J Pharm Innov (2015) 10:99–108
DOI 10.1007/s12247-014-9210-5

RESEARCH ARTICLE

Operational Excellence in Practice—the Application of a Takt-Time Analysis in Pharmaceutical Manufacturing

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Published online: 10 January 2015

Abstract
Introduction Due to increasing cost pressures and structural changes in the pharmaceutical industry in recent years, pharmaceutical manufacturers have been forced to focus on the optimization of their production processes. Therefore, operational excellence is receiving broader attention throughout the pharmaceutical industry. However, too many of these practices are attempting to reduce the cycle time or increase the output of single-process steps rather than optimizing the overall process from a holistic perspective.
Objective This paper addresses the concept of a "Takt-time" analysis for pharmaceutical manufacturing. A Takt-time diagram is a tool to identify bottlenecks in a production process. It visualizes the cycle time of a product and the times per process step and relates it to customer demand (Takt time). Thus, the bottlenecks in the production flow are revealed, and production can be reorganized. However, the application of the Takt-time analysis to pharmaceutical manufacturers shows specific challenges because of their manufacturing characteristics, such as batch processing.
Methods The concept for a Takt-time analysis was developed while working on a project with a CMO of an imaging agent to address the practical challenges in implementing its concept in pharmaceutical manufacturing.
Results The concept creates the basis for a process redesign at a multiproduct production site. It lays the foundation that customer demands can be matched with an aligned production process, and that a seamless production flow driven by customer demands can be realized.

Keywords Takt time · Pull production · Lean production · Pharmaceutical industry · Cycle time

Research Focus Pharmaceutical production, optimization of production, lean philosophy

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Introduction

The pharmaceutical industry is currently undergoing significant changes and is facing various environmental challenges, such as R&D productivity decline, generic market entry, and patent expiration of blockbuster products.

This situation among brand-name pharmaceutical companies is mainly triggered by a R&D productivity crisis. In the last 60 years, the number of drugs approved per billion dollars spent on R&D has halved approximately every 9 years [13]. Although investments in R&D are increasing, the product pipeline is not really promising.

This situation is aggravated by the expiration of blockbuster products of brand-name companies. As soon as the patent expires, various generic companies are ready to enter the market and aggressively win market share. The new market entry can account for substantial loss of sales and revenue for brand-name manufacturers, impacting the financial resources available for R&D activities. An often cited example for this is Zantac, a brand-name product, that lost patent protect in 1997 and experienced a price erosion of 90 % within 2 years after the generic ranitidine appeared on the market [2]. So, of 4 billion prescriptions in the USA, the share of generic drugs account for 80 % [5].

One of the responses of the pharmaceutical industry to these challenges has been to increase its focus on

manufacturing operations. Some approaches aim at cutting cost, while other approaches aim at improving the whole manufacturing process and value chain holistically.

For the latter, commonly, the first step to unveil improvement potentials is to undertake process mapping or value stream mapping (henceforth VSM). VSM originated from the automotive industry and was introduced as "material and information flow mapping" [15]. To identify inefficiencies, VSM helps to visualize and understand the process holistically and facilitates the examination of the value creation within the production process. Thus, the whole "as-is" (current state) production process can be visualized and improved comprehensively in order to realize an ideal "to-be" (future state) process.

Kletti and Schumacher [9] describe VSM as a tool to analyze manufacturing bottlenecks and to eliminate non-value-adding processes. It serves as a basis to differentiate value-adding process steps from non-value-adding process steps so as to eliminate waste and reduce overall *cycle time*.

Szendrovits [14] defines cycle time as the period from starting the first operation on the first unit of the lot until the whole lot is delivered to its destination. The term cycle time includes loading and changeover times as well. Szendrovits relates cycle time to the aggregated time needed for all processes and therefore represents a "total cycle time" for the production process. The term cycle time in the context of the paper differs in two respects. First, cycle time is measured for one process step only. Second, cycle time refers to the time it takes to process single units of a batch, such as a vial or a bottle and not necessarily the whole batch.

In order to design an efficient and agile to-be manufacturing process with low cycle times, it is important to align the cycle time of each process step to the customer demand in order to implement a flow production model. A flow production model is one where products are processed in an optimized sequence without waiting time between the process steps. It can significantly lower the time required to route the products through the manufacturing process [10].

However, to implement a production flow which is adjusted to the customer demand is difficult in the pharmaceutical production environment since pharmaceutical production is typically organized as a batch process (see Fig. 1). Manufacturers would have to match batch size to a specific customer demand, meaning minimizing the number of production units in a batch so that manufacturers are not as dependent on forecast and they can be more agile and flexible to environmental changes [10]. The advantages of an optimized value stream, in combination with a customer-aligned production, can bring about significant lower cycle time, lower inventories, lower costs for transportation, and more efficient usage of plant layout as well as reduction of planning and control efforts [9]. In comparison, pharmaceutical batch production processes are typically scheduled around equipment utilization and minimization of clean-down and changeover activities.

