REVIEW ARTICLE

Artificial intelligence and use of robotics in drug development process in pharmaceutical industry: A review

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Abstract

The development of a drug from an initial idea to its entry into the market is a very complex process which can take around 5–10 years and cost $1.7 billion. The idea for a new development can come from a variety of sources which include the current necessities of the market, new emerging diseases, academic and clinical research, commercial sector. Once a target for discovery has been chosen, the medicinal industries or the associated academic centers work on the early processes to identify the chemical molecules with suitable characteristics to make the targeted drugs. This review article will look into the key concepts of drug discovery, medicine the primary ideal of medicinal chemistry is the design and discovery of new compounds that are suitable for use as medicines. This process involves a team of workers from a wide range of disciplines such as chemistry, biology, biochemistry, pharmacology, mathematics, and medicine. The discovery or design of a new drug not only requires a discovery or design process but also the synthesis of the drug, a method of administration, the development of tests, and procedures to establish how it operates in the body and safety assessment. Drug discovery may also require fundamental research into the biological and chemical nature of the diseased state. These and other aspects of drug design and discovery require input from specialists of many fields and so medicinal chemists need to have outline knowledge of the relevant aspects of these fields development and clinical stages of the drug discovery.

Key words: Automation, clinical research and clinical trials, drug development, drug discovery, laboratory, robotics

INTRODUCTION

The development of new drugs is very complex, costly, and risky. Its success is highly dependent on an intense collaboration and interaction between many departments within the drug development organization, external investigators, and service providers, in constant dialogue with nonsupervisory authorities, payers, academic experts, clinicians, and patient associations. Within the different phases of the medicine life cycle, medicine development is by far the most pivotal part for the original and continued success of a drug on the market. The process of medicine discovery involves a combination of numerous disciplines and interests starting from a simple process of relating an active emulsion. The discovery of a new chemical entity that modifies a cell or tissue function is but the first step in the drug development process. Once shown to be effective and picky, a emulsion which is to be discovered must be fully free of toxin, should have good bioavailability and marketable before it can be considered to be a therapeutic entity.[1]

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What is Robot

A robot is a mechanical or virtual artificial agent. In practice, it is usually an electro- mechanical system which, by its appearance or movements, conveys a sense that it has intent or agency of its own. The word robot can refer to both physical robots and virtual software agents, but the latter are usually referred to as bots. There is no consensus on which machines qualify as robots, but there is general agreement among experts and the public that robots tend to do some or all of the following: Move around, operate a mechanical arm, sense and manipulate their environment, and exhibit intelligent behavior, especially behavior which mimics humans or animals.[3]

The International Organization for Standardization gives a definition of robot in ISO 8373: "An automatically controlled, reprogrammable, multipurpose, manipulator programmable in three or more axes, which may be either fixed in place or mobile for use in industrial automation applications."

The Robotics Institute of America defines a robot as Re-programmable multi-functional manipulator designed to move materials, parts, tools, or specialized devices through variable programmed motions for the performance of a variety of tasks.[4]

Three Laws of Robotics

1. A robot may not injure a human being or, through inaction, allow a human being to come to harm
2. A robot must obey orders given to it by human beings except where such orders would conflict with the First Law
3. A robot must protect its own existence as long as such protection does not conflict with the First or Second Law.[5]

How Robots Entered in Pharmaceutical Industry

Robots first became commercially viable in the early 1970, and were principally deployed in rugged and repetitive duties such as welding and handling in automotive manufacturing lines. The first ABB robot, for instance, was installed in 1974 in the automotive field.[6] Since then, more than 150,000 have been installed globally including a large proportion in the pharmaceutical field. Many of these early clinical robots were little more than programmable liquid handlers that provided a mechanical arm for high-throughput screening (HTS) systems, where the arm moved samples from one instrument to another. The industry was slow to adopt robots into manufacturing and packaging processes. One reason for this was, undoubtedly, the industrial nature of robots. Large, apparently oily, machines associated with metal manufacturing processes hardly seemed right for pharmaceuticals.[7]

