

ROBOTICS IN PHARMACEUTICAL MANUFACTURING***Shubham Mukherjee, Dr. Falguni Patra and Dr. Beduin Mahanti**

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ABSTRACT

Advanced pharmaceutical manufacturing technologies have the potential to make substantial contributions toward reducing waste, cost, and cycle time. However, the steady introduction of advanced manufacturing systems such as continuous manufacturing processes, automated microbioreactors, robotics, etc. create both challenges and opportunities for nonclinical statisticians who support chemistry and manufacturing control (CMC) activities in the pharmaceutical industry. Not only will closer collaboration be essential for optimal utilization of statistical tools, but CMC statisticians may need to acquire new engineering statistical skills as well as some knowledge of how to deal with “big data” issues. It is also expected that the confluence of advanced manufacturing technologies and statistical methods will require input from nonclinical statisticians on some regulatory issues. The purpose of this article is not only to alert CMC statisticians to these opportunities and challenges, but to provide a call-to-action for the industry and academia to better prepare statisticians for careers in modern manufacturing environments.

INTRODUCTION

Robots can carry out pharmaceutical manufacturing tasks faster, more consistently and more cost-effectively than manual labour. As significant as these benefits are, however, they are far outweighed by the fact that every activity that a robot performs is verifiable. Not only does the robot perform its tasks exactly as it is told to, everything it does can be thoroughly documented. When a human technician places a drug sample into an oven,

sets the oven's temperature to a particular temperature, sets a timer for so many minutes, then removes the sample, questions can always remain: Was the temperature correctly set? Was the timer correctly set? Was the sample actually removed at the specified time? With a robot, not only are such tasks carried out with an extremely high degree of repeatability, but every parameter in the process can be automatically monitored, recorded and verified.

**Figure-1: Human Power & Robotics.****Choosing the right equipment**

The success of any automation project depends first of all on choosing the right equipment. There are three types of industrial robots most commonly used in pharmaceutical

manufacturing — cartesian, SCARA and articulated.

Cartesian robots: In their simplest form, cartesian robots consist of two linear slides placed at 90-degree

angles to each other, with a motorised unit that moves horizontally along the slides in the x- and y-axes. A metal rod called a quill can be added as a third axis (z), which moves up and down in the vertical plane. The quill holds the robot's end-effector, such as a gripper. A fourth axis (t , or θ) allows the quill to rotate in the horizontal plane.

The chief advantage of cartesian robots is their low cost, although their restricted range of motion limits their usage. They are often incorporated into automation subsystems or machines dedicated to a single purpose, such as assay testing.

SCARA robots: SCARA stands for "selective compliance articulated robot arm." This refers to the fact that a SCARA's arm segments, or links are "compliant," that is, they can move freely, but only in a single geometrical plane. Most SCARAs have four axes. Even though three- and five-axis SCARAs are also found, the

terms "SCARA" and "four-axis robot" are often used interchangeably to refer to a four-axis SCARA.

Articulated robots: Articulated robots not only have more joints than SCARAs, they have both horizontal and vertical joints, giving them increased freedom of movement. Whereas a Cartesian robot has a cube-shaped work envelope and a SCARA has a cylindrically shaped one, the work envelope of an articulated robot is spherical. With their greater flexibility of movement, articulated robots can perform almost any task that can be performed by a human arm and hand.

The most common articulated robots have six axes. The first link rotates in the horizontal plane like a SCARA, while the second two links rotate in the vertical plane. In addition, six-axis articulated robots have a vertically rotating "forearm" and two vertically rotating "wrist" joints, which let them perform many of the same types of movements as a human forearm and wrist.



Figure-2: Robotics in Tablet Manufacturing

Determining the type of robot needed.

The first step in automating a process with a robot is to establish the process parameters, including.

1. The required type and size of end-effector, or end-of-arm tooling (EOAT),
2. Cycle time,
3. Repeatability,
4. Reach and
5. Payload capacity.

Taken together, these will usually determine whether a cartesian, SCARA or articulated robot is necessary. Another essential consideration is the environment in which the robot will be operating. Robot models are available for use in cleanrooms, and in applications where bio-contamination control is required, aseptic models have special seals, outer coatings and other construction features that allow them to be cleaned with hydrogen peroxide.