Due to the contextual changes in the pharmaceutical industry, pharmaceutical manufacturers have started to focus on optimizing their production processes through operational excellence approaches. These initiatives aim for holistic methods in which production processes are aligned, and waste and cost are minimized stepwise and consequently operational. Therefore, operational excellence has received broad attention recently [7]. However, practices which only focus on improving the cycle time or on increasing the output of single-process steps rather than streamlining the overall production process will not be effective. Optimization efforts in a flow production model which are aimed at single steps which do not take into consideration their respective up- and downstream processes will not be effective. For instance, if the optimization effort in a production flow aims at optimizing the cycle time of process other than the bottleneck process, a process flow cannot be established. Consequently, tools and methodologies taking the whole process flow into consideration have to be applied, in order to derive the right decisions.

One of these tools, which are already widely used in other industries, is the Takt-time analysis. Takt-time analysis results in an easy-to-understand visualization of the process cycle times and relates them to the frequency of customer demands [12]. Thus, bottlenecks in the process flow can be identified, and the specifics of one production step are examined in the context of the entire production flow of the entire product.

This paper addresses the concept of a Takt-time analysis in pharmaceutical manufacturing and tackles the specifics of the industry's production processes.

Objectives

The study discusses a concept of an adoption of a Takt-time analysis in the context of pharmaceutical production, which varies significantly from the common deployment of such a tool in other industries [12]. The underlying concept was developed in cooperation with a pharmaceutical production site in Germany and thus takes industry specifics into account. This study served as the basis for reorganization in the production area in that company.

Aside from the mere results of the Takt-time analysis, this paper's aim is to provide the methodology for developing a concept. Even within the pharmaceutical industry, the specific manufacturing operations vary so much that this concept would have to be further developed and adopted on a case-by-case basis.

The paper will not only discuss how to identify bottlenecks on the basis of the Takt-time analysis but it will also disclose the identification of potential improvement levers in the production process.

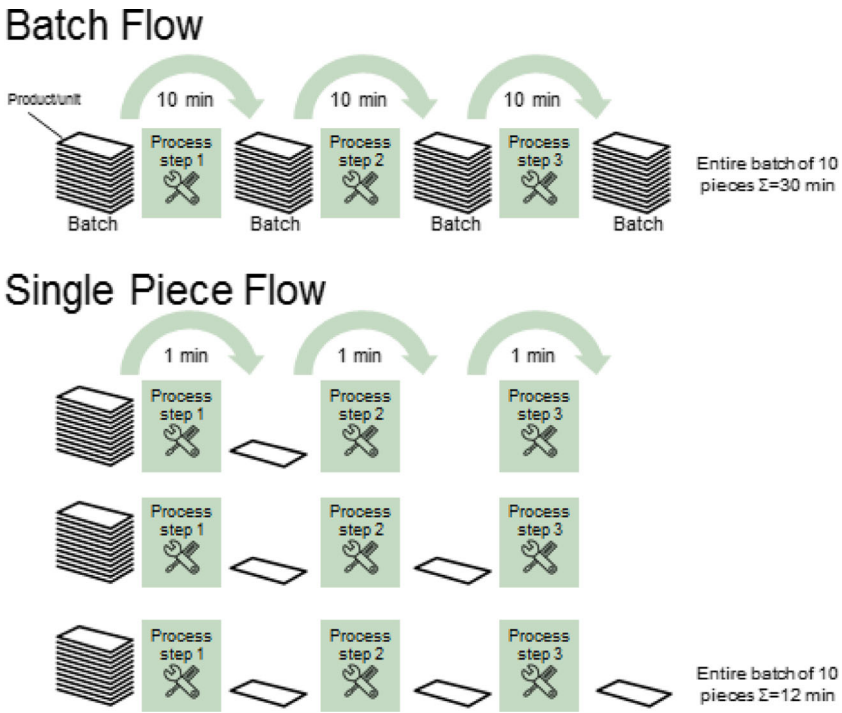

Fig. 1 Difference between batch production and single-piece flow

Methodology

A complex manufacturing operation may initially appear to be puzzling to researchers and managers alike. The starting point for this study was how operations might be improved and what effects these changes would have on production planning. In order to infer practical relevant implications, the concept of the Takt-time analysis was developed and tested in close cooperation with a contract manufacturing organization (henceforth CMO).

The German CMO, which produces a diagnostic imaging agent, introduced the concept of Takt time discussed in this paper. Prior to the implementation of a Takt-time model, the company's operation was facing several problems as a result of bottlenecks in the production flow. This project took place in 2012 and 2013 during which all data was collected partially through interviews and partially by extracting existing data from the company's ERP system. In a multilevel procedure, the data was validated with shop floor as well as management employees in order to ensure accuracy. This concept was subsequently tested with a tool, which provides the flexibility to change parameters affecting the Takt-time calculation such as the product itself, forecast utilization, or cycle time and was then presented to all involved parties and stakeholders.