The Generations and Categorization of Pharmaceutical Robots

The typically squat, one -armed, occasionally mobile first-generation robot originate in the 1960s. Usually, it was single purpose and was used in such occupation as welding, painting, and machining. Today such robots are in a wide use, having matriculated through the early stages of laboratory development and technical, feasibility to economic feasibility in early 1980s. Second generations of adaptive, sensor based robots, at a laboratory stage in the 1970s are just arriving at the stage of technical feasibility.[8] These are diverse robots with some intelligence, but still largely single function. Like first generation robots they are used primarily in manufacturing. A Third generation of robots is needed to work outside the factory. The industrial robots employed in manufacturing operate in highly structured environments. Often the manufacturing environment is altered to accommodate them.[9] Altering to any great extent the environments that service robots will be called on to operate in (e.g., undersea and construction environments, space mines, nuclear power plants, hospitals, offices, and homes) is inconceivable.[10]

APPLICATIONS OF ROBOTS PHARMACEUTICAL INDUSTRY

In the world of pharmaceuticals, there is a key role for robotics to play in the complicated processes of research and development (R&D), production, and packaging.[11] Justification for robots ranges from improved worker safety to improved quality. Speeding up the drug discovery process is another benefit of robotics. A number of robot manufacturers have products specifically designed for this industry.[12]

R&D

Robots now also play an essential role in the development of new drugs. In HTS for instance, millions of compounds are tested to determine which could become new drugs. There is a need for the use of robotics to test these millions of compounds. The use of robotics can speed this process up significantly, just as they can any other process where a robot replaces a person completing any repetitive task.[13]

