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Adapting Agile in Regulated (Pharmaceutical) Environment

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Abstract

Pharmaceutical software industries practice traditional approach for years, and when it comes to a change they are struggling to adapt new software methodologies such as agile; which is most commonly used by IT industries. The most significant factor required for successful agile adaptation is to make sure new practices should be aligned with the pharmaceutical regulations and the process should be validated and properly documented as per the guidelines. Apart from this, there are few challenges that Pharmaceutical companies are facing to adopt new changes. Those challenges mentioned in various research articles are highlighted in this research paper. This research paper also mentions the possibility to overcome those challenges while adapting the agile practices for regulated software developments projects. This research contains the proposal of actionable items to make transition easier by making changes to traditional approach. The adaption plan will be developed by using findings from Diagnostic Grifols successful adaptation plan. This research paper highlights the insights of agile approach and the way to customizing the agile activities to meet safety and regulatory needs. Besides, QA activities and its contribution will be explored to ease adaptation processes.

Keywords: Agile in pharmaceutical, Project management, Regulated environment, Adapting agile, Agile in FDA environment.

Preface

The goal of pharmaceutical industries is to provide quality products to the global population, and number of regulatory committee monitor things like patent, quality and pricing. Pharmaceuticals have wide range of complex projects, and these organizations are following waterfall methodology for years. The dilemma of using other methodology that it could affect the product quality and it may not be aligning with the regulatory requirements. After seeing the growth and tremendous success of adapting agile practices in software industries, there is a possibility that agile practices can be adapted in regulated pharmaceutical industries and it could be beneficial as well as productive. While I am pursuing masters in Project management studies at Harrisburg university, the studies in agile encouraged me to discover the possibility and suitability of using agile in pharmaceutical industries and develop the approach for adapting it. Agile can be more suitable and productive to achieve successful result in pharmaceutical industries as well. I am very thankful to Prof. Sheives who has been very supportive throughout my research work and provided all the feedback required to improve my work.

The goal of this research paper is to establish the understanding agile practices, its necessity and its contribution to improve quality processes and team building especially in pharmaceutical industries.

Prachiben Shah

Introduction

While software industries are using agile to deliver high – quality software to the market, on the other hand FDA regulated industries are trying to identify the challenges while adapting agile for their software development projects. The primary question is why Agile? Agile is an interactive method and where team work plays important role in the success of a project. Agile has been gaining recognition in regulated industries because it leads to successful, cost-effective and time sensitive outcomes.

This research paper covers the challenges from various scholar articles and literature reviews, which identifies fundamental issues related to documentative approach required by the guidelines. Few noted challenges faced by regulated industries are regulatory standards, unidentified requirements, validating system and cultural changes.

Today technology infused in many major industries, like other regulated industries pharmaceutical domain gradually carrying wide range of software development projects. The combination of agile and software development could go perfect together, but, in regulated environment it could be a different scenario. Pharmaceutical domain where the companies need to focus on quality and safety, and because of that they need to follow various guidelines like FDA-Food and Drug Administration, ICH- International Counsel of Harmonization, GAMP-Good Automated Manufacturing Practices and ISO-International organization of Standardization. All these guidelines summarize the standard operating procedure, quality testing, tools and well-organized documentation. Various regulatory associations and their stakeholders work closely with the industries to make sure company follows the guidelines, for that they conduct audit at working site on regular intervals.

Documentation is the most important part of regulated industries. but, in agile environment it would be quite difficult to follow these guidelines and maintain all the required documentation. The aim of this research on adapting Agile software development practices in regulated environment is to gain knowledge and insight of the challenges and better initiation of new techniques in traditionally working environment. The research will provide modern techniques and solutions to overcome challenges faced by the regulated industries.

