Examination and evaluation of GMP-compliant pharmaceutical production standards in the context of Industry 4.0

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Summary

Research questions:	Is it possible for pharmaceutical companies to apply the concepts of industry 4.0, such as the smart factory, completely in their GMP relevant production processes? Are the GMP guidelines generally open to modern production methods enabled by I4.0? Are those responsible in the pharmaceutical industry familiar with the possibilities of I4.0?
Methods:	Hypotheses are tested by means of quantitative primary research in form of an online survey. The people interviewed are from the fields of technology and maintenance, quality control and management of leading, globally active pharmaceutical companies. The questionnaire was developed specifically for the topic of this paper by literature research and personal communication with leading managers for strategic development in the pharmaceutical production branch.
Results:	The hypotheses could not be supported completely. The survey shows that the potential of industry 4.0 concepts has not yet arrived in large parts of the workforce and the management level. The GMP regulations allow innovations in many areas, but with considerable effort during the implementation phase. The complete introduction of a smart factory means a reinterpretation of the existing regulations. This leads to very cautious first steps which are in the area of employee support, not the introduction of new processes in the workflow itself.
Structure of the article:	Introduction; Literature Review; Research questions & methods; Empirical results; Conclusions; About the author; Bibliography

Introduction

These days, drug manufacturer are facing various and novel challenges. Consumers, in this case patients, expect new forms of self-medication due to habits out of the consumer goods sector, existing supply chains around the globe reveal difficulties in terms of security of supply and the influence of counterfeit medicines in the legal flow of products causes difficulties. In order to meet all these requirements, a future concept from the Digitization Strategy of the Federal Republic of Germany, namely Industry 4.0, was defined as a solution approach by the Autor. The importance of the rules on good manufacturing practice for medicinal products is as crucial for today's forms of production as it is for future concepts. WHO (2014) states in its guiding principles that existing rules must not be changed to the detriment of patient safety. From this, the author deduces the need to examine the application of GMP rules to the idea of the smart factory in order to get a basis for discussion for future application.

A survey among pharma experts reveals major market trends indicating various similarities to other much stronger technology-driven sectors such as the automobile and food industries. According to the survey, forty percent of those asked see personalised medicine as a trend in the years to come (Statista-Expertenbefragung, 2017). The author's professional experience in special machine construction for drug production shows that this industry faces completely new challenges, since previous machine concepts are aimed at batch production of drugs. Other trends are covered by the keywords technological progress, self-medication or digital health (Statista-Expertenbefragung, 2017).

The increasing trend with regard to personalized medication is also substantiated by drugs approved by the FDA in this sector. Namely in the year 2016, 132 drugs were authorized with a personalisable status, as opposed to 5 in 2008 (Personalized Medicine Coalition, 2017). This report proves how important new approaches are for a high-quality production of small batches. To enable this sort of medication, the general public is also willing to accept the transfer of personal and disease-related data. According to 90% of surveyed Germans, they are in favour of making personal data accessible to doctors and hospitals (PwC, 2016).

In this study it is concluded that these approaches imply new strategies in the production of medicinal products and also show similarities to solving supply problems. The production of personalised drugs, i.e. the exact formulation of active ingredients and auxiliary products to match previously analysed symptoms (Bundestag, 2016), brings about the need to produce and combine different components into one product which cannot be produced economically on machinery for serial production. Given the varying mixtures, the need for source materials fluctuates and will therefore require an increase in the storage capacities for these materials unless a new way of producing these basic components is found. One solution could be a more flexible production of source materials within the vicinity of the actual production plants. Cutting transport routes would minimise the risk of branched supply chains and substantially reduce shortages and changes on the market. Generally speaking, flexibility appears to be a promising concept in the entire production process. As is common practice in other sectors, the pharmaceutical producers pursue the market requirements and try to address these requirements to the best of their ability. The production of medicinal products is planned and carried out on the basis of predictions. Flu outbreaks in the spring and autumn, for example, are firmly assumed factors in annual cycles. If they do not occur owing to the non-occurrence of very cold weather, the products stay put in pharmacies and medicine cabinets until their expiry.

Outsourcing production sites for active ingredients and auxiliary products to low-wage countries pursued general industrial trends and is hard to comprehend considering the gross margins of leading pharmaceutical companies beyond 70% (Pharmaceutical Executive, 2019). The relocations described involve risks which, according to current events, should no longer exist without critical discussion.

In this article, various key elements of good manufacturing practice (GMP) are compared with the industrial environment of tomorrow (Industry 4.0) and a first approach is developed on how these two concepts can work together.

Literature Review

Good Manufacturing Practice

The aim of this literature research is to identify what needs to be changed in the present mindset in order to achieve future security, and what should not be neglected under any circumstances in order, at the same time, to ensure patient safety? The leading conception in the production of medicinal products is a consistent superior quality in conjunction with highest standards with regard to processing and packaging drugs (WHO, 2014).

The number of deviations from the required quality standard annually reported by pharmacists to the Drug Commission of German Pharmacists (AMK), an expert committee of the Chamber of Pharmacists and Pharmacists' Associations (ABDA), shows how great the need for improvement is. In 2018, as many as 9486 drug risk cases were reported (ABDA, 2019). The causes varied from packaging errors, mechanical defects and galenic deficiencies to declaration errors and substandard quality (ABDA, 2019). The aim of the entire industry should be, according to GMP (WHO, 2014) regulations, faultless production and a continuously monitored supply chain. The diversity of the reported quality fluctuations and infringements also manifest that no sector in the entire pharma value added chain can be exempted from constant improvement of the way they are used to doing things (ABDA, 2019).