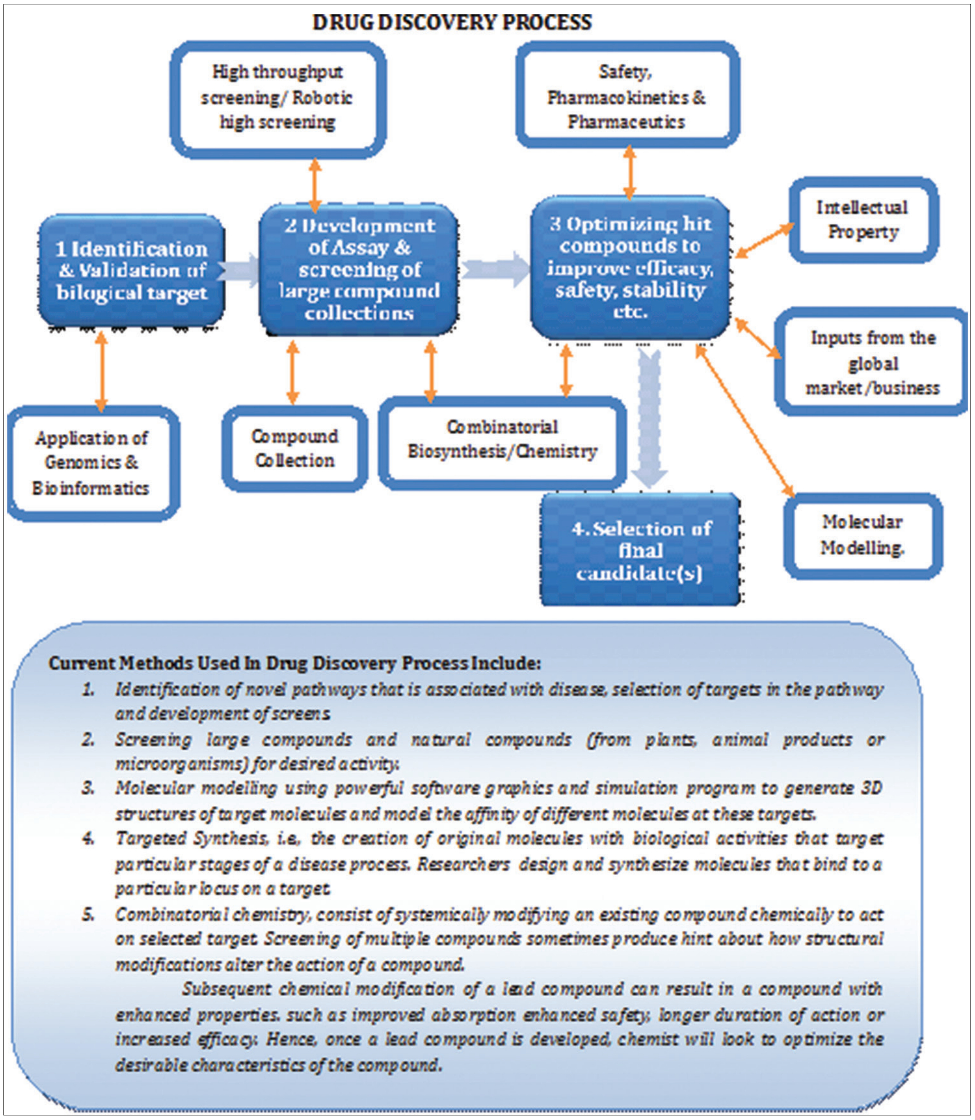

Figure 1: New drug development process

Laboratory Robotic

This new technology allows human talents to be concentrated on sample selection and submittal, and scrutiny of the resulting data, rather than monotous tasks that lead to boredom and mistakes. The desired results of this automation are of course better data and reduced costs. Using laboratory robotics, new experimental procedures are eliminating human tedium and miscalculation in washing and transferring. This includes experiments in radioactive, fluorescent, and luminescent analysis Laboratory robotics is being increasingly applied in pharmaceutical development to help meet the needs of increasing productivity, decreasing drug development time and reducing costs.[14]

Control System

Most robots have onboard controllers that communicate with other machines' programmable logic controllers (PLCs) or with personal computers (PCs) networked to the line. Robot controller is an industrial VME bus controller that connects to PCs for networking and for graphical user interfaces.[15]

Vision Systems

A vision system provides a valuable tool for determining the accuracy of text and graphics in pharmaceutical and medical packaging. The chief benefit offered by adding a robot to the vision system is speed. It inspect insert in <2 min. The same inspection performed by one operator and checked by a second operator could take from 30 min to an h.[16]

Sterilization and Clean Rooms

Robotics can be adapted to work in aseptic environments. Clean room robots have features that protect the sterile environment from potential contamination. These features include low-flake coatings on the robotic arm, stainless steel