This paper includes comparison between two methodologies and how documentative approach can be initiated to the agile practices. Diagnostic Grifols, one of the reputed regulatory industry; who has gained success in developing combined approach. This approach is to introduce documentative approach to the agile approach. They developed the Mapping of regulatory activities and highlighted the solution to how conflicts can be balanced. Their findings on implementation of modified agile practices will be covered in this research paper. This research paper would help to intricate combination of agile software practices and software development practices in Pharmaceutical environment. This research could help to change the perception and rigidity towards the adapting the new practices in pharmaceutical software development environment.

Problem Statement and Justification

A topic for this research is covering possibility of adapting agile software development practices in pharmaceutical environment. The question is; Is agile suitable for regulated environment? Apart from few challenges it is quite possible to adapt new practices in traditional environment Agile has been adopted successfully in software industries for many years. Though it has been successful, FDA regulated industries are resistant to adapt agile practices.

The resistance pertaining to three criteria mentioned below

-Pharmaceutical industries need to be safe because they are connected to peoples' safety and health. So, industries are not ready to take this risk. Furthermore, agile is still under the process to prove their reliability and superiority to be used in critical system.

-As agile is iterative process, it avoids any planning, documentation and planned processes. And FDA's in detailed planning and documentation requirements are opposite to what agile offers.

-Even we consider agile is suitable for FDA regulated industries, many scholars believe that FDA suggest waterfall as an appropriate method.

The points mentioned above are nothing but a misunderstanding, if agile methodology properly applied, agile practices could prove their reliability, effectiveness and safety to pharmaceutical projects as well. Agile could be compatible with quality system and be recognized as a consensus standard by FDA. To eliminate these myths and misconception, management needs to work on communication channels, training and mentoring activities within the industries. Transparent communication and exchange of the facts could help the organization to change the perception on adapting agile. Apart from this, management needs to study regulatory guidelines and gather the information that how agile could be used in traditional environment. They need to prepare the facts and present to the employees and team members.

As highlighted above documentation, FDA regulations and resistance to adapt changes are the biggest challenges towards adaptation. This research paper mentions the potential of agile in pharmaceutical environment by exploring the practical options from various research papers. From the gathered data, strategic plan for adaptation will be developed. The research paper highlights the high level agile practices in planning and focuses on developing and designing the suitable agile practices inclined with the regulatory requirements. Moreover, successful approach would be taken from the industries who are currently using agile in regulated industries. The mapping of regulatory activities to agile and balancing of conflicts will be covered. apart from this, how agile core values could be helpful in productive way especially in pharmaceutical industry; that will be emphasized. The fact is FDA does not restrict the usage of agile practices, and it indicates the opportunity to merge agile and regulatory activities practically under one roof.

Literature Review- Analysis of Related Work

There are quite a few literature reviews are available on the web on adapting agile in regulated environment. These literature reviews have variation of opinions to solve this confusion of having agile or not. They covered suggestions like having agile software development estimation, compatibility of documentation and tools to maintain quality and safety processes within industries.

There are few points that should be considered using agile for the software development projects. First, organization and management should understand the difference between the project management and product management. For any organization, this practice should be considered. Second, planning is crucial and principal factor for adaptation. Organization need to plan to decide their boundaries when run project management practices. Third, communication is must between the team members or whoever plays active role in managing projects. These facts should be considered before adopting the new practices in any stage of application.

According to Kim, Maria, and Casper's (2016) "It should be expected that not everyone will be willing to change, even so that some employees will never adapt to the new way of working". (p.94) We cannot deny the fact that lack of attempt and change resistance plays significant role in adaptation and transformation process. In conclusion, these articles were not able to identify the measures as different articles have different views on collected information.

Research by Ankit Lodha (2016) supports there are two major concerns for the pharmaceutical industry. The one, agile concentrates to value individuals rather than focus on processes and tools. And the other, value to get working software rather than comprehensive documentation done. (p. 41) He also says that following agile method would help to bring skilled workers and makes robust team and process. The focus area is team need to constantly ask

themselves if any improvement required. And regulators also support this theory and expect to do to the same to every industry. The agile and regulated principles have same purpose, if we associate them with quality product. Documentation is not an end to any process, if agile and regulated principles showing the effective results to achieve safe and effective product.

