Robotics of the future in the pharmaceutical industry

Dr. Carl-Helmut Coulon • INVITE GmbH, Leverkusen

Correspondence: Dr. Carl-Helmut Coulon, Head of Future Manufacturing Concepts, INVITE GmbH, CHEMPARK, Geb. W32, 51368 Leverkusen;
e-mail: carl-helmut.coulon@bayer.com

PEER REVIEW

Abstract

This article differentiates applications of "modern robotics" from classical automation in order to illustrate that technical advances in recent years have made a new type of automation possible. It discusses the drivers and applications within the pharmaceutical industry which will benefit from this modern robotics and gives an indication of the industry-specific requirements. Section 5 outlines how machine learning will simplify and speed-up developments in future. Finally, the article envisions major opportunities for the pharmaceutical and robotics industries justified by the availability of the described new type of applications in combination with the outlined demands.

Key Words

- Robotics
- Pharmaceutical industry
- Automation
- Production
- Laboratory

1. Introduction

Requirements regarding quality, ergonomics and efficiency reveal the necessity to a much higher degree of automation for the production of pharmaceuticals. In addition, for safety reasons the industry is asked to technically separate humans and high potent substances wherever possible [1, 2]. However, looking at production, many activities are currently still carried out by humans, even though there are strong reasons to avoid it.

The main message of this article is the hypothesis that modern robotics will provide the pharmaceutical industry with cost-effective and easy-to-use flexible applications as soon as the pharmaceutical industry specifies these applications and their requirements. Phrased the other way round: There will be a relevant market for robots in the pharmaceutical industry in future.

Author

Dr. Carl-Helmut Coulon

Since 2015 Dr. Carl-Helmut Coulon heads the "Future Manufacturing Concepts" group at the Research Institute INVITE including the subarea "application-oriented robotics research". After his PhD in artificial intelligence in 1997 he started at Bayer AG in the automation department followed by various functions around the production technology up to his switch to INVITE 2015.

2. Modern Robotics: New abilities by new technologies

What distinguishes modern robotics from traditional automation? This section names the differences and will show experiments and previous implementations as examples. The aim is to prove that modern robotics can often provide solutions that are suitable for the challenges mentioned above in terms of flexibility and cost-effectiveness.

2.1 New technologies enable flexibility and cost-effectiveness

Industrial robots are used worldwide in large numbers at correspondingly attractive conditions, especially regarding the ratio of costs to functionality. If flexibility and cost efficiency at low throughput are important, such a "universal machine" is superior to a specialized machine. Figure 1 shows how developments in recent years have contributed to the necessary features which support cost-effectiveness.

Today's development environments simplify programming significantly. In particular, the increasingly simple integration of sensors and grippers in integrated development environments speeds up development considerably. This means that simple applications such as removing objects from a conveyor belt in packaging can be taught to the robot in minutes.

In contrast, modern sensor technology such as image recognition and touch sensors is not simple per se. Anyhow these technologies are