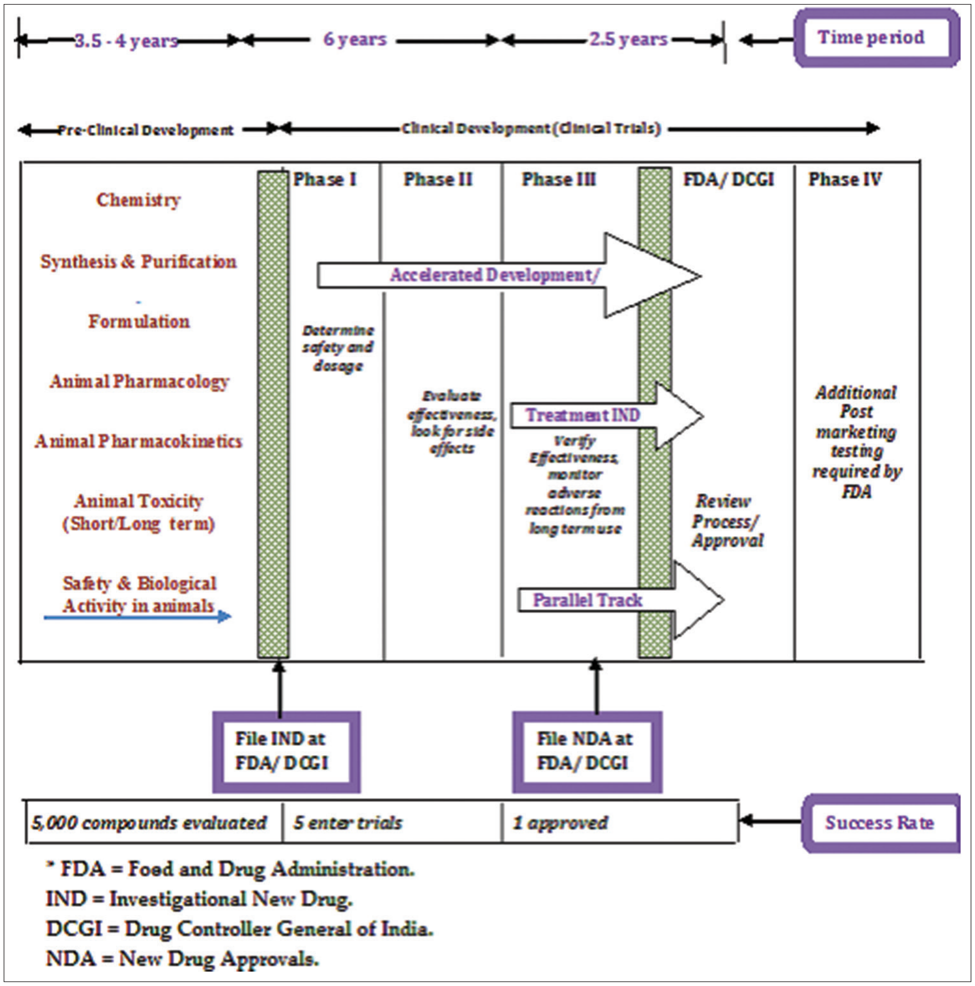

Figure 2: Cylindrical Robot for High Throughput Screening

fasteners, special seal materials, and enclosed cables. Clean room robots reduce costs by automating the inspection, picking and placing, or loading and unloading of process tools. Benefits of robot use in the clean room include:

- Robots reduce scrap by minimizing mishandled or dropped parts
- Robots minimize scrap caused by contamination
- Robots reduce the use of clean room consumables such as bunny suits
- Robots reduce the amount of costly clean room space by eliminating aisles and access ways typically required for human clean room workers. Robots can also be enclosed in mini environments
- Training costs and clean room protocol enforcement are minimized.

Flexible Feeding

Robots are also better than hard automation at flexible feeding, a task that involves handling multiple types of products or packages whose orientation always varies. Conventionally, packaging lines have used high-speed, automated bowl feeders that vibrate parts and feed them to fillers, labelers, or product-transfer mechanisms. Bowl feeders, however, cannot always handle a variety of products at once, and their vibration can damage fragile parts.[17]

Packaging Operations

Packaging processes, like other pharmaceutical operations, benefit from the speed and repeatability that automation brings. Robotics in particular provides flexibility and accuracy. In some packaging applications such as carton loading, robotics also performs more efficiently than dedicated machines. Pharmaceutical packaging machines are often custom-designed to handle specific product configurations such as vials.[18]

Advantages Over Traditional Automatic Packaging Machines

In contrast to packaging machines that automatically stop if too much product accumulates at the discharge, robotic loaders and unloaders meet or exceed the in feed and discharge rates that packaging machines require. This ability allows the robot to keep the packaging process running at full production capacity.

Advantages of Robotic Automation of Packaging

Speed

Robots work efficiently, without wasting movement or time. Without breaks or hesitation, robots are able to alter productivity by increasing throughput.

Flexibility

Packaging applications can vary. Robots are easily reprogrammed. Changes in their end of arm tooling (EOAT) developments and vision technology have expanded the application-specific abilities of packaging robots.

Savings

Automated packaging minimizes costs across the board. Not only is output increased, but robots are tireless. There are no labor expenses with robot packaging - no vacation or insurance costs to pay.