An overview showing the milestones of the evolution of pharmaceutical development and production at the industrial level by the" researching pharmaceutical companies " describes the historical significance of the introduction of GMP rules (vfa, 2019). Around 1900, production and sale were completely unregulated and therefore not bound by any legislation. As a result, products on the market were neither sufficiently tested nor manufactured with the care that is necessary from today's point of view. This has resulted in a constant stream of new preparations with sometimes devastating effects for the people who are treated with the drugs (vfa, 2019). The lives of many people, including children, were taken in 1937 following the guileless sale of compounds without verified effectiveness and, more importantly, without the exclusion of significant side effects by clinical studies. After being introduced on the market, a children's antibiotic cough syrup containing Sulphanilamide proved to be toxic according to subsequent investigations. At that time, an expertise regarding a drug's harmlessness was not required prior to it being launched on the market either in the USA or in the rest of the world (Niggemann, 2019). The following year, the United States Congress adopted the Federal Food, Drug and Cosmetic Act from which today's Food and Drug Administration (FDA) was to draw its legal basis (Niggemann, 2019). The absence of such regulations and administrations in Germany only became evident, but all the more tragic, later on. After 1957, the tragedy known as the Thalidomide Catastrophe (Contergan Scandal) left some 10,000 newly-borns worldwide with permanent damages and deformities as a consequence of the introduction of a remedy for insomnia and nausea. The producer, Grünthal GmbH, was not permitted to distribute the drug on the American market due to the lack of approvals, this being the FDA's first success and confirmation of the need for regulations (Niggemann, 2019). Imposed in 1969, the first official guidelines defined by the WHO (2014) on this topic safeguarded the traceability of production processes. The conception of Good Manufacturing Practice (GMP) first found its way into codes of law in 1978. Since that day, GMP guidelines can be regarded as a living set of rules. Various incidents in individual sectors of the industry or in individual companies or parts of a supply chain continue to flow into the formulation of the legal texts (Niggemann, 2019).

At an international level, the World Health Organisation (WHO, 2014) determines guidelines and standards which are then used as a directive by countries and alliances such as the EU. The principles elaborated by expert committees only reach reference status through global participation, therefore constituting the foundation for the harmonisation of national and international legislation (WHO, 2019). This forms the basis for simplified registration of drugs already authorised in other countries. Meanwhile, over 100 countries have completely transposed the WHO GMP standards into their national law. For many others, the wording of the WHO constitutes the legal basis in legislative texts and guidelines for relevant formulations (WHO, 2019). The American authority (FDA) and the authorities responsible for Europe (EMA) derive their regulations from this set of rules.

The main focus is on the demand on pharmaceutical product manufacturers to provide and verifiably ensure consistent high quality of drugs (WHO,

2014, pp. 80-81). This is preferably done by applying a Pharmaceutical Quality System (PQS) which implements the rules of good manufacturing practices and monitors them by means of a quality management system (WHO, 2014, pp. 85-86). Item 1.5 of the guideline refers to the demands placed on a PQS which needs to be involved at all levels of the product development. Essentially, the PQS is a continually improvable adaptive system that accompanies the knowledge incurring about the product itself and the underlying process throughout the entire life cycle (WHO, 2014, p. 86). All involved production and monitoring processes must be defined in detail beforehand so that potential risks are clarified upfront. Necessary in-process controls need to be defined and prepared prior to the start of production. The entire production process must be monitored and documented. In particular, any deviations from defined standards must be logged and listed with their cause. The results of these recordings are used as reference for subsequent productions in order to initiate measures to prevent the causes recurring (WHO, 2014, pp. 86-88).

The WHO guidelines for good manufacturing practice require correctly trained personnel throughout all conditions of a manufacturing process. The specialists involved must constantly be able to take decisions and implement action evolving on the basis of all the information relevant to these (WHO, 2014, p. 90) (WHO, 2014, p. 114). The ultimate evaluation of the products and production process and the release of the medicinal products for sale is up to the human being. Based on the recordings made and their level of training, all individuals involved must be able to reconstruct the production process and initiate corresponding measures for their area of responsibility (WHO, 2014, p. 99) (WHO, 2014, p. 115). The directives of the WHO regarding the design of processes stipulate that all involved instruments, devices, machines and equipment must be tested according to their previously defined functionality and correct mode of operation in the interests of GMP. These test routines are carried out during installation or during any change to the process and are referred to as qualification tests. By combining different qualified elements in one process, its specifications are similarly checked and summarised under the heading “process validation” (WHO, 2014, pp. 91-92). Any change to these audited and documented processes that could potentially impair the quality of the manufactured product requires another implementation of the test routines (WHO, 2014, p. 92).

A reliable and conclusive documentation of processes is not only the basis of all evaluation possibilities for medicinal products prior to their release for sale, but also for anticipatory measures and learning processes. This documentation system needs to be mapped for all sections of a GMP-relevant process chain. The documents created need to be versioned and all changes recorded. Critical interventions in the database must be carried out and acknowledged by two independent persons (dual control principle). The created data need to be protected against access by unauthorized persons and against loss by means of suitable safety measures (WHO, 2014, p. 116).

Industry 4.0

After explaining the emergence and global independencies of the principles for good manufacturing practice, the concepts of their feasibility are addressed in the following within the context of advancing technological possibilities.

In contrast to the revolutions mentioned above, the trend term ‘Fourth Industrial Revolution’ is still a concept which is in the process of being implemented. In essence, all forms of Industry 4.0 describe an evolution of the production industry. With the help of technological advances in the form of compatible objects and data transfer rates enabling an exchange of massive amounts of data without noticeable delay, new paths and forms of production can be developed. They do not always involve the use of new technology, but more and more the collaboration of existing approaches which, however, are only feasible by means of the technological progress of so-called embedded systems. The integration of physical and digital worlds is the key element to the future project Industry 4. (Kagermann, Wahlster, & Helbig, 2012).

The underlying concept is described by the term cyber-physical system (CPS) and forms the fundamental innovation reflected in all concepts of Industry 4.0. A physically existing object receives a data model as its virtual counterpart. It obtains relevant information on the state of the given equivalent and gives access to the information externally (Kagermann, Lukas, & Wahlster, 2011) (Drath, 2014) (Roth, 2016).

New products and services can be developed from this data model and by linking many to a virtual production environment. Exchanging the utilization information of individual machinery within a production

process enables much more accurate planning of procedures, yet to call it a revolution would be exaggerated. However, taking customers' requirements and suppliers' information into planning production processes gives hints as to the complexity of such processes but also demonstrates the potential of present-day procedures. Networking entire facilities and supply chains is also referred to as a Cyber-Physical Production System (CPPS) or Smart Factory (Forum Industrie 4.0, 2019) (Kagermann, Wahlster, & Helbig, 2012).

Combining the content and concepts of Industry 4.0 sets up the overall picture of a Smart Factory in which individual components, production and process levels, superimposed planning and decision levels and entire production facilities in the global context all communicate with each other. All this is made possible due to a few technological principles. At the lowest level, components are integrated in devices and products for information processing. As a result of the communication between intelligent products, intelligent production resources and intelligent machines, the embedded hardware and software permit fundamental decisions at process level (Kagermann, Wahlster, & Helbig, 2012) (Roth, 2016).