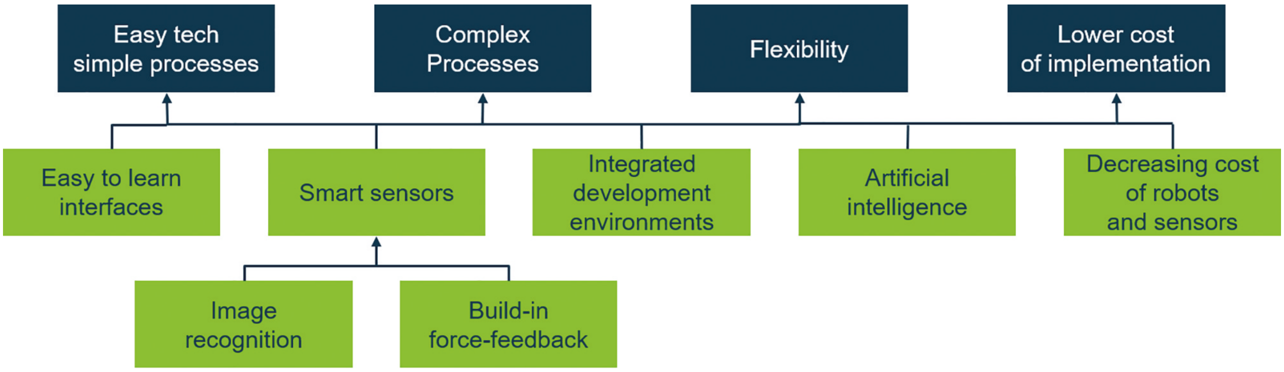

Figure 1: Overview on new abilities supporting cost-effective applications enabled by new technologies (source of all figures: INVITE GmbH).

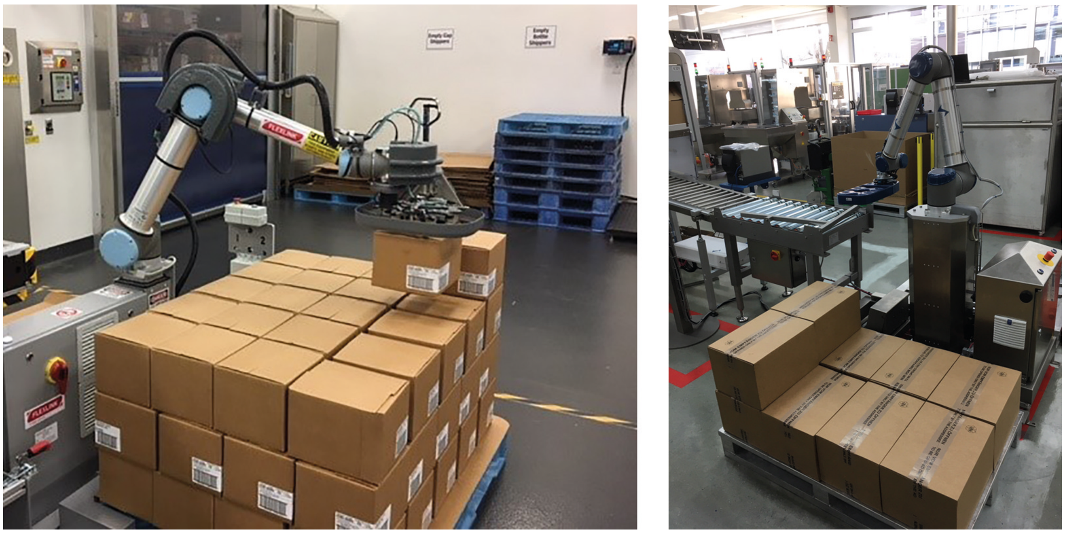

Figure 2: End-of-line-Palletizing without safety fence.

now available and integrable in high quality and variety for the engineer. Recognizing an object with an accuracy of a tenth of a mm or monitoring the correctness of the performed action via the tactile sensor system can now be integrated into robotics applications more easily than before. This makes it increasingly easier to develop highly flexible and complex applications like the one described in the next section. The necessity to apply artificial intelligence and its impact to flexibility and cost-effectiveness will be explained in section 5.

In addition, new safety concepts can reduce the space requirements of solutions and integrate them better into the workflow if, for example, they can do without a separating safety fence by utilization of safety-sensors (fig. 2).

2.2 Modern robotics as an alternative to classic automation based on process adaptation

In classical automation, it is common practice to standardize the world so that it is easier to automate. However, if the existing standard cannot be handled by classical automation or if it would be very costly to adapt existing processes to automation due to regulatory requirements restricting changes within the process, no automated solutions have been developed so far.

A relevant example is the handling of solid substances in containers of all kinds in the incoming goods department of companies (fig. 3). Inliners in drums are the worldwide standard, especially for active substances. Millions of them are produced annually in the chemical, pharmaceutical and food industries. Since there is no automation available to date that can handle the variety of hundreds of different types of these containers in the incoming goods department of the sites, the vast majority of containers of this type are now handled by humans.