Purpose of a Takt-Time Analysis

As previously mentioned, changes in the pharmaceutical industry are increasing the pressure to focus on more lean and efficient processes in operations. Phenomena like overproduction, overcapacity, underutilization, unsynchronized processes [4], and noncompliance with customer orders are being addressed [7]. The automotive industry is certainly one of the leaders with respect to addressing this issue. The automotive industry is probably also most advanced with lean approaches and in the implementation of lean thinking [11, 16]. Manufacturers in this industry have managed to establish the right prerequisites in order to comply with customer orders and to implement continuous flow in production such as pull production, synchronization of processes, and improvement of OEE [8]. However, in order to realize each of these practices, it is essential to visualize an overview of the manufacturing situation on site. Only then can the right levers be identified and designed to implement continuous flow production.

One approach to prepare this visualization involves the introduction of the concept of Takt time. "Takt" is originally a German word and is derived from musicology. Koch[1] defines Takt as the measured motion of the tuneful melody or the sequence of equal length or uniform segments. Takt in an orchestra is the beat or timing at which musicians play and which the conductor controls. By analogy, in a lean production environment, "Takt is the rate at which the customers require the product" [12] and thus controls the speed of the production process and helps to overcome unsynchronized processes,

[1] In Allgemeine Theorie der schönen Künste: in einzelnen, nach alphabetischer …
von Johann Georg Sulzer 1794

excess buffering inventory between processes and to identify bottlenecks within the production flow. In this case, the customer demand assumes the role of the conductor in an orchestra, which controls, navigates, and coordinates all the elements.

Womack and Jones [16] defines Takt time (*tt*) as determined by dividing the number of orders placed by customers in a given period *D* into the amount of available production time in the period *T*. In accordance with the prior definition, he states that establishing Takt-time is critical in avoiding the natural tendency to produce too fast, building up wasteful inventories and thus implementing the process flow. Cuatrecasas Arbos [3] provides another definition of Takt time as the cycle time allowing production attuned to the demand to be carried out in the time available.

Translated in mathematical notation, the following term will be the basis for the subsequent discussion:

$$tt = \frac{T}{D}$$

This relation helps to visualize the cycle time of a product per process step and relates it to customer demand. Therewith, the inability to meet customer demand can be easily revealed if the cycle time exceeds the Takt time. Consequently, the alignment of all process steps toward the Takt time ensures the compliance of the customer pull. Therefore, the Takt-time analysis provides the view of the production processes from the customer perspective.

The application of the Takt-time analysis is vastly known in discrete manufacturing industries with long cycle times and with manageable customer demands. In the case of Womack and Jones [16], relating to a manufacturer of wrapping machines, cycle times of 1 week for certain machines were common. However, within the pharmaceutical industry, this variable differs significantly since cycle times relate to batches.[2] Therefore, to apply the same concept of the Takt time in other industries unveils that to apply the same concept in the pharmaceutical industry requires certain challenges to be met. These challenges will be discussed in this paper. These challenges are non-dedicated machines, batch processing, cleaning and changeovers between products, and the multitude of different technologies to mention a few. However, the aim of the Takt-time analysis remains the same—the transformation from batch-production to continuous flow production.

Case of an Imaging Agent CMO

As stated earlier, the concept for a Takt-time analysis in the pharmaceutical industry was developed in cooperation with a CMO of an imaging agent in Germany. This medium-sized CMO initiated lean initiatives and was at the very beginning[3] of their process of implementing lean thinking.

Their diagnostic imaging agents are distributed worldwide to more than 60 countries. The global customer base leads to a high complexity in packaging because of the CMO's need for different packaging formats for different regions. Production is split in two divisions, an upstream division including weighing, formulation, stopper preparation, filling, and autoclaving. The downstream division comprises optical control and packaging. One important difference between the upstream and downstream divisions is that they run in different shift models and length. Single-piece flow implies that while a unit is processed during a production step, the preceding and the following units are processed at the same time with approximately the same processing time as the respective preceding and following process steps. Thus, a unit can be pulled through all production steps without building inventories. In the underlying case of the imaging agent CMO with a different shift timing pattern, multipurpose equipment, and a mix of continuous processing (e.g., preparation of the solution or autoclaving) and discrete production (e.g., filling and packaging), a continuous flow seems counterintuitive from the view point of a single-flow company's perspective. However, one of the crucial differentiators of the CMO lies in its hybrid production type and explains that alignment of production processes and customer demand is feasible with different shifts.

In theory, there is commonly a distinction between discrete manufacturing and continuous processing [12]. While in the first type, the discrete unit is processed before the following unit can be processed; in the latter, production type batch comprised by a group of units is commonly processed at the same time (see Fig. 1).

In the case of the CMO, in the upstream section, there are processes involved in which unit (which is a single product of a batch) and batch (which is the total of all units within this batch) require the same cycle time (for instance, autoclaving a unit takes the same time as autoclaving the complete batch of all units to be produced). In order to overcome this obstacle, a common dimension, the "smallest reasonable manufacturing unit" has to be introduced for arithmetical reason only.