The networking enabled from the product and production control known as the Industrial Internet of Things (IIOT). Reference is not only made to the global Internet, but also linking a local network at production level through the same way of communication. The ubiquitous acquisition and processing of information is also referred to as Ubiquitous Computing (Siepmann, 2016).

The information generated by the participants can also be evaluated in the wider context. This is usually done in an outsourced data centre with scalable capacity to enable decisions with response times that are as short as possible. This is referred to as Cloud Computing (Kagermann, Wahlster, & Helbig, 2012) (Roth, 2016) (Siepmann, 2016).

Combining these approaches and functions constitutes the technical implementation of cyber-physical systems. Other requirements come to light when several CPS are incorporated in a Smart Factory. In order to implement the partial or fully automatic operation of a plant, the participating machines need a communication channel between each other. This data exchange is done via standardized interfaces and is summarised under the heading of Machine-to-Machine communication (M2M) (Kagermann, Wahlster, & Helbig, 2012).

This exchange of information from machine to machine enables processes to be controlled and regulated based on situative decisions and requirements with a minimum of effort. The product and the resultant processing steps are customised situatively on the basis of the quality specifications (Kagermann, Wahlster, & Helbig, 2012) (Roth, 2016).

In a Smart Factory, human-machine-interaction (HMI) provides for systems with virtual and augmented reality (Kagermann, Wahlster, & Helbig, 2012) (Siepmann, 2016) which supply the human, in his role as the decision-making body, with all required data visually. The data are generated and read out to a headset with integrated monitors. The operator now sees a local correlation between the problem that arose and the information which the system can provide on it. In the event that a similar situation occurred previously in an operation, the context and solution approaches can be projected. Sharing CPS and other interfaces among the participating bodies enables the implementation of a cyber-physical production system. The ultimately decisive component enabling a Smart Factory to develop from a high-tech automated production environment is the capability to build a bridge between the two worlds for the factory's managers. Their contribution will be to recognize the potential in their own processes and to have the courage to make changes, and hence improvements, based on the visions of Industry 4.0. The role of correct change management under way to the age of digitalisation is synonymous with the challenge to the technological feasibility and must not be neglected under any circumstances.

Research Questions & Methods

The previous literature research gives evidence of the disparity existing in some places between Industry 4.0 and the production of medicinal products. On the other hand, consistently enhanced approaches demonstrate the potential the GMP process has to offer for further development. A tangible improvement arises from paperless documentation of GMP processes. The practice of collecting, filing and evaluating data is a basic principle of cyber-physical systems and hence offers a direct application with tremendous added value. The entire structure of a GMP-compliant production is a constantly adaptive system which, with the help of

Industry 4.0 approaches, has the potential to mature to a transparent knowledge database with in-depth process knowledge.

Those are the intersections of the various subject areas. However, the strict rules governing the pharmaceutical sector clearly indicate what really matters in the production of medicinal products, namely the quality of the products and no compromises. Whatever could impact the production quality or process in a negative sense, must be kept away from the production process. These requirements are precisely noticeable in data integrity and security standards. The retraceability of measures initiated during a process on the basis of data and information must be in place. This is only possible to a certain extent with automated processes and poses new challenges to systems with artificial intelligence. Designing autonomously operating process chains according to the conventional GMP guidelines is hardly conceivable and is extremely complex as far as the risk analysis is concerned. Given that in a risk assessment each autonomous link in a process chain reveals itself as an unknown factor, it soon becomes clear that describing processes requiring validation seems almost impossible.

If the principles of good manufacturing practice are not able to be entirely guaranteed and fulfilled over the long term by Industry 4.0, the approaches are considered not viable.

A common intersection is given between GMP and Industry 4.0. The overall concept of a Smart Factory, the major objective of the fourth industrial revolution, is not viable. My hypothesis is therefore as follows:

H1: “Smart Factory is not a concept that can be applied entirely to GMP-relevant production processes.”

Given the formulations which, with a small number of exceptions, ignore the application of computer-based methods and only refer to human actions and the age of the laws, my second hypothesis is:+

H2: “The formulated GMP guidelines have not been drawn up from the point of view of suitability for Industry 4.0 applications and therefore follow different standards.”

The complexity of the two subject matters, and the topicality of Industry 4.0 suggests that the knowledge required for a successful implementation of Industry 4.0 solutions in the pharmaceutical sector is not yet sufficiently available. This hence leads to my last hypothesis:

H3: “The application potential of Industry 4.0 concepts is not yet available in sufficient form in the pharmaceutical industry.

The methodology used for collection of the data comprises a three-stage process. First, due to the complexity of the GMP guidelines and the possible Industry 4.0 projects, experts from the field of technological development in the pharmaceutical industry were interviewed. This procedure is a qualitative research approach aimed at reducing this extremely broad area of research to practically oriented questions. This step was considered necessary in order to establish a meaningful data basis for the subsequent quantitative evaluations. As there is yet hardly a comparable research base in this field, literature research produced no insights into how to limit the thematic diversity. Subsequently, a questionnaire was created and verified with a small test group. A revised questionnaire was created based on the feedback from this test group and distributed to the target group. The anonymized collection of the data itself was conducted via an online survey. The interviewees were selected from the contact database of a mid-sized engineering company operating in the field of diverse automation solutions for the pharmaceutical industry and invited to take part in the survey.

As literature research and the interviews with experts from the field of innovation management in the pharmaceutical industry show, it is not easy to generate a reliable database in this very specialized area of the Industry 4.0 applications. For this reason, when designing the questionnaire, great attention was paid to the depiction of the thematic areas covered by the questions.

As an introduction to the survey, interviewees were first asked about their prior knowledge in the fields of GMP and Industry 4.0, thus pointing out the core areas of the survey. This initial self-assessment was intended to encourage the interviewees to reflect on their previous experience with the specified topics. This was followed by a question leading over to the topic of the core areas of Industry 4.0, in order to highlight already possible application scenarios. One special feature of this question is that it contains all options for definition of the goals of Industry 4.0 and can thus also serve as a control question with regard to the interviewees' own assessment of their prior knowledge in this area. The interviewees' evaluation of expected investments in various sub-areas of production is intended to provide insights into expectations within the pharmaceutical industry with regard to the products of technology suppliers. The section of the

survey comparing concrete statements on feasibility and risks can be considered as the core element of the survey. The interviewees were asked to give their assessment of the challenges of the use of new production processes in the field of Industry 4.0. The selected topics cover the entire range of activities in production. They are intended to generate a picture of the framework conditions for the use of new technologies, from technical feasibility to new personnel requirements, rated on a scale from extremely critical (1 point) to not critical (5 points). A similarly phrased question on the chances of success, no chance of success (1 point) to very promising (5 points), in individual sub-areas is intended to show whether there are connections between the framework conditions and concrete application in various process steps. These questions are phrased using a 5-point Likert scale. As the survey is conducted based on fields of work and activities, the scaled structure was selected to allow an evaluation based on tendencies. This allows assessment on the basis of tendencies despite the fact that it cannot be assumed that all interviewees will be able to make a valid statement on all topics. Evaluation of the sources in the environment of the pharmaceutical manufacturing companies from which support is offered is intended to show where on one hand assistance is requested and on the other, where there is a need for action.