Obviously, the processes would be much easier to automate at this point and also more secure if a new standard of containers could be introduced which would not only be easier to handle automatically but would also allow a closed handling of the substances so that contact with the environment is avoided during handling.

Despite these strong drivers for standardization it is not to be expected that the task will become ea-

Figure 3: Variety of incoming containers with solids.

sier for automation in the near future either.

For these reasons, there was an open innovation challenge in 2016/2017 that asked to develop prototypes of an automated solution for the following process:

- Open drum
- Open inner bag/inliner
- Take sample and place into sample holder
- Close inner bag/inliner
- Close drum and attach new seal.

Further details of the challenge are described within [3].

This challenge has shown that modern robotics offers new flexible approaches to solve a complex task like this. 2 characteristics of the prototypes should be described in detail:

- Image recognition: The state of the art has evolved in the last few years in such a way that today there are not only many systems on the market that can recognize 3-dimensional point clouds with sufficient accuracy, but the costs of these systems have decreased to such an extent that it does not significantly increase the system costs to use several cameras. As a result, clearly defined objects such as the barrel, the closure or even the cable tie can be detected without any problems, even if the colors of the objects vary. After all, even a white cable tie on a white bag must and can only be recognized by its shape.
- Tactile sensors: There is hardly a simpler, more reliable and more precise way of determining a position than by touch. Meanwhile, force feedback sensors are built into many robot arms and are alternatively available as standard modules for the wrist of the robot. If, for example, the robot arm (supported by force feedback sensors) drives against the edge or closure of the barrel or hooks under the cable tie with a tool, the situation is perfectly detected to reliably enable the desired robot action.

Finally, the combination of image recognition and tactile sense in a "human-like" way is very effective. For example, the camera can detect the position of the cable tie and the force feedback sensor can then verify the position during the opening process and monitor the success of the action.

Based on the results of the competition and further research, an industrial solution for this task is currently being developed.

The insight from this example is that even without adapting the processes, modern robotics can make it possible to automate processes that were previously seen as not automatable. The next section will line out the drivers behind applications like this with focus on different areas within the pharmaceutical production.

3. Drivers and future applications of modern robotics

Some tasks have a high attractiveness for automation but cannot be automated in an economically viable way by "classical" automation because it is not about high-frequency and big business cases. The attractiveness is given by other drivers (fig. 4), such as

- separation of product and human,
- work ergonomics,
- automatic "perfect" documentation,
- high repetitive accuracy or
- 24/7 availability of the sub-process.

Efficiency and thus increased profitability are of course goals as well, but rather as a consequence of reaching the mentioned goals and as boundary conditions for any investment.

Even though the drivers are obviously relevant as drivers for automation operational units have difficulties to identify the corresponding opportunities. In order to reveal these potentials, an assessment for the individual companies and organizational units is helpful:

- *Ergonomics*: Where is the highest sickness-rate?
- *Monotony*: Job "hated most"...
- *Safety/Separation of Product & Human*: Where is the highest need to protect human and/or product?
- *Efficiency*: Which is the single process step with the highest demand of manual work?
- *Quality*: Which is the most "trickiest" manual process causing variances in the quality? Where do human errors cause deviations?
- *Documentation*: In which process is the documentation effort for the manual work the highest in comparison to the work itself? Where are higher GMP requirements on data integrity?
- *Missing 24/7*: Which function causes the highest "impact" due to missing 24/7 availability?