Liquid Handling

Innovative liquid handling of flexible pipetting platforms brings improved efficiency, safety and throughput to laboratories around the world. It includes scalable sample storage and retrieval systems with unique sample tube technology, cutting-edge detection instruments, micro plate washers, and micro array products

Robotic automation of High Performance Liquid Chromatography (HPLC) Laboratories

HPLC is a technique commonly employed in a variety of laboratories. Because of its inherent flexibility, HPLC is suited to a wider range of analytical separation problems than any other single analytical method HPLC has been a major analytical technique in the pharmaceutical industry, in clinical laboratories and in commercial environmental laboratories. Through the use of interchangeable hardware and an endless variety of separation media, almost any type of chromatographic separation is possible. Although HPLC is capable of rapidly separating many different substances with resolution, its suffer from being a labor intensive technique.[19]

Grinding Applications

Manual grinding is tough, dirty, and noisy work. The metal dust produced by grinding is harmful to a worker's eyes and lungs. Grinding robots save manufacturing employees from having to endure hazardous work environments.

Sterile Syringe Filling

Sterile clean, the result of a three-way collaboration between robotics specialist Staubli, factory automation firm ATS and pharmaceutical manufacturer Sanofi-Aventis, was introduced at Interphex with the claim that it is the only robot arm on the market that can be used in barrier isolation systems. Stericlean has replaced manual processes and given us a significant increase in productivity.

Biopharma and Diagnostic Applications

It provides standardized solutions that offer high throughput and ensure reproducible, accurate results in areas such as genomics, cells, and proton sciences and forensics. It covers an extensive portfolio of biopharma applications, supplying pharmaceutical laboratories with automated solutions for cell culture, nucleic acid extraction, normalization, genotyping, protein purification and analysis, hit-picking, ADME screening, PCR applications, and protein crystallography.[20]

Industry: Cylindrical Robot for High HTS

ST Robotics presents a new 4-axis cylindrical robot for DNA screening in applications such as forensic science, drug development, bacterial resistance, and toxicology. The R19 is a totally new design that may be supplied as a precise 4-axis robot, or as a simple 2-axis plate mover. It is usually mounted on a track, which can be up to five meters long, surrounded by various laboratory instruments. The robot moves samples from instrument to instrument according to a protocol decided by the user. Advanced drives create swift and smooth motion while maintaining quiet operation in the lab environment. Like all Sands Technology robots, the new R19 is a totally reliable workhorse, tested to ISO 9000 quality assurance.

The KUKA KR 1000 Titan

The KUKA KR 1000 Titan is the company's latest product and with its heavy weight capabilities has earned an entry in the Guinness Book of Records. The KR 1000 Titan is the world's first industrial robot that can lift a payload of 1000 kilograms with a reach of 4000 mm and will be handling a Chrysler Jeep body. The Titan is ideally suited to handle heavy, large, or bulky work pieces. The heavyweight champion was developed for sectors such as the building materials, automotive, and foundry industries.

Food/Pharmaceutical Handling System with m-430ia Robot Arms and Visual Tracking, Fanuc Ltd.

This robotic food and pharmaceutical handling system features a visual tracking system and a pair of multi-axis robot arms that each can accurately pick up 120 items per minute as they move along a conveyor belt. The arms can work non-stop 24 h a day, are resistant to acid and alkaline cleaners, and feature wrists with plastic parts that eliminate the need for grease. The sanitary design provides the cleanliness required of machines tasked with handling food and medicine. With a proven record of success in reducing manufacturing costs and improving quality, about 150 systems have been sold to manufacturers worldwide since October 2006.

Pharmaceutical Container Replacement Robot

This autonomous robot is capable of navigating tight spaces at factories for the purpose of transporting containers used in the pharmaceutical manufacturing process. The robot can automatically connect itself to large containers (or cases packed with products) weighing up to 200 kg (440 lbs) for transport. The robot only needs to be charged once per day, it can be freely programmed and customized to suit the manufacturing process, and it is safe and easy to use on existing production lines. Three robots are now working on production lines at a pharmaceutical factory, where they have reportedly boosted productivity by (30%).