Data Collection

First and foremost, it was necessary to understand the process flow at the site. Therefore, interviews were conducted with 24 employees in order to understand the manufacturing process at this site. The interviewees were selected equally from all divisions and functions and

[2] In the industry cycle times according to the definition in chapter one relating to batches are referred to as batch times.

[3] Lean thinking according to Womack and Jones' [17] definition.

comprised shop-floor employees (machine operator, work schedulers, and supervisors), engineers, and representatives of the planning department. The aim of the interviews was to map single-production processes from weighing to packaging and identify all the machines involved (henceforth APL: the company's internal term for different machines which is derived from the German word for workstation "Arbeitsplatz"). Each production process comprises of several machines due to the different technologies and formats manufactured on site.

A total of 37 APLs were identified, two in weighing, six in formulation, one in stopper preparation, seven in filling, and two in autoclaving. In the downstream division, there are three APLs in optical control 1 (exclusively semiautomated machines), eight in optical control 2 (exclusively fully automated machines), and eight machines in packaging.

The site uses different technologies to manufacture more than 500 different formats or SKUs (stock keeping units) of the existing products. In order to manage this high number of product variants and formats, product families were built which have similar manufacturing characteristics such as type of API, bottle size, packaging size, or the type of equipment used in the manufacturing process. Within a product family, the variants and formats are processed on the same APLs and have similar cycle times.

Thus, the entire product portfolio comprising a multitude of different SKUs was categorized in 27 product families in order to analyze their process flow and cycle times. As a result, a matrix was compiled showing the cycle time of all product families (shown in rows in Table 1) on the different APLs (shown in columns in Table 1).

Customer demand data was extracted from the current forecast and is provided in numbers of units per product family. Additionally, common batch sizes were assigned to the various product families in order to calculate the Takt time per batch at the different machines.

The compiled matrix was distributed as a template to all the involved departments. The data came from IT systems of the involved APLs. Some data from older APLs were generated by historical records, and some others were obtained by performing actual measurements. However, all data in this sheet was reviewed by at least two representatives of the department concerned before it was approved for use in this analysis.

The Takt-Time Concept

The major differences in this case from industries such as the automotive industry where a Takt-time analysis is commonly used include large, inflexible machines; long setup times; and the general difficulty in producing in small batches.[4] The aim is to transform a batch production into a one-piece flow driven by customer demand with lower work in process (see Fig. 1). However, in other discrete manufacturing industries for instance, the focus lies on one or few products which require a significant cycle time. In turn, in the pharmaceutical industry, the cycle time of one unit and per process step can be substantially lower. In the underlying case, for example, it took seconds to fill, pack, or optically check a single unit such as a vial or a bottle. On the other hand, in a lot of processes within the pharmaceutical manufacturing chain, a great number of units—usually a whole batch—will be processed at the same time: to formulate or autoclave a single vial or bottle consumed the same time as formulation and autoclaving takes for the whole batch.

Although pharmaceutical production is considered as process manufacturing, in the case of the CMO, downstream production processes show characteristics of a discrete manufacturing type. These hybrid forms of manufacturing types exist since the reagent, such as API, is transformed into discrete units of bottles or vials.

A comparison of the cycle times of single units and per process step would not provide any useful information in terms of lean thinking. Whereas it took hours to sterilize a unit (a vial or bottle) of a chosen product family, it would only take seconds to pack the same unit. In Fig. 1, it would take the same time to process a single unit as it would take to process the whole batch.

For these reasons, it is advisable to introduce aggregated manufacturing units. There are two possible approaches: the first approach focuses on smallest reasonable manufacturing units (SRMU). The SRMU is defined by the longest cycle time (ct) of the unit operation in the production flow. The numbers of units which can be processed in this period yield the SRMU. In other words, the SRMU is the optimal utilization of the process step with the longest cycle time.

The second approach focuses on batch size as the basis for the analysis. The cycle time is determined per process and per batch as the basic quantity for the Takt-time analysis.

After determining the basic quantity for which the analysis was conducted, there are two further variables required according to the Takt-time equation. As mentioned in the prior section, the customer demands of the several product families were extracted from the current records. The second variable is the available time per machine per year in hours. The analyzed period covered a calendar year since the customer demands were also provided for this time frame. The basis for the available time per year is composed by the number of hours per shift, shifts per week, and weeks per year. The product of these values needs to be reduced by times when

[4] Abdulmalek and Rajgopal [1] are referring to managers in the process industries to adopt lean manufacturing tools

Table 1 Product APL combination (batch size in output number)