Following these questions, the next sections name drivers and concrete applications for different segments of the pharmaceutical industry. Some of these applications are already the subject of current individual developments, others are the result of the first meeting of the In-

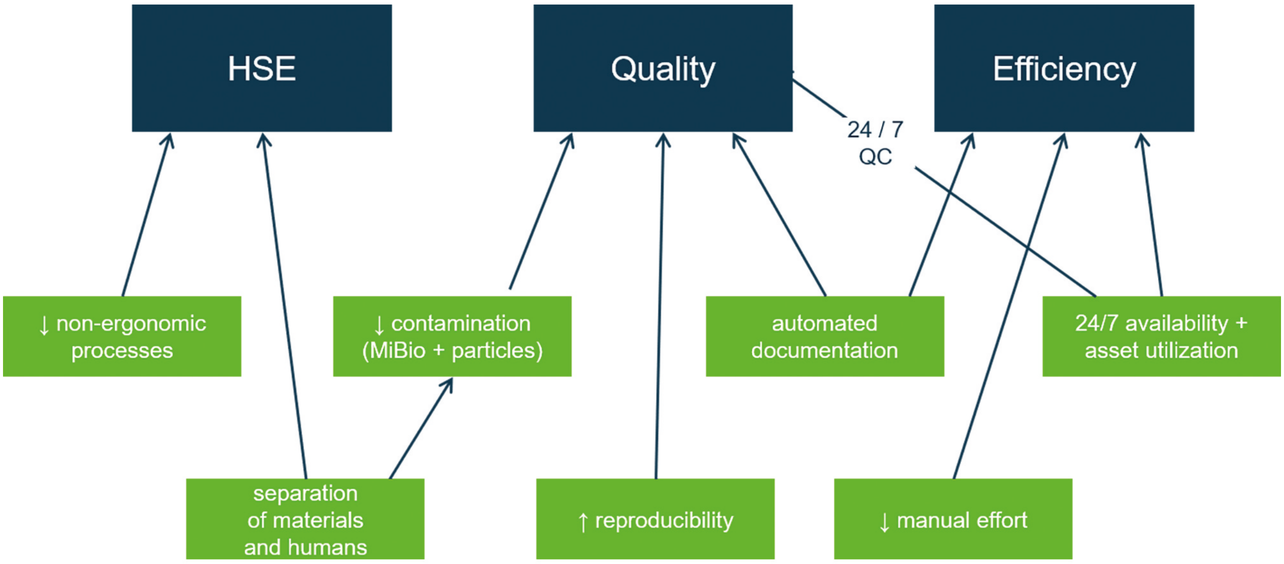

Figure 4: Overview of drivers of modern robotics in the pharmaceutical industry (HSE: Health, Safety and Environment targets).

ternational Society for Pharmaceutical Engineering (ISPE) Special Interest Group Robotics (DACH) [4]. This Special Interest Group (SIG) will continue to detail and prioritize the most attractive applications. The final goal is to get access to these applications at best conditions (with respect to implementation effort and costs compare section 5).

3.1 Production

Changeover, cleaning and preparation of material are physical activities for people working in production in the process industry. These activities are characterized by high demands on flexibility, documentation and/or the ability to master complexity. Automation that goes beyond the previous level must be particularly flexible here.

Examples of such applications are:

- Depalletizing and re-palletizing (e.g. order picking or from wooden to aluminum pallets)
- Opening of containers for solids, sampling of solids for Quality Control (QC) and dosing of solids setup and cleaning of standardized production equipment such as tableting turrets or format parts/handling parts

Within the first session of the ISPE SIG Robotics the participating companies added many demands for automation within production with a special focus to the production core process, transportation and cleaning (table 1).

3.2 Packaging

For large-volume standard packaging, classic packaging systems are established. They

- have a high performance,
- require a lot of space, as each "operation" is carried out in a different part of the line,
- are profitable for large quantities, since they consist of many components which leads to high costs in construction and system integration, and
- have to be extensively changed over for handling different products and are therefore unsuitable if the products change frequently.

However, as soon as the number of pieces is low and/or the variants are frequent, one sees people performing monotone and ergonomically questionable tasks. In contrast to traditional automation, humans are much slower, but much more flexible – and they require much less space.

