the authors in normal face, upper case (font size 12) followed by the address(es) in normal face lower case. The author to whom all correspondence be addressed should be denoted by an asterisk mark.

ABSTRACT - Start on a new page after the title page and should be typed in single-space to distinguish it from the Introduction. Abstracts should briefly reflect all aspects of the study as most databases list mainly abstracts. Short Communications, as well as Review Articles, should have an Abstract.

KEYWORDS – 4 to 5 Keywords related to topic

INTRODUCTION - Start immediately after the Abstract, as the next paragraph, but should be typed in double-space. The Introduction should lead the reader to the importance of the study; tie-up published literature with the aims of the study and clearly states the rationale behind the investigation.

MATERIALS AND METHODS - Start as a continuation of introduction on the same page. All important materials used along with their source shall be mentioned.

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DISCUSSION - This section should follow results, deal with the interpretation of results, convey how they help increase current understanding of the problem and should be logical. Results and discussion of results can also be combined with one section, Results, and Discussion.

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ARTICLES IN JOURNALS

- Comerford, J. and Micks, R.H. (1961) Successful pregnancy in sheehans syndrome. Irish Journal of Medical Science. 37(1); 42-44.

BOOKS AND OTHER MONOGRAPHS

- Personal author(s): Ringsven MK, Bond D. Gerontology, and leadership skills for nurses. 2nd ed. Albany (NY): Delmar Publishers; 1996.
- Editor(s), compiler(s) as author: Norman IJ, Redfern SJ, editors. Mental health cares for elderly people. New York: Churchill Livingstone; 1996.
- Chapter in a book: Phillips SJ, Whisnant JP. Hypertension and stroke. In: Laragh JH, Brenner BM, editors. Hypertension: pathophysiology, diagnosis, and management. 2 ed. New York: Raven Press; 1995. p. 465-78.

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References

1. Comerford, J. and Micks, R.H. (1961) Successful pregnancy in sheehans syndrome. Irish Journal of Medical Science. Jan 1961; 37(1); 42-44.
2. Ganong's Review of Medical Physiology, Page 349-351, 385, 23rd ed., Mc Graw Hill, 2010.
3. Goulart, L., Silva, A.G., Shiampi, K.B., Patrício, K.C.M., Barbosa, M.V.J. and Alves, S.T. (1998) Síndrome de sheehan: Relato de caso. RevistaUniversitáriaAlfenas, 4, 63-65.
4. Guardia, O.G., Herrera, E.S., Brealey, A.G. and Hao, C.K.C. (2011) Sheehan's syndrome in Costa Rica: Clinical experience with 60 cases. Endocrine Practice, 17, 337-344.

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