Cycle time				Weighing		Formulation		–	–	Packaging		
Technology	Product family	Customer demand (′000)	Batch size (′000)	APL 1	APL 2	APL 3	APL 4	–	–	APL 35	APL 36	APL 37
Vials	Product family 1	900	8	4.5		9.0	5.6	…			64.4	
	Product family 2	200	20	4.5		9.0	13.8	…			77.2	
	Product family 3	5′000	40	4.5		9.0	16.8	…				
	Product family 4	600	190	3.0					…			
	Product family 5	1′000	66	3.0					…			
	Product family 6	500	66	2.0		9.0	23.2	…				
Ampoules	Product family 7	20	4	3.0			8.2	…				
	Product family 8	5′000	10	3.0			5.3	…				
	Product family 9	600	20	3.0			7.6	…				
	–	–	–	…					…			
	Product family 27	500	40	3.0			12.4	…				

the site is closed or machines are not running. In the case of the imaging agent CMO, these reduction times were vacation closedowns, annual downtime for maintenance, and audits to name a few. Setup and cleaning times are included in the cycle time. Hence, where bottlenecks are identified in the course of the analysis, setup and cleaning are common levers to eliminate these very bottlenecks. If a tracking system is installed, these times can be demarcated separately. In the underlying case, there were no such systems installed.

Parameters and Levers—How to Change

Essential for the concept was the provision of a visualization of the status quo of the manufacturing situations. Hence, single cycle times of process steps were visualized with respect to the available time dictated by the customer so as to identify bottlenecks. Most commonly, the shop-floor supervisor had a precise idea where these bottlenecks were. So, the concept helped to verify the source of the bottlenecks. In other cases, the analysis might help to identify the true cause which lies in upstream or downstream production steps. By varying parameters in the analysis, one can see the results of improvement efforts immediately and thus give guidance to identify the right levers to eliminate the bottlenecks.

Available Time

The used available time assumed a utilization ratio of 100 %. However, this ratio is merely adequate in most cases. Unforeseen downtimes caused by quality issues or machine breakdowns are not included. Therefore, a parameter for the utilization ratio was incorporated, which could be changed. Each of the 37 APLs utilization ratios was regulated separately in order to regard the specifics of each machine: older machines are prone to breakdown more easily. Further utilization depends strongly on the function. In this case, there is a new filling APL which has experientially a lower uptime than other APLs and has therefore a lower utilization ratio.

Machine Capacity

In the case of bottlenecks, capacity matters will be discussed. One option is to lower utilization by shifting a product family to other machines. Another alternative is to invest in new machines and thus add capacity. In the underlying case, a parameter for each APL was integrated which provides the possibility of capacity extensions. Thus, the presented concept could provide an assessment of how much additional capacity is needed to meet customer demands.

Shift Model

Another lever to eliminate the bottlenecks is the modification of the underlying shift model. In the imaging agent CMO's case, there were two different shift models for the upstream and downstream divisions. This initiated the discussion of an extension of the downstream two-shift model extensions to a three-shift model to increase capacity or vice versa for the upstream division. Therefore, working weeks and shift length are incorporated as parameters as well.

According to the prior description, machine capacity is included into the parameters. However, process robustness is not implied but is considered as an essential prerequisite in order to successfully implement a Takt time. Commonly, process robustness is measured in process capability (Cpk)

whereas a value greater than 1.6 is considered excellent to serving the concept of Takt time in practice [18].

Calculation Methodology—Applying the Concept to the Case

After defining the drivers and levers affecting Takt time, we will discuss the practical challenges in implementing and conducting the analysis, with focus on the specifics of the pharmaceutical industry.

The crucial difference to other industries and a major challenge of the implementation in the case of the imaging agent CMO were the non-dedicated machines in operations. The size of the production site and the variety of formats and product variants entailed that different product families were assigned to the same APLs. This decision brings about the advantage of high utilization and the avoidance of redundant manufacturing equipment. However, setup and cleaning times occur more frequently, and as a result, resources need to be invested. In terms of our Takt-time calculation, it means that the available time is affected.

Based on the prior introduced definition of Takt time, the available time T was refined and specified to the available time per machine and product family (PF) due to varying shift length. The time period was defined on a yearly basis for both available time and customer demand.

$$tt = \frac{t_{APL\,\&\,\mathrm{PF}}}{d_{\mathrm{PF}}}$$

But this term needed further refinement since the available time of an APL was not exclusively dedicated to one product family. Therefore, a ratio needed to be calculated in order to prorate the available time per APL for a specific product family. The ratio is APL and product family specific since every APL had a different set of product families which were processed on the equipment. The idea behind the used ratio was an ideal prorate assignment of capacity to each product family. In other words, it is the time which is needed to process a specific product family as proportion of the whole process time of all product families being processed on a particular APL.