The second set of questions is geared more toward the focal areas of GMP and is intended to allow an evaluation of the situation from this perspective. The interviewee is asked to name the source of error that is most frequently decisive for GMP-relevant measures in order to compare the perspectives in connection with the use of new technologies. Assessment of the percentage of time needed for actual production, preparation and post-processing is intended to indicate the time required for GMP-compliant preparation and post-processing of a produced batch. This ratio allows comparison with the technological possibilities and chances of success. An evaluation of flexibility as against the efficiency of a production process will allow the generation of similar values for comparison. In some places, new paths within the scope of Industry 4.0 make it necessary to reinterpret these interrelationships. To obtain an assessment of temporal feasibility, the interviewees are asked to enter the main topics in a grid. Participants are asked to name their area of activity in order to compare the intended target group and the target group actually reached.

Empirical results

Test Group

A total of 76 persons from the pharmaceutical production environment replied to the questionnaire. Thirteen persons are from the management area (17.1%), 24 from the production area (31.6%), 14 responses come from the technically commissioned environment (18.4%). 12 respondents (15.8%) assigned themselves to the GMP relevant environment of quality management and validation. The missing 13 persons (17.1%) could not find themselves in this list and indicated their field of work by a free designation. The above-mentioned areas are found in project management and various engineering activities and are therefore relevant to the survey. If one assumes that the production employees have a strong connection to the rules of good manufacturing practice, there is almost a ratio of 50% participants with technical and strategic positions and 50% from the GMP environment.

H1: "Smart Factory is not a concept that can be applied entirely to GMP-relevant production processes."

In order to be able to gain an assessment of the potential for the future of the Smart Factory in the pharmaceutical production sector, the currently most important topics of GMP-compliant production are compared with the evaluated concepts of Industry 4.0. This comparison is carried out using correlational statistics in the form of the Spearman test. The data sets were tested for normal distribution using Kolmogorov-Smirnov and Shapiro-Wilk. Both of these disproved the assumption of normal distribution. Due to the sample size of N = 76, however, the significance of the tests can be questioned. The questions together with the chosen 5-point Likert scale are not particularly well suited to prove a normal distribution on the basis of histograms or the evaluation according to skewness and kurtosis. The present data sets are ordinally scaled and thus exclude various tests for metric data. In order to be able to detect statistically significant correlations, the Spearman Test is used in SPSS. The rank correlation according to Spearman is based on a null hypothesis according to which the data sets tested against each other are independent of each other.

The most frequent causes of quality deviations in GMP-compliant production processes are carelessness

on the part of the employees (32.9% of the respondents) and inadequate qualification and training (26.3% of the answers). Industry 4.0 already has concepts for both problems. Intelligent assistance systems that know the operator and his environment help to prevent careless actions, for example by pointing out deviations in checklists or warning against careless interventions in the process. Modern means can be used to achieve a higher quality level of training. With these the trained person can, for example, test different scenarios and their effects on a data model of the training object, its CPS. As there is no danger from the actions and no necessary of direct use of materials, these training courses can be conducted more often and in more detail as if an entire production line had to be contaminated for training purposes. To implement an assistance system, a knowledge database and an anomaly detection by artificial intelligence will be necessary. The respondents see a significant correlation with medium effect (Cohen, 1994) between the topics mentioned (rs = .418, p = .000, n = 62). Thus, the null hypothesis is rejected and the substitute hypothesis, according to which a correlation exists, is accepted.

To get a better understanding, what the respondents think about the fundamental question of the possible uses of I4.0 technologies or how critical they are of introducing them in their overall vision, they were asked to compare the challenges of industry 4.0 concepts with an assessment of their possibilities and chances of success. In this block of questions, the scale is no chance of success (1 point) to very promising (5 points), no answer was also possible. The following results show the assessment of the respondents in this respect. Here, the sometimes-high number of replies without any statement is striking. The category Batch One production does not allow 25% of the respondents to make a statement. Similar values were found for simplified serialization and aggregation (21%) and error prevention through the use of artificial intelligence (21%). On the subjects of new products and packaging, as well as a generally more flexible production, 16% would not like to make an assessment. These figures also indicate a lack of information flow about new opportunities from suppliers to the manufacturing companies and their employees. If they are not sufficiently familiar with industry 4.0 concepts, they cannot identify potential in their areas of responsibility and expertise and thus do not see the Smart Factory as solution approach for their GMP relevant production.

In order to be able to make statistical statements on the basis of the mean values shown (Table 1), the data sets are checked against the assumption that the respondents have a neutral attitude towards the respective topic (M = 3) using the one-sample t-test. Industry 4.0 technology is most promising in the area of simplified documentation and reporting (M = 3.91, SD = 1.02, N = 70) ($t(69)$ = 7.515. p < .001). Furthermore, the respondents see better planning of maintenance intervals (M = 3.84, SD = 1.02, N = 67) (t(66) = 6.682. p < .001), more flexible production (M = 3.83, SD = 1.08, N = 64) (t(63) = 6.150. p < .001) and less downtime of machines and equipment (M = 3.81, SD = 1.02, N = 68) (t(67) = 6.411. p < .001) as promising approaches in Industry 4.0. A significant (p < .05) difference can be seen in almost all mean values considered. The positive test value indicates a higher value than the assumed one. This speaks for the trend towards the category "promising". The statements on the subject of new products and packaging are considered neutral (t(63) = 1,608. p = .113). Here, the null hypothesis of a statistically significant difference cannot be rejected, so this hypothesis remains and with it the assessment of the mean as neutral. According to their mean values, all categories have a tendency towards the rank “promising”. These statements indicate an interest in new technologies. The respondents do not categorically reject new approaches but seem very cautious when it comes to implementation. If some of the mentioned topics were already present on a large scale in the industry, there would be even clearer excesses in the direction of the answer possibility very promising due to already completed feasibility studies. A correlation analysis of these two data sets is intended to show whether these Trends are already being followed but fail due to various challenges.