Robot integration

After a robot is selected, it needs to be integrated into the process. Robots are usually mounted in an enclosed

automation work cell. The robot and any other associated equipment are bolted to the cell's steel base or, in the case of an overhead mounting, from a steel superstructure. The upper walls of the cell are generally made of aluminium-framed, shatter-proof clear plastic or see-through, metal-mesh screening. This keeps operators safely separated from the robot, while still allowing them to observe the cell's activity.

As a safety precaution, opening the cell's access door automatically stops all robot motion. In cases where the robot is not enclosed in a cell, light curtains or pressure-sensitive floor mats can also provide automatic safety shutoff. The robot's computerised controller, which contains the electronic circuits that run the robot and interfaces to external equipment through a variety of network inputs and outputs, is usually situated on a platform underneath the cell. Programming the robot is accomplished by means of either a teaching pendant—a handheld interface device that communicates with the controller—or by a computer. Most robot manufacturers offer user-friendly programming software that does not require specialised engineering skills. Some robot controllers can also interface with third-party software,

such as National Instruments LabVIEW, which allows the user to program the robot without having to learn a new programming language.

The teaching pendant allows an operator to move the robot from one point to another and instruct it what to do

at each location, thus, “teaching” it the desired routine. With available software, robots can also be programmed offline on a remote computer, saving development time. A virtual, simulated 3-D environment lets the user configure the robot and any peripheral devices without having to actually operate them.



Figure-3: Robotics in store Management.

Robots Used In Pharmaceutical Industry

1. 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 kilograms (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%.

2. Cylindrical Robot for High Throughput Screening

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 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.

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 hours 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.

3. 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.

4. 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 800mm, 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.

5. Metal Detector Targets Pharmaceutical Industry
Incorporating Quadra Coila system, Goring Kerr DSP Rx screens pills and capsules at out feed of tablet presses



Figure-4: Robotics Arms.

Robots for filling, inspection, and packaging

Robotic technology is being used for vial-filling applications on slower speed applications. "Robotic vial manipulation transfers components from station to station both before and after filling and pack-off," says Walt Langosch, director of sales and marketing at ESS Technologies. The company also has experience with handling plastic and glass prefilled syringes in pre-process, buffering, and initial and end-of-line packaging. "Automated syringe assembly, inspection, and preparation for packaging is an ideal application for robotics," says Langosch. "The primary advantage in sterile environments is reduction of risk due to environmental contamination and contamination generated from human intervention during component transfer." In addition, productivity is increased because of the accuracy and efficiency of robots, which often

and capsule filling machines. It offers adjustable in feed heights from 760-960 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.

perform at increased speeds and produce less scrap.

Automatic inspection, as part of a robotic system, has the advantage of enabling 100% part inspection. Vision-sensing technology can be used in pharmaceutical packaging to verify serialization numbers for compliance with track-and-trace regulations. "Robotic dexterity and accuracy combined with current and future optical technology and serialization software is the ideal technology for an automated solution," says Langosch.

An advance in vision sensors is color imaging, which, for example, allows systems to distinguish between bottle caps of different colors, noted PMMI in a trend report (3). Vision sensors have also led to advances in end-of-arm tooling design that improve the ability of robots to accurately identify and place objects.



Figure-5: Robotics in store Management.

Robots for producing personalized medicines

Custom automation and contract-manufacturing company Invetech recently partnered with biopharmaceutical company Argos Therapeutics to develop automated manufacturing systems based on Argos' Arcelis technology platform for personalized immunotherapies. "The Arcelis platform uses two, five-axis robotic arms in the production of the mRNA from a patient's tumor, which is used as the antigen for loading into the dendritic cells produced in the cellular processing equipment," explains Richard Grant, director of cell therapy at Invetech. "The cellular equipment uses automation to manipulate the white blood cells throughout the manufacturing process to control their development and maturation into dendritic cells. These cells express the desired antigens, which when delivered to a patient, will trigger the patient's immune system to produce killer T-cells that will target the metastatic tumors."

"The RNA robots manipulate closed disposables to perform the process within the common Class 100,000 cleanroom space," says Grant. "The use of the closed disposables allows multiple patients' materials to be processed in the same manufacturing space, driving the facility capital and operating costs down significantly."

Argos' lead candidate is currently in Phase III clinical trials, and the automated technology is designed to be modular and easily scalable. Clinical processes are generally manual, skill-based processes that cannot operate practically or economically at commercial scale, notes Grant. Use of robotics, however, allows the processes to be scaled up commercially. "In addition, robotics allows new sites to be replicated around the world in a scale-out model, with minimum training for set-up and validation of new sites and minimal site-to-site variability in production processes," explains Grant.