The data to calculate this capacity ratio (cr) are available from the cycle time which were collected prior (Table 1) and the number units (customer demand d), which were processed on the APL (Table 1). The result of the process time and the customer demand per product family is the process time of the product family of the specific APL. Therefore, the capacity ratio to determine the available time per APL and product family is the ratio of the process time of a product family and the sum of all product families' process time.

$$cr_{\mathrm{PF/APL_o}} = \frac{d_{\mathrm{PF}(t-1)} * ct_{\mathrm{PF/APL_o}(t-1)}}{\sum_{n=1} \left(d_{\mathrm{PF}(t-1)} * ct_{\mathrm{PF/APL_o}(t-1)}\right)}$$

However, this capacity ratio relates to last year's process times and customer demands: Therewith, the ratio is based on actual numbers and does not reflect any desired changes. Thus, it reflects how much time of an APL was dedicated to a product family based on achieved output and is scalable to any degree of complexity of scheduling on a machine. By no means, the capacity ratio should relate to current or planned process times. As a consequence, an identified bottleneck could not be remedied by decreasing the process time for a specific product family since the process time is part of the capacity ratio. A shorter process time would allocate less capacity to the said product family on an APL.

Where a product family has either a very high process time or a very high customer demand compared to the other product families on an APL, the ratio will be comparably high and vice versa. The capacity ratio is therefore only an approximation relying on actual of preceding years and lies between 0 and 100 %.

With the capacity ratio and the overall time, all elements are available to calculate the Takt time. The basic Takt-time equation in combination with the capacity ratio yield is as follows:

$$= \frac{T_{APL} * cr_{\mathrm{PF}/APL}}{d_{\mathrm{PF}}} = \frac{T_{APL} * \dfrac{d_{\mathrm{PF}(t-1)} * ct_{\mathrm{PF/APL_o}(t-1)}}{\sum_{n=1} \left(d_{\mathrm{PF}(t-1)} * ct_{\mathrm{PF/APL_o}(t-1)}\right)}}{d_{\mathrm{PF}}}$$

This equation projects the available time for operations to manufacture a SRMU of a specific product family and per machine. If the cycle time of a machine to process a SRMU falls below the Takt time, there is excess capacity which may be used otherwise. Either operations can expand the customer demand which affects Takt time (which will be decreased) or the excess capacity is used to shift products from other machines. In turn, if the Takt time is below the process time of a machine, this is evidence for a bottleneck. The levers will be valid likewise: lower the accepted customer demand of a machine or shift product families to other equipment to eliminate the bottleneck.

The specific calculation of the Takt time per machine and per product family is called process Takt. The minimal Takt time of all processes within a value chain is called the customer Takt.

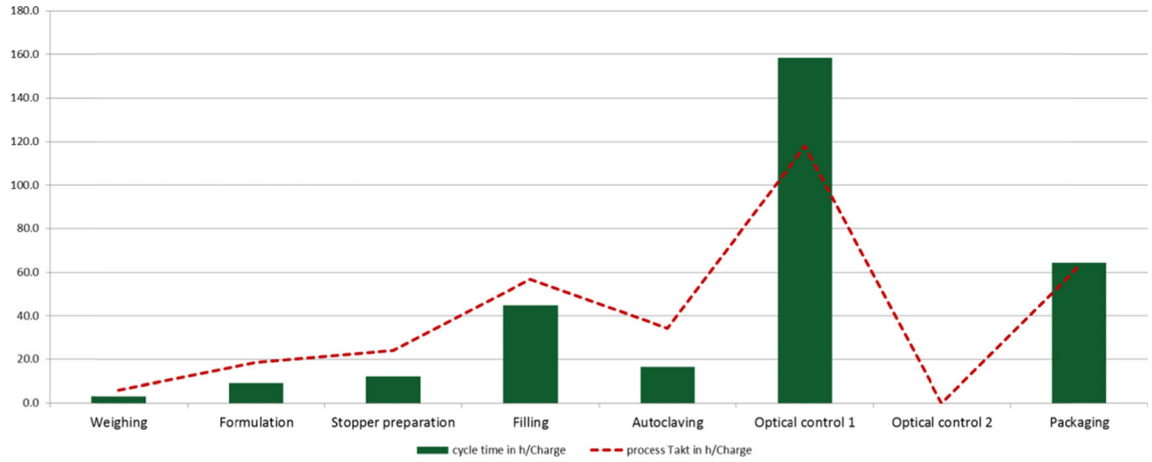

Fig. 2 Takt time of a chosen product family

The aim of the concept is to display in an aggregated form the bottlenecks for each product family. In order to visualize the cycle times with respect to customer Takt, APLs were aggregated. Nevertheless, product families were chosen on the basis of similar processing. Therefore, a specific product family is commonly processed on one APL or on equivalent machines. To achieve an aggregated overview on a process step level, the average of the process times of the involved APLs within the process step was calculated. In a second step, the specific process times can be comprehended in a flow chart which is part of the concept too.

Results—Identifying the Bottlenecks

In summary, the metrics which were introduced in the foregone section were applied to data which were provided by the imaging agent CMO. Twenty-seven product families were analyzed and their Takt time was calculated in order to compare it to the respective cycle time of each process step. Thus, the analysis visualized the cycle times and process times and revealed actual bottlenecks in the production.

Figure 2 shows an exemplary one Takt-time diagram for one of the 27 product families. On the abscissa, the single process steps of the imaging agent manufacturing process are plotted. The ordinate shows two metrics. The first one is indicated by the bars; this is the cycle time of the single process steps. The second metric is process-Takt shown by the line. The dimension of the ordinate depends on the selection of batches or SRMU. In the figure, it is time in hours per charge.[5] However, one of the adjustable parameters is the selection of SRMU.