Table 1:

Descriptive Statistics and one sample t-test

Prospects of applying I4.0 technology

	N	M	SD	p
More flexible production	64	3.828	1.077	.000
Better quality of products	69	3.608	1.032	.000
Lower production costs	66	3.560	1.097	.000
Individual products – Batch One Production	57	3.473	1.070	.001
Better planning of maintenance intervals	67	3.835	1.023	.000
Less downtimes	68	3.808	1.040	.000
Simpler documentation of production processes	70	3.914	1.017	.000
New products and packaging	64	3.203	1.010	.113
Simpler serialization and aggregation	60	3.416	1.013	.002
Error prevention and analysis through AI	60	3.716	1.059	.000

Furthermore, the participants were asked, what their biggest concerns are regarding implementation of Industrie4.0 techniques in their GMP relevant production. The assessment is based on a 5-point Likert scale with the designated extreme values very critical (1 point) to non-critical (5 points). The 10% of answers with missing information expected on the basis of the test survey are only confirmed by half of the questions. In some cases, the values are significantly higher. The respondents had the most difficulties with the issue of transparency of the decision of an artificial intelligence. Here 20 of 76 persons could not make a statement, which corresponds to 26% of the respondents. Further gaps in data collection are found in the lack of a legal framework (17%) and lack of standards within the company (16%). A lack of prospects of success is also something that 16% of those surveyed cannot assess. This information confirms the lack of previous knowledge of the interviewees, especially in the expert disciplines (legal framework or Artificial Intelligence) of the two priorities. What industry 4.0 applications offer in the area of Return on Investment (ROI), 96% of those surveyed dare to estimate.

In order to be able to make statistical statements on the basis of the mean values given (Table 3), the data sets are checked against the assumption that the respondents have a neutral attitude towards the respective topic (M = 3) using the one-sample t-test. The greatest concerns expressed by the participants are in the area of data integrity (M = 1.70, SD = 0.83, N = 69) (t(68) = -13.087, p < .001) and data security (M = 1.79, SD = 0.95, N = 70) (t(69) = -10.736, p < .001), followed by the probability of failure (M = 2.10, SD = 0.93, N = 69) (t(68) = -8.062, p < .001) and increasing system complexity (M = 2.20, SD = 0.86, N = 71) (t(70) = -7.907, p < .001). A significant (p < .05) difference can be seen in almost all mean values considered. The negative t-test indicates a lower value than the assumed one. This shows a tendency towards the category “Critical”. The statements on the topics Absence of legislative framework (t(62) = -1,926, p = .059), Resistance through workforce (t(65) = -1,723, p = .090) and Absence of prospects of success (t(63) = 0,000, p = 1,000) are considered neutral. Here, the null hypothesis of a statistically significant difference cannot be rejected, so this hypothesis remains and with it the assessment of the mean values as neutral. In summary, the evaluation of the obstacles shows that the participants have certain reservations about the introduction of new technologies. The mean values of the answers are located on the half of the scale, which is represented by the categories very critical or critical.

The increased use of modern technology and the networking of many components into a Smart Factory also entails the use of many different systems. Reviewing this system architecture and acting correctly in maintenance scenarios or production downtime will be part of the new industry 4.0 working environment. The job profiles arising from the changed environment are a very unique field of observation of upcoming projects. Due to their independent working methods and ability to learn, the new systems mean in some parts a reduction in the competences of different occupational groups. This certainly includes the expertise currently required to assess the condition of a production plant and to plan the right maintenance intervals. This affects the resistance of the workforce to such systems.

Table 2:

Investments in the coming 5 years[a]

	Responses		% of
	N	%	Cases
Virtual reality in employee training	23	9.5%	31.5%
Reporting and paperless documentation	48	19.9%	65.8%
Operator assistance systems	43	17.8%	58.9%
Operation without operating personnel	32	13.3%	43.8%
Automated line clearance process	25	10.4%	34.2%
Product and material tracking during production	41	17.0%	56.2%
Multipurpose production lines	25	10.4%	34.2%
None apply	1	0.4%	1.4%
Other	3	1.2%	4.1%
Total	241	100.0%	330.1%

a. Dichotomy group tabulated at value 1.

The planning of maintenance intervals by the plants themselves correlates significantly positively with the resistance of the workforce to Industry 4.0 projects ($r_s = .258$, $p = .043$, $N = 62$), but at the limit values ($p < .05$) of the significance $p = .043$ and a low correlation coefficient, which, according to Cohen (1994), indicates a weak effect. The data sets result in further correlations, which are directly related to the question of new professional requirements. New requirement profiles for employees correlate significantly positively with the error rate of new systems ($r_s = .246$, $p = .041$, $N = 69$) and a more flexible production ($r_s = .291$, $p = .020$, $N = 64$). Both correlations have also a weak effect in terms of statistical power. Similarly, both issues represent fundamental effects on the current way of working. The diagnosis of modern systems takes place from a control station, by software that shows the health state of the machine, and no longer by means of staff with a tool case on the machine level. More flexible production requires more coordination as well as control of the process steps and no longer just the execution of the work steps.

The machine operators teach a collaborative robot directly on the machine level to solve a new task, instead of performing it themselves in monotonous work. A significant correlation with medium statistical power can be observed between more flexible production and better planning of maintenance intervals ($r_s = .479$, $p = .000$, $N = 64$). This reinforces the demand for Industry 4.0 systems to have simple alternative options in possible maintenance or interference situations.

The independent planning of maintenance intervals by machines themselves shows a strong significant correlation with the use of knowledge databases ($r_s = .594$, $p = .000$, $N = 66$). This connection is an important support for two approaches. At first, the calculation of the failure probabilities is carried out, which is the necessary basis for planning maintenance intervals. This becomes more accurate when reliable comparative values can be calculated. This data base can be collected in two different ways. Through the observation of components up to their wear limit and failure, or through the collection of knowledge already gained in the workforce and the documentation of past maintenance work.