Examples of such applications are: (all for small batches and different products)

- Palletization at packaging lines
- Simple pick-and-place applications, e.g. from the belt into the box
- Complex packaging, e.g. multiple different components in one package
- Closing and labelling the carton

Table 2 lists further demands discussed within the SIG Robotics.

3.3 Quality Control/Research & development laboratories

In QC, many people perform routine tasks – if QC cannot be integrated into production inline. Complex analyses are often carried out by analytical equipment, but the complete material flow and the partially necessary sample preparation is done by humans.

Due to the variety of tasks and necessary steps, traditional laboratory automation is only suitable if its use is worthwhile due to high throughput and low sample and process variance, e.g. preparation of microtiter plates.

Examples of such applications unmatched by classical automation are:

- Sampling from containers (drums, bags, barrels, buckets, Big Bags)
- Sample preparation in the microbiological laboratory
- Separation and dosing of samples for the different analysis needs

Table 1

Selection of needed applications for production named within the first meeting of SIG Robotics.

Process	Transport	Cleaning
Homogenizing/Mixing	Package handling between process steps	Format parts, punches in tableting, complex shaped components, also wash of organic substances
Filling	Handling in interim storage: stacking, sorting	Cleaning equipment within campaigns
Unpacking/dosing of excipients and active ingredients	Trolley transport	Inspect cleaning
Mixing of raw materials	Change of equipment (e.g. replacing a full container with an empty one)	Room cleaning
Unpacking/dosing active ingredients		
Unpack and supply consumables (sterile)		
Automatic loading, docking, undocking of containers		

Table 2

Selection of needed applications for packaging named within the first meeting of SIG Robotics.

Packaging
Pallet box loading/unloading with collaborating robot (FS/bundles/tray)
Gluing, filling and regluing folding boxes
Packaging of bottles and blisters for current manual packaging (very small batches -> high flexibility)
Repacking (de-bottling, de-blistering) under a protective atmosphere
Removing labels from boxes

- Transport of samples between specialized analytical instruments

Table 3 lists many more processes named within the SIG Robotics which are executed by humans today and are meant to be attractive for automation.

4. Industry-specific requirements

Robotics applications must fulfill similar requirements in different industries – mainly regarding maintainability, usability, reliability and safety [1, 2]. By targeting applications which are applied not only in one plant but within the whole industry, the companies within the pharmaceutical industry must align their requirements. Today it is quite common that e.g. the safety regulations are applied differently by different companies leading to unnecessary development and costs.

Within the pharmaceutical industry there are many requirements on top. The most specific requirements are the necessity to avoid cross contamination and the required ability to qualify an application with respect to regulations. Table 4 lists concrete features discussed within the SIG Robotics workshop and related to these 2 major requirements.

5. Machine learning will further increase flexibility and cost-effectiveness

Looking at the technical advances in automation it is obvious that the pharmaceutical industry is not anyhow close to the limit. Looking at the sample of incoming goods it is also obvious that it still costs an enormous effort to handle the variety of real life by automation.

The higher the variance of processes and objects to be handled in an application, the higher the development effort increases accordingly.

In the coming years, the use of machine learning will reduce this development effort. Today, machine learning is already used intensively in image recognition and data analysis. However, the "manipulation" of an object to be handled is usually engineered "by humans". Even though it is already possible to teach a robot relatively easily by demonstration, this is rarely used for development of industrial applications. Inserting an

Table 3

Selection of attractive applications for automation in laboratories named within the first meeting of SIG Robotics.

Preparation and sample management	Assay/Process Performance	Finishing, disposal, cleaning, rennet maintenance
Sample transport and distribution	Titration process	(Sterile) cleaning: Wiping, suction and rinsing of robots
Buffer and solution preparation	Determination of drying loss and sulfate ash	Ample storage (stability sample supply, retained samples, samples for microbiological analyses)
Distribution and provision of consumables, materials to the work-places	Passenger process of a cell culture	Disposal
Sample Weighing and Dilution	Cutting off blood tubes	Preliminary cleaning of (glass) vessels
Preparation of standards and test solutions	Performance of thin layer chromatography	
Goods receipt for samples/Sample Separation	Bacterial Endotoxin Test (LAL)	
Quality Tests: particles, tightness, level/weight/volume	Microbial sterility testing	
	Wet chemical analysis	
	High Pressure Liquid Chromatography (HPLC) preparation and measurement	

Table 4

Selection of industry specific requirements named within the first meeting of SIG Robotics (RRKL: clean room class).