In the case of this product family, there are two bottlenecks indicated by the intersecting line and bars at the process steps optical control 1 and packaging. For these product families, demands exceed the current capacity.

In order to eliminate these bottlenecks, more detailed knowledge about the involved machines is necessary. Figure 3 [6] shows an overview of all on-site manufacturing APLs, arranged according to the process flow. The highlighted APLs provide the key performance indicators (KPIs) cycle time and capacity ratio for a selected product family. In the production steps filling and sterilization, more than one APL are involved because capacity was shifted to different machines. The knowledge of the APL-related KPIs is necessary to identify the appropriate levers and thus eliminate the bottlenecks.

Actions Affecting Process Time of a Product Family—Identifying the Levers

The analysis was the basis for reorganization decisions, which can be assessed by changing the parameters. The levers which were introduced above are shift model, available time, and machine capacity will be exemplarily modified to see their effects on the production flow and bottlenecks. Aside from the parameters, there is always the option of optimize the cycle time to optimize the processes.

One parameter allows multiplying the capacity of each machine. In the model, doubling (adding 100 %) capacity is realized by halving the customer demand which is processed on an APL customer demands which is processed by a specific APL. If an identical machine is acquired and used for the same product families, the customer demands which are processed by the first machine can be reduced by 50 %. This consideration leads to $tt = \frac{T_{APL} \rightarrow cr_{PF/APL}}{1/2 \rightarrow d_{PF}} = \frac{2 \rightarrow T_{APL} \rightarrow d_{PF(t-1)} \rightarrow ct_{PF/APL_o(t-1)}}{\sum_{n=1}\left(d_{PF(t-1)} \rightarrow ct_{PF/APL_o(t-1)}\right)} \rightarrow d_{PF}$

[5] In the underlying case, the CMO used the German word "Charge" instead of batch.

[6] Process step weighing was excluded from this analysis.

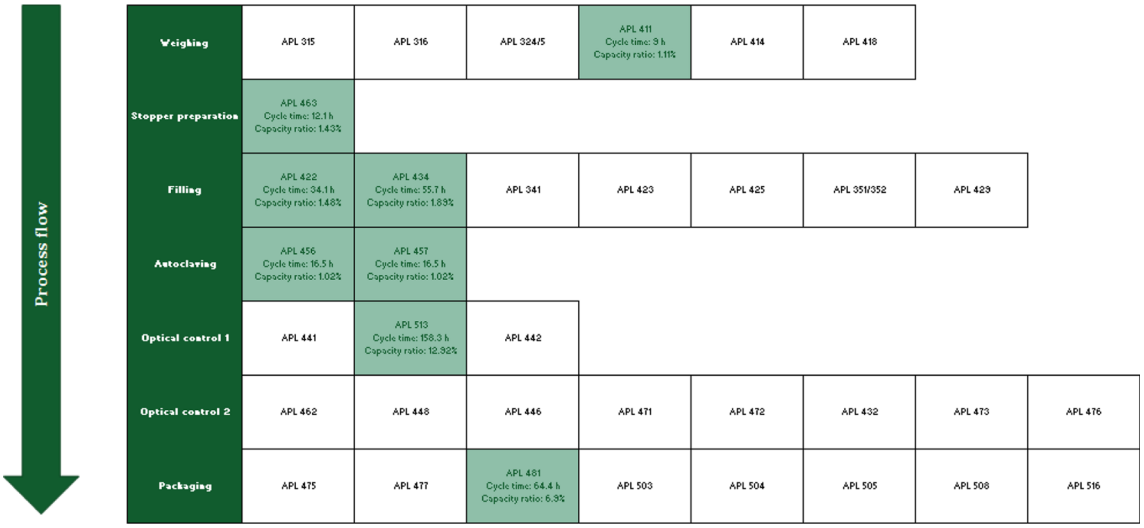

Fig. 3 Automated APL KPI control for a selected product family

In the case of the imaging agent CMO, the downstream process steps ran two shifts, while upstream was running three shifts. If the involved APL in downstream process steps would add one shift, the available time would increase by the factor 3/2 and leads to

$$tt = \frac{\frac{3}{2} * T_{APL} * cr_{\mathrm{PF}/APL}}{d_{\mathrm{PF}}} = \frac{3 * T_{APL} * d_{\mathrm{PF}(t-1)} * ct_{\mathrm{PF}/\mathrm{APL_o}(t-1)}}{2 * \sum_{n=1} \left(d_{\mathrm{PF}(t-1)} * ct_{\mathrm{PF}/\mathrm{APL_o}(t-1)} \right) * d_{\mathrm{PF}}}$$