The interviewees' current focus of attention involves entry-level projects which are intended to generate direct added value from simply collected data. The participants consider the thematic areas data integrity, data security and the fault probability of the systems to be critical. Currently existing error causes provide no indication that speak against the increased use of technology for the production. The comparison between Industry 4.0 concepts and their fields of activity in pharmaceutical production does not give a clear statement opposing the use. Uncertainties exist more in connection with the companies' internal standards and their applicability. Reservations against the new concepts do not come in large numbers and are hence no criteria for exclusion. There is no indication of mistrustfulness against the decisions of artificial intelligence i.e. the basis of many Industry 4.0 concepts. The collected and evaluated data sets show Industry 4.0 concepts are limited as far as their degree of freedom is concerned, but not infeasible for use in GMP-relevant processes. There is a lack of new ways in evaluating the processes in order to secure essential standards in the production of pharmaceutical products and to evaluate risks upfront.

The concepts themselves appear to be applicable. For these reasons, the null hypothesis must be rejected and an alternative hypothesis adopted. The alternative hypothesis is: "A Smart Factory is implementable subject to particular requirements regarding the qualification and validation of concepts for GMP-relevant processes".

H2: "The formulated GMP guidelines have not been drawn up from the point of view of suitability for Industry 4.0 applications and therefore follow different standards."

To estimate how survey respondents rate the feasibility of various Industry 4.0 projects and therefore see how close their understanding of GMP rules in respect to Industry 4.0 topics is, they were asked to estimate in what timeframe they think various topics can be implemented (Table 2). The possible answers were classified as follows. For periods of less than one year, the company implemented GMP rules only need to be applied to the new concepts. If it is considered feasible to implement them within three years, the internal company guidelines need only be adapted to the new process, but in principle remain valid. If the projects are considered feasible in a time window of three years or more, this is in an area of complexity that suggests a reinterpretation of the Directives based on a completely new framework.

As with the previous evaluations, the number of missing answers per question provides information on how far the topic is known and can be estimated. The answer options are described in a more specific way in order to explain the implementation of the respective concept, but also require a little more technical competence and understanding. This can explain the slightly higher values of the missing data. These are much higher than expected in the expert areas of GMP, validation in the area of QM and Line Clearance in the production environment. 26% of respondents cannot even imagine validating a process using intelligent or sensory products. 21% of participants do not see camera and robotics support in parts of production as a substitute for personnel-and time-intensive process steps like Line Clearance or in the field of in - process controls (18%). In view of the comparatively low values of the assessments not submitted, the following projects have arrived at the concept collections of the pharmacists. The sub-areas of predictive maintenance (11% missing statements) and the collection of process knowledge (9%) in Central databases. However, these are still at the limit of the expected 10% and thus give further indications of the lack of knowledge of concrete application areas of Industry 4.0 among the respondents.

Table 3:
Descriptive Statistics and one sample t-test - Challenges of applying I4.0 technology

	N	M	SD	p
Investment costs	73	2.246	.924	.000
Data protection provisions	70	1.785	.946	.000
Data security – Data integrity	69	1.695	.827	.000
New jobs and new demands on employees	70	2.614	.996	.002
Increase in complexity	71	2.197	.855	.000
Failure susceptibility of systems	69	2.101	.925	.000
Absence of legislative framework	63	2.746	1.046	.059
Absence of assessment and evaluations through authorities	66	2.636	1.090	.009
Resistance through workforce	66	2.787	1.000	.090
Absence of standards within the company	64	2.328	1.054	.000
Absence of prospects of success	64	3.000	1.195	.000
Decisions of artificial intelligence are not transparent	56	2.660	.958	.011

The classification of the scale used in the categories explained above results in the following distribution of points. Projects directly implementable with existing regulations correspond to the scale value one, which with adjustments of the valid interpretations corresponds to the value two, all concepts that require a redefinition and Interpretation of the guidelines are marked with the score three and larger.

In order to be able to make statistical statements on the basis of the mean values given, the data sets are tested using the one-sample t-test against the assumption that the respondents see the respective topic implemented in a time horizon of three years or more (M = 3). The mean values of the listed subareas are all well above the area of the intended line of feasibility at the 2-point limit. This allows at least a clear statement. The topics are seen not easy to be implemented on the entire industry. The planning of maintenance intervals by the machines themselves is estimated to be most feasible (M = 2.86, SD = 0.97, N = 69) (t(68) = -1.236, p = .221). This scenario was the subject of many trade fair demonstrations in the automation industry in 2019, which can explain the awareness of the concept and the opinion of the respondents. The most unknown concept is also the one with the widest time horizon to implementation and therefore the worst rating for the current interpretation of GMP guidelines. Participants see the validation of a process by a product not implemented within three years (M = 3.30, SD = 1.09, N = 56) (t(55) = 2.076, p = .043). In this statement, the null hypothesis of no difference to the assumed time horizon of three or more years cannot be rejected.

Further the respondents were asked which source of error most often leads to quality deviations in production. This assessment allows a comparison of the current causes of errors, thus, the fields of action of the quality assurance in the GMP process, with the concepts of industry 4.0. According to this question, only 6.6% of the respondents do not have enough insight into the production processes to make an assessment. The remaining participants define two main areas as noteworthy causes of error. First, the carelessness of employees with 32.9% of respondents, followed by poor qualification and training with 26.3% responses. Only 10.5% of participants see the failure of technical devices as the main source of errors for quality differences in production. According to 9.2%, the high-quality standard only fails due to the communication between the parties involved in the process. These clearly discernible differences show that mistakes occur simply through human error. Whether the error was caused by inadequate employee training or carelessness, both can be counteracted by Industry 4.0 concepts. The relatively low number of technical causes suggests that there is confidence in technology.

The participants answers regarding the use of automated documentation methods (Table 4) show a positive correlation between simpler documentation and less downtimes of their machines (rs = .450, p = .000, N = 67) and also between simpler documentation and lower production costs (rs = .278, p = .025, N = 65). The data shows also a slight negative correlation when it comes to data security and data integrity (rs = -.106, p = .391, N = 68). In order to be able to implement such concepts, the decisions of an AI must be equated with those of a human being and data integrity must be guaranteed. The expected negative correlation between the deployment and the reservations against an AI cannot be established (rs = -.092, p = .511, N = 53). Neither is there any correlation between anomaly detection and error prevention by an AI (rs = .128, p = .346, N= 56).