A Pair of Robots to Recognize and Handle Small Containers, etc. on a Conveyer using Visual Tracking and Arm Control Capabilities, FANUC Ltd's

FANUC Ltd's technology that allows a pair of robots to recognize and handle small containers, etc. on a conveyer using visual tracking and arm control capabilities won the METI Minister Award (Grand Prize), which is granted to a technology that wins the highest appreciation from juries. This technology primarily targets applications at manufacturing facilities of food and medical equipment.[22]

Metal Detector Targets Pharmaceutical Industry

Incorporating Quadra Coila system, Goring Kerr DSP Rx screens pills and capsules at out feed of tablet presses and capsule filling machines. It offers adjustable in feed heights from 760 to 960 mm and angular adjustments of 20–40°. System features open-frame design and polished, stainless steel finish. For maximum hygiene, pneumatics and cables are contained within unit stand. Mounting bars have round profiles to remove risk of debris and bacteria traps.

Labeling System Targets Pharmaceutical Industry

Featuring stainless steel construction, Pharmaceutical Grade Labeling System can label variety of oval plastic and glass containers from 75 to 450 mL at speeds up to 450 ppm. It includes sanitary style conveyor, bar code scanner, eject station with eject verification, and Video Jet laser imprinter for date and lot number on each label. Options include Vision System by Systec, Allen Bradley PLC control, color touch screen operator interface, and full validation package.[23]

Figure 3: M-430iA Robot Arms and Visual Tracking

Figure 4: Pharmaceutical Container

Figure 5: Visual tracking and arm control

Figure 6: Quadra Coila system, Goring Kerr DS

Six-axis Robots Suit Class 1 Clean Room Applications

Running on Smart Controller (TM) CX controls and software platform, Adept Viper (TM) s650 and Adept Viper (TM) s850 bring precision motion and 6-axis dexterity to clean room assembly, handling, testing, and packaging applications. With integrated vision and embedded networking, robots target customers in solar, disk drive, LCD, semiconductor, and life sciences markets.

Space Saving Ceiling Mounted Robot

Adept Technology has introduced a ceiling-mounted version of its s800 series Cobra robot. The inverted robot offers high-speed packaging and assembly with a wider reach, while leaving a much clearer working area. The new robot offers several advantages over its predecessor, which is floor-mounted and traditionally sits beside the conveyor belt or packing line. While the Cobra s800 Inverted Robot has a reach of 800 mm, the same as the previous floor-mounted model, being mounted on the ceiling above the conveyor effectively doubles this reach. The machinery can also be supplied with a vision system of up to four cameras, which identify the position of products on the conveyor belt and link back to the robot so it can accurately pick up and orientate the product for assembly or packaging.[24]

ADVANTAGES AND DISADVANTAGE

Advantages of Industrial Robots

1. Tirelessness: A robot can perform a 96-man-hour project in 10 h with more consistency and higher quality results
2. Return on investment (ROI): There is quick turn-around with ROI. Plus, with the increase in quality and application speed, there are the benefits of increased production possibilities
3. Accuracy: Robotic systems are more accurate and consistent than their human counterparts
4. Reliability: Robots can work 24 h a day, 7 days a week without stopping or tiring
5. Affordability: With the advancements in technology and affordable robotics getting available at lower cost, more pick and place robotic cells are being installed for robotization applications18
6. Quality: Robots have the capacity to dramatically improve product quality. Applications are performed with precision and high repeatability every time. This level of consistency can be hard to achieve any other way
7. Production: With robots, outturn pets increase, which directly impacts product. Because robots have the capability to work at a constant speed without breaking for breaks, sleep, recesses, they have the eventuality to produce further than a mortal worker
8. Safety: Robots increase plant safety. Workers are moved to administrative places, so they no longer must perform dangerous operations in dangerous settings
9. Savings: Greater worker safety leads to fiscal savings. There are smaller healthcare and insurance enterprises for employers. Robots also offer unflagging performance which saves precious time. Their movements are always exact, so less material is wasted16
10. Speed: Robots work efficiently, without wasting movement or time. Without breaks or vacillation, robots are suitable to alter productivity by adding outturn
11. Flexibility: Packaging operations can vary. Robots are fluently reprogrammed. Changes in their EOAT developments and vision technology have expanded the operation-specific capacities of packaging robots.
12. Redeployment: The inflexibility of robots is generally measured by their capability to handle multiple product changes over time, but they can also handle changes in product life cycles
13. Smaller is Better: The expenses of biological assays are