The third lever is the available time of an APL, which would be practically influenced by decreasing planned downtimes as planned maintenance or annual site closures. Assuming that the available time could be increased by a factor α, this would lead to a similar change as above

$$tt = \frac{\alpha * T_{APL} * cr_{\mathrm{PF}/APL}}{d_{\mathrm{PF}}} = \frac{\alpha * T_{APL} * d_{\mathrm{PF}(t-1)} * ct_{\mathrm{PF}/\mathrm{APL_o}(t-1)}}{* \sum_{n=1} \left(d_{\mathrm{PF}(t-1)} * ct_{\mathrm{PF}/\mathrm{APL_o}(t-1)} \right) * d_{\mathrm{PF}}}$$

Figure 4 shows the results of changing the parameters of the equation regarding the exemplarily shown product family from Fig. 2. The left-hand side shows a change of investing in two APLs where the bottlenecks occurred. On the right-hand side, a shift in the downstream division was added.

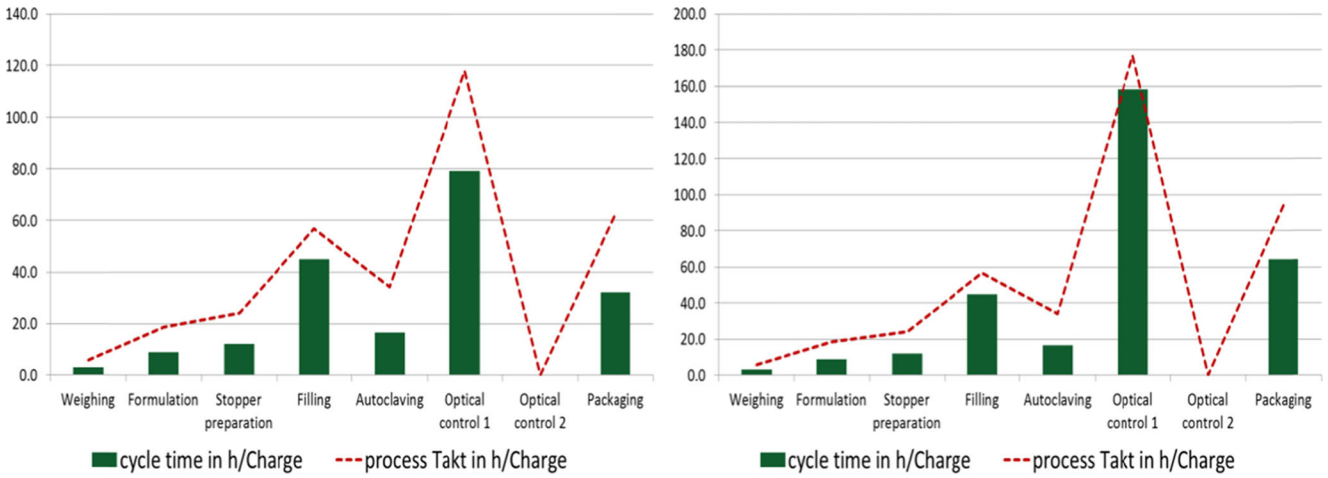

Fig. 4 (*Left*) Investment in two machines and (*right*) adding a shift in packaging eliminates the two bottlenecks

Summary and Conclusions

In this paper, the concept of a Takt-time analysis was introduced. Takt-time analysis is commonly used and well established in other industries, such as the automotive industry or in machinery and plant manufacturing. Through contextual changes and manufacturing trends within the pharmaceutical industry, lean approaches and tools continue to gain popularity. However, production characteristics vary significantly from other engineering-based industries.

This study addressed the specifics of pharmaceutical production on the basis of an imaging agent CMO. One of their major problems was their product complexity, which had led to a lack of understanding regarding cycle times and machine loading. The developed Takt-time concept helped to visualize the bottlenecks and to identify the respective levers. These levers included their shift model, the manufacturing time, and investment in machine capacity. However, the presented model describes not the maturity of an implementation of a flow production model over time. Modifying levers, such as investments in new equipment or changing the shift time model, will be dependent on other context factors such as regulatory or social aspects. These context factors are not incorporated in the model.

This Takt-time analysis proved to be a very useful tool to visualize the production flow and to enforce a seamless pull production by aligning the production processes. In the presented case, the CMO has just initiated the use of lean methodologies and gained significantly from increased process understanding as a result of the study. One element that became clear during the course of the analysis was that they still have significant variability in their cycle times. A guiding principle of operational excellence is to 'Stabilize First and Then Improve.' This concept has been widely examined at St. Gallen University through the operational excellence benchmarking program.[7] In this scenario, the benchmark will be the shortest process Takt time of all, the customer Takt time. Accordingly, the next step for this CMO on their continuous improvement journey using lean concepts will be the stabilization of their cycle time, followed by an optimization of their cycle times. The benchmark for this optimization process will be the attainment of the shortest possible process Takt time, i.e., the customer Takt time.

[7] The University of St. Gallen conducts a benchmarking since 2004, http://www.opexbenchmarking.com. The theoretical foundation has been thematized in Friedli et al. [6].

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