Avoid (cross) contamination	Capable of CSV (computational systems validation)
Cleanability of the robot in contact with OEB 4/5 materials (effectiveness & solvent resistance)	Qualifiable
Surface condition (roughness required by cleanroom-class (RRKL))	Data Integrity/Audit Trail
Cleaning validation concept	Implementation of pharmacopoeia methods
Hygienic Design	
Suitable IP class for each cleaning specification	
Limited emission of particles (according to RRKL)	

object into another object with an accuracy of a tenth of a mm, pouring 100 ml from a bottle or reacting to tactile sensors or image recognition is still done by programming today.

Future systems will learn by themselves to deal with new situations in a targeted manner. In 2016 Google published a video where robots learn from more than 800 000 attempts to pick different unknown objects out of a drawer [5]. Although learning robotics is currently still primarily a research topic, the video demonstrates the opportunities to increase the flexibility and cost-effectiveness of robotics applications in future.

6. Major opportunities for the pharmaceutical and robotics industries

By screening the current robotics applications at more than a dozen pharmaceutical production sites the named palletizing application is the only known off-the-shelf solution. All other robotics applications within the pharmaceutical production are custom-built. This results in

TechnoPharm 10, Nr. 3, 150–157 (2020)

high effort in engineering, development, qualification and implementation.

Especially in processes that are similar in all companies, the flexibility of modern robotics can enable standard solutions that are not only rewarding for suppliers due to their number of units but are also highly attractive for the applying industry in terms of implementation effort and costs. What is necessary to get there?

First, the pharmaceutical industry must identify the applications and their requirements. Looking at organizations like ISPE and others this topic gets more and more awareness. It is just a matter of time until the application targets are published.

Second, robotics companies are needed which are engaged enough to envision the selling potential of such applications and willing to deliver the most flexible, most easy to qualify, most easy to install and therefore most competitive robotics application.

The palletizer in fig. 2 might not be the most typical pharmaceutical application, especially because it can be applied aside from regulative requirements. Anyhow it is flexible enough so serve the different clients, is already sold in hundreds, is set up in minutes instead of weeks and therefore a good example where "industry" can get if "industry" really wants to!

Literature

[1] European Council Directive 89/391/EEC of 12th June 1989 on the introduction of measures to encourage improvements in the safety and health of workers at work

[2] Information der Deutschen Gesetzliche Unfallversicherung (DGUV) 213-083; Section 6.2

[3] Open Innovation Challenge: *https://grants4tech.bayer.com/robotic-competition/*; Bayer AG Corporate Technology & Manufacturing – Innovation Management

[4] *https://ispe-dach.org/arbeitsgruppen/sig-robotic/*; Results of first constituting meeting 18th Dec 2019

[5] Google Develops Robot Arms that Learn to Pick Up Objects: *https://ai.googleblog.com/2016/03/deep-learning-for-robots-learning-from.html*

All links were checked most recently on 14th Apr 2020.

Chefredakteur: Claudius Arndt, Leitender Redakteur: Jens Renke. Verlag: ECV · Editio Cantor Verlag für Medizin und Naturwissenschaften GmbH, Baendelstockweg 20, 88326 Aulendorf (Germany). Tel.: +49 (0) 7525-940 120, Fax: +49 (0) 7525-940 127. e-mail: redaktion-tp@ecv.de. www.ecv.de. Herstellung: rdz GmbH / Holzmann Druck GmbH & Co. KG. Alle Rechte vorbehalten.