Cleanroom robots

Robotic technology is ideal for cleanroom processes, such as aseptic filling, because it eliminates human contamination risk. Robotics can provide an ISO 5

environment to preclude the possibility of microbial ingress, says Langosch. ESS Technologies partners with Fanuc Robotics for secondary packaging and palletizing of pharmaceuticals, and Fanuc has several robots that will operate in an ISO 5 environment. The Fanuc M-430iA/2PV can withstand hydrogen peroxide vapor sterilization and has a waterproof rating; all wiring and cabling is routed through the robot's hollow arm.

Robots designed for use in cleanrooms must minimize particulate generation to maintain cleanroom classifications, typically ISO Class 5 or 6. Cleanability, including minimizing crevices and ensuring the robot is resistant to cleaning and sterilizing agents, is also a requirement, notes Grant. Operator safety must be ensured by guarding or containing the robot. Another requirement is controlling the speed of robot movement to minimize impact on airflow and particle generation and to a lesser extent, managing heat generation and its impact on the heating, ventilation, and air-conditioning system of the cleanroom, explains Grant.

Robots in the laboratory

Robotics has come a long way in the pharmaceutical laboratory, notes Mike Ouren, Life Sciences manager at Precise Automation. In the laboratory, robots are used, for example, to transport microtiter plates between instruments. "Although the instruments can be loaded manually, a robot tied to a scheduling software system eliminates human error, maintains the quality of the experiment, and allows scientists to focus on the content of the experiment, instead of how they will execute it," explains Ouren.

Laboratories differ from industrial applications in that, although tasks are repetitive, they are not as consistent and may change depending on the experiment, says Precise Automation's Ouren. The need to access equipment near the robot quickly and the space limitations of a laboratory can be met with new collaborative robots that do not require safety guarding. In 2012, Precise Automation introduced a collaborative SCARA robot (or "cobot"), the PreciseFlex (PF)400,

which handles less than 1-kg loads and is designed to allow operators to work safely next to the robot without barriers. The smaller footprint of the robot reduces cost, and the space savings is useful in benchtop laboratory applications. The robot is user friendly, and the Precise Guidance Controller inside the PF400 allows laboratory personnel to "teach" the robot using only their hands. "Because there are no barriers, instead of using a complex remote-control pendant to teach the robot, the operator can show the robot what to do by simply grasping the end of the robot arm. This accessibility is unheard of in industrial automation," explains Ouren.

Other laboratory applications for robots include vial

handling. A Fanuc robot is being used in a laboratory, for example, as a single-point handling solution for vial processing. "A handling tool was designed and attached to the end of the robot to enable it to handle ten vials at a time. A variety of components were also placed around the robot cell—including indexing tables for full rack staging, a thermostatically controlled water bath for precise sample temperature, a retrieval system for dumped vials, a washing-brushing-rinsing-drying station, a preservative spray station, and a recapping station," explained Sumner in a press release.

In the laboratory and on the manufacturing floor, robots are increasingly used to improve quality and efficiency.



Figure-6: Robotics in Packing Technology.

DISCUSSION AND CONCLUSION

Incorporating robots into pharmaceutical processes has many advantages. Robots can perform operations three or four times faster than humans and can function 24 hours per day. These characteristics make robots good at producing large quantities of products efficiently. By performing simple, repetitive tasks, robots can free employees for creative work such as developing new products.

The pharmaceutical industry, in turn, is favorable to robotic systems because its processes generally require low forces, take place in clean environments, and include predictable sets of operations. Pharmaceutical industries are intently seeking ways to reduce their expenses, increase their efficiency, and make high-quality products. Robots can help companies achieve these ends by providing speed, precision, repeatability, and flexibility. Because they can improve discovery, pilot production, and small-scale production, robots can be a particularly powerful foundation for the growing biotechnology industry.

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Certificate

This is to certify that project work embodied in this report entitled "Robotics in Pharmaceutical Manufacturing" was carried out by SUBHAM MUKHERJEE (ID No- 171001018037) studying at School Of Pharmacy, Techno India University for partial fulfilment of B.Pharm. Degree to be awarded by Techno India University. This project work has been carried out under my guidance and supervision and it is up to my satisfaction.

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