This indicates that the functionalities of the systems for monitoring are not questioned, but that no concept is seen for predictive intelligence. Interestingly, the answers to the question of missing Standards in one's own company correlate with the data sets for the statements of the intransparency of AI decisions (rs = .358, p = .007, N = 55) and those of data integrity (rs = .330, p = .008, N = 63) both significantly positive with a medium effect. These correlations illustrate the picture: the applications of Industry 4.0 are certainly seen in the production processes, but their implementation is not yet compatible with the guidelines of the pharmacists themselves.

The timeframes specified by the interviewees as realistic for the implementation of Industry 4.0 projects suggest that the GMP guidelines have not been drawn up with respect to the fast-evolving technological development and therefore not with respect to upcoming possibilities. The longer these turn out to be, the further away the project is from the current implementation of rules. The possibilities proposed in the survey regarding automated processes reserved for human beings in the GMP guidelines are seen very critically by the interviewees. Hence, hypothesis H2 cannot be rejected.

H3: "The application potential of Industry 4.0 concepts is not yet available in sufficient form in the pharmaceutical industry."

Previous knowledge in the area of Industry 4.0 is tested by means of the control question "What do you think are the objectives of Industry 4.0 projects?". All eight possible answers describe objectives of projects related to CPS. Only 3.9% of respondents have already internalized the full scope of the possibilities of Industry 4.0. The mean value *M = 3.71* (*SD = 1.68, N = 76*) shows that only about half of the respondents rated only about half of the mentioned possibilities as industry 4.0 capable. An one-sample t-test against the assumption that the respondents identify six (M = 6) of the eight possible projects as targets of an Industry 4.0 concept yields a significant ($p < .05$) difference ($t(75) = -11.826$, $p < .001$). The negative test value together with the difference of the mean values of $\Delta M = -2.289$ indicates a difference that indicates a much lower value.

According to their self-assessment, the respondents' previous knowledge of Industry 4.0 is on a scale of points from Beginner (0 points) to Expert (100 points) in the range between beginner and advanced (50/100) (*M = 33.09, SD = 21.76, N = 76*). On the same scale, employees and managers rate themselves with better knowledge in the area of GMP, ranging from advanced to expert (*M = 60.29, SD = 23.88, N = 76*). The level of standard deviation shows a distribution of the self-assessments over the mentioned sub-ranges of the scale. An one-sample t-test against the assumption of self-assessment as advanced (M = 50) in the Industry 4.0 range yields a significant ($p < .05$) difference ($t(75) = -7.963$, $p < .001$). The negative test value shows a difference towards the level "Beginner". The same self-assessment assumption for the field of GMP results in a significant difference to a higher value than the chosen reference value ($t(75) = 2.789$, $p = .007$).

In order to show which concepts are currently being considered within the framework of Industry 4.0, the respondents select any number of project proposals from a list. The projects currently in focus are paperless documentation and reporting with 65.8%, operator assistance systems with 58.9% and product and material tracking along the production process which is

Table 4

Correlations between the possibilities and obstacles to the use of automated documentation

Spearman's rho correlations

		Simpler documentation of production processes	Less downtimes	Lower production costs	Data protection provisions	Data security – Data integrity
Simpler documentation of production processes	r_s		.450**	.278*	-.037	-.106
	p		.000	.025	.764	.391
	N		67	65	69	68
Less downtimes	r_s	.450**		.449**	-.058	-.120
	p	.000		.000	.640	.332
	N	67		65	67	67
Lower production costs	r_s	.278*	.449**		-.099	-.282*
	p	.025	.000		.433	.023
	N	65	65		65	65
Data protection provisions	r_s	-.037	-.058	-.099		.734**
	p	.764	.640	.433		.000
	N	69	67	65		69
Data security – Data integrity	r_s	-.106	-.120	-.282*	.734**	
	p	.391	.332	.023	.000	
	N	68	67	65	69	

**. Correlation is significant at the 0.01 level (2-tailed). *. Correlation is significant at the 0.05 level (2-tailed).

mentioned in 65.2% of the data. All these sub-projects of the Smart Factory do not have the goal of a completely automatic production but are instruments to better monitor existing processes or to directly support the operators in their work.

The previous evaluated questions about how promising Industry 4.0 projects seem to be for the asked experts show a sometimes-high number of replies without any statement. Same results can be seen regarding the feasibility of implementation possibilities or classification of risks and obstacles coming with new technologies. The respondents had the most difficulties with the issue of transparency of the decision of an artificial intelligence. Here 20 of 76 persons could not make a statement, which corresponds to 26% of the respondents. Further gaps in data collection are found in the lack of a legal framework (17%) and lack of standards within the company (16%). A lack of prospects of success is also something that 16% of those surveyed cannot assess. This information confirms the lack of previous knowledge of the interviewees, especially in the expert disciplines (legal framework or Artificial Intelligence).

This already shows that the industry is still at the beginning of the Industry 4.0 era and is taking its first steps in this direction. The first possible intermediate goal of the companies is to reduce production costs without large investments in order to be able to benefit quickly and easily from the new technologies.

The consistent 10% to 20% of the questions without an answer, and therefore lack of connection with the surveyed topic, clearly shows that the potential of the applications has not reached various specialist fields to the full degree. Hence, hypothesis H3 cannot be rejected.

Conclusions

The article considers the tendencies of producing goods for the mass market in which the production of drugs is included. Personalised drugs and the reorganisation and back sourcing of supply chains in addition to the production of active ingredients in small companies at several locations are the drivers for a new mindset in the pharmaceutical sector. Regardless of where and how products are produced, GMP is the basic principle. It must be viewed as a separate world of ongoing improvement whose sole purpose is to secure the quality of products without compromises.

The demands on projects in the age of I4.0 do not only involve the use of new technology but increasingly the combination of existing approaches that are indeed only rendered possible through technological progress.

According to today's interpretation of the GMP guidelines, the human being plays an indispensable role as decisive authority in pharmaceutical production. However, the number of decisions required to be made by a human being can be reduced substantially when intelligent systems, as basis for action, are provided with already reached decisions that are defined during the process development. Learning from human beings' decisions and adopting these procedures can give completely new ways of acting in a production process.

Survey results and interviews with managers and other people responsible for innovation management and development show how difficult it is to integrate the mentioned thematic areas into a common approach. Currently favoured concepts are ones which work with the facilities and machinery available and only involve the expansion and optimisation of existing processes. Other intended solutions must be questioned in the light of internal standards and imply effort and new mindsets. This clearly shows that there are not enough platforms for technology suppliers, users in the pharma sector and auditing authorities to exchange and discuss future technologies and processes.