Figure 7: Systec, Allen Bradley PLC control

Figure 8: Smart Controller (TM) CX controls

high and getting higher. Robotics gives researchers the advantage of using tiny quantities of assays and to keep samples safe when moving them within the laboratory

14. Reduced chances of contamination: Removing people from the webbing process reduces the eventuality for impurity and the eventuality for dropped samples when handling them in laboratories. Robotics performs these tasks much briskly with further perfection and delicacy
15. Cost: Requitals for the purchase of robotic outfit in the pharmaceutical assiduity, given the high hourly labor rates paid to workers, number of product shifts, and the low cost of capital. A typical robot installation, complete with accessories, safety walls, conveyors, and labor, could bring around$,000. If that robot was to replace four manual workers each earning approximately $30,000/year, the robot would be paid for through salary savings alone in a little more than a year and a half
16. Increase Efficiency: Robotics can increase efficiency, which means the price of the drug itself will become more competitive. When it comes to pharmaceutical production, people are not as efficient as robots, especially when they are wearing a protective suit. People in protective suits also require more room to work in
17. Can work continuously in any environment: Another advantage in the laboratory is that robots are impervious to numerous surroundings that would not be safe for humans. A robot can operate 24 h a day, 7 days a week without a dip in delicacy.

Disadvantages of Industrial Robots

1. Dangers and fears: Although current robots are not believed to have developed to the stage where they pose any threat or danger to society, fears and concerns about robots have been repeatedly expressed in a wide range of books and films. The principal theme is the robots' intelligence and ability to act could exceed that of humans, that they could develop a conscience and a motivation to take over or destroy the human race
2. Expense: The initial investment of robots is significant, especially when business owners are limiting their purchases to new robotic equipment. The cost of automation should be calculated in light of a business' greater financial budget. Regular maintenance needs can have a financial toll as well
3. ROI: Incorporating industrial robots does not guarantee results. Without planning, companies can have difficulty achieving their goals
4. Expertise: Employees will require training in programming and interacting with the new robotic equipment. This normally takes time and financial output
5. Safety: Robots may protect workers from some hazards, but in the meantime, their very presence can create other safety problems. These new dangers must be taken into consideration.[25-26]

CONCLUSION

Industrial robotics for pharmaceutical applications has a bright future. With a rapidly aging population that urgently requires sophisticated medical devices and newer drugs, robotics systems are increasingly adopted for improved productivity and efficiency to meet this growing demand. As technology improves, more features are likely to be added to robotics systems, not only for delivery, but also for testing and analyzing the samples. This will enhance the efficiency of the robots, and in turn, boost the throughput of the laboratories.

Robotics has been present in the pharmaceutical industry for more than two decades. Once confined to clinical laboratories, the machines have found their way into the packaging processes and will continue to find new applications throughout the manufacturing arena. The future is always hard to predict, but it will be determined by technological developments, commercial factors and by changes within the pharmaceutical industry. What is certain is that robotic automation will continue to spread within the sector. Such are the commercial and financial pressures globally that, within a relatively short time, those who have failed to invest will struggle to compete.

However, industrial robotics manufacturers face several challenges in their effort to establish themselves in pharmaceutical applications. Key among these is the incompatibility of their controller software with existing installed equipment. In most cases, this proprietary software is not upgraded frequently to meet the changing application requirements.

Since it is hardly feasible for end users to replace existing equipment to interface with robotics systems, manufacturers need to find a way to address this problem. The introduction of open architecture controllers expects to go a long way in reducing the impact of this challenge.

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