One of the most critical points worth mentioning in the summary of results of this article is today's existing knowledge about Industry 4.0 concepts in the pharmaceutical sector. The results of the survey clearly show that there is still a backlog demand in all occupational sectors. The lack of knowledge in the field of i4.0 among the respondents must lead to critical reflection of the results. Parts of the questions were based on a better prior knowledge of specific topics and application areas of i4.0 concepts within pharmaceutical production. The results obtained must therefore be placed in relation to the lower level of existing knowledge and thus lose their significance. The respondents were confronted with specialised areas of information technology and conceptual engineering and may have made statements here due to a lack of knowledge that do not fit the general mood of the pharmaceutical industry. Further interviews in the relevant expert areas on specific

topics of the survey within the companies should be used to evaluate the results of this survey.

The hypothesis at the centre of the article, whether industry 4.0 and GMP are fundamentally compatible, was sufficiently substantiated to be able to use it as a basis for further research on the implementation of specific tasks. The information gathered on success factors and hurdles provides information on further research fields, for example in the area of change management. However, these statements are not specifically linked to the pharmaceutical sector and can therefore also be compared with other industries and thus be researched together.

The creativity of engineered solutions is always dependent on the knowledge of their developers. Industry 4.0 concepts offer an opportunity to reconsider one's own approach by means of new methods in each specialist field and at each workplace and to recognize greater links between individual actions in one's own environment.

About the author

As an engineer with a passion for technology and human creativity, Roland Wölfle is committed to future-proof concepts in the field of pharmaceutical production. He acquired the necessary technical knowledge through training and studies while working full time in the fields of mechatronics and robotics as well as working in the research and development department of a family-run medium-sized company in the south of Germany. The special R&D environment with freedom to think out of the box and the company's distinctive team culture make him want to continue working on himself and his skills. An increased interest in human interaction and the urge to look beyond the engineer's horizon lead him to complete the International Business Management and Leadership course at the Professional School of Business and Technology in Kempten. With Industry 4.0 as a field of research and his role as an innovative thinking leader, Roland is able to make his vision of man and machine as partners, complementing each other with their respective strengths to form an effective and resource-saving unit, become reality.

Bibliography

ABDA. (2019, Juni). *ABDA - Die Apotheke 2019.* Retrieved from https://de.statista.com/statistik/daten/studie/76328/umfrage/apotheken-meldungen-zu-arzneimittelrisiken-seit-1994/

Bijedic, T., & Hoffmann, M. (2018, November). *Digitale Geschäftsmodelle - Chancen und Herausforderungen für den Mittelstand.*

Bundestag, D. (2016, Oktober 18). Personalisierte Medizin - Definition, Anwendungsbeispiele sowie Fördermaßnahmen. *WD 9-3000-060/16.*

Cohen, J. (1994, Dezember). The Earth Is Round (p < .05). *American Psychologist Vol 49(12)*, pp. 997-1003.

Drath, R. (2014, Mai 16). Industrie 4.0 - eine Einführung.

EUROPEAN COMMISSION. (2011). EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines. *Annex 11: Computerised Systems*.

Forum Industrie 4.0. (2019). *Guideline Industrie 4.0 - Guiding principles for the implementation of Industrie 4.0 in small and medium sized businesses.*

Kagermann, H., Lukas, W.-D., & Wahlster, W. (2011). Industrie 4.0: Mit dem Internet der Dinge auf dem Weg zur 4. industriellen Revolution. *VDI nachrichten*, p. 2.

Kagermann, H., Wahlster, W., & Helbig, J. (2012). *Umsetzungsempfehlungen für das Zu kunftsprojekt Industrie 4.0.* Berlin: Forschungsunion Wirtschaft und Wissenschaft.

Manohar, S. (2018). Megatrends: A Research Study 2018. BlackRock.

Niggemann, B. (2019, Juni). *Die Historie der Good Manufacturing Practice.* Retrieved from pts.eu: https://www.pts.eu/anlagen/1104_07112019063952.pdf

Personalized Medicine Coalition. (2017, Januar). The Personalized Medicine Report 2017., (p. 18). Retrieved from Opportunity, Challenges, and the Future: https://de.statista.com/statistik/daten/studie/686970/umfrage/anzahl-der-personalisierten-arzneimittel/

Pharmaceutical Executive. (2019, September). *pharmexec.com.* Retrieved from

https://de.statista.com/statistik/daten/studie/471961/umfrage/bruttomarge-fuehrender-pharmaunternehmen-weltweit/

Plattform Industrie 4.0. (2014). Industrie 4.0. *Whitepaper FuE Themen*.

PwC. (2016). PwC - Personalisierte Medizin 2016., (p. 13).

Roth, A. (2016). Industrie 4.0 – Hype oder Revolution? *Einführung und Umsetzung von Industrie 4.0*. Springer-Verlag Berlin Heidelberg.

Siepmann, D. (2016). Industrie 4.0 – Grundlagen und Gesamtzusammenhang. *Einführung und Umsetzung von Industrie 4.0*. Springer-Verlag Berlin Heidelberg.

Statista-Expertenbefragung. (2017, März). *Welches sind Ihrer Meinung nach die drei größten Trends der Pharmabranche?* Retrieved from statista.com: https://de.statista.com/statistik/daten/studie/687795/umfrage/umfrage-unter-pharmaexperten-zu-den-groessten-branchentrends/

STAUFEN AG. (2018). DEUTSCHER INDUSTRIE 4.0 INDEX 2018.

Steinhoff, R. D. (2016). *Aktueller Begriff - Industrie 4.0.* Deutscher Bundestag.

vfa. (2019, Februar 27). *Meilensteine der Arzneimittelentwicklung.* Retrieved from vfa.de: https://www.vfa.de/de/arzneimittel-forschung/meilensteine-der-arzneimittelentwicklung.html

Welter, F., May-Strobl, E., Wolter, H.-J., & Günterberg, B. (2014). *Mittelstand im Wandel.*

WHO. (2014). Annex 2: WHO good manufacturing practices for pharmaceutical products: main principles. *WHO Technical Report Series No. 986, 2014*.

WHO. (2014). Annex 2: WHO good manufacturing practices for pharmaceutical products: main principles. *WHO Technical Report Series No. 986, 2014*.

WHO. (2014). Annex 2: WHO good manufacturing practices for pharmaceutical products: main principles.

WHO. (2019, Januar 23). *Good manufacturing practice.* Retrieved from who.int: https://www.who.int/biologicals/vaccines/good_manufacturing_practice/en/