According to Collyer, K., & Manzano, J. (2013) "Well-established medical device manufacturer Grifols has adopted agile development practices in its highly regulated field. Organizations that work in other regulated fields could use a similar approach". Grifols took the first step towards agile and set the example that there is a possibility to make changes to the rigid environment where everyone is resistance to adapt new change. And they are hoping that other regulatory industries will be inspired to do the same by studying their approach.

Methodology: Description of Approach

Due to the advancement experienced team members are open to take the steps towards new challenges in process and tools improvement. As a result, to that, many Pharmaceutical industries are considering the option to have agile in regulated environment to gain promising results in software development projects. Still many industries out there doing their research to get clear idea on adapting new practices. But the possibility is high that in near future pharmaceutics will happily take a step forward to practice agile.

This research paper covers the results from various research studies conducted by the researchers or experts. The basic approach would be developing the requirements and identify changes in documentation required while adapting agile practices. Moreover, identification of required documentation will be highlighted here which are specified by the FDA. There are countless number of literature reviews available, those reviews have their findings whether there is any possibility to have agile practices in pharmaceutical industries or not. The purpose of this research paper is conducting further research and collect required information. The keywords such as “Agile in Regulated environment” or “Agile adaptation” will be used to search articles or literature reviews. Gathered documents will be reviewed and difference between waterfall and agile documentation will be clearly mentioned in methodology result section. Apart from this, results will be identified and specified in this research document.

The next approach would be collecting data, results and opinions from various research articles and write them up in this research paper After analyzing various literature reviews, it shows that many organizations are in favor of this changes but due to the restriction of rules and regulation they are quite resistance to take them into effect. Researchers identified quite promising results and that results will be summarized here. Apart from the results challenges will be identified when

adapting agile practices. Some of the challenges may have impact on processes; that challenges will be further explored and briefly mentioned in this paper. The solution of challenges and conflicts will be covered and topics which are critical and not clearly identified in result section then it would be included in the discussion of further research. The next approach would be creating strategic plan of how pharmaceutical industries can adapt agile. Strategic plan will cover high level activities that are important to focus to ease adaptation process. The high level activities will include planning, requirement management and QA activities. Before adapting agile, necessary information should be gathered and analyzed for planning stage. The research will be done on how agile or customized agile approach can be useful. This agile plan can help to make documentation process easier. Because documentation is the most important requirement for any regulatory industries. Moreover, mapping of regulatory activities to agile will be done. And analyze how agile principles can be used and interpreted as the regulatory requirements. Though it seems like agile principles and regulatory requirements are collide with each other, but on other side those principles can be adjacent to each other. The approach would be covering requirement management especially documentation ,and how documentation activities can be merged in agile practices. Moreover, high level QA activities will be covered to ease adaptation, and highlight the fact that how they can help to make the transformation process easier.

Exports from Diagnostic Grifols and IBM defined how Grifols is using agile for software development projects in regulated settings. They mentioned that many industries believed that waterfall approach must be used in regulated environment. But Grifols successfully adapted these changes and it is possible to any regulated industries. Their approach would be taken as an example and as per their findings, the customized agile approach will be developed for pharmaceutical industries.

Results or Findings

Agile Vs Waterfall

Transition from a traditional approach to iterative approach would be quite challenging to any regulatory industries. Waterfall is also called as traditional approach. In Traditional approach stakeholders are working on projects where they are used to finalize the requirements at the beginning of the project. In Iterative approach, each stage involves the feedback. And after getting a feedback required changes can be initiated. Waterfall developed before agile and it has several characteristics that make them unique from Agile.

Waterfall is step by step project management process. In waterfall customers' requirements are gathered before development stage. At the beginning of the project, feedback and questions are initiated and goal will be set. This methodology has less flexibility and adaptability compares to agile. It is useful for big complex projects where scope is clear and requirements are not changed frequently. The framework diagram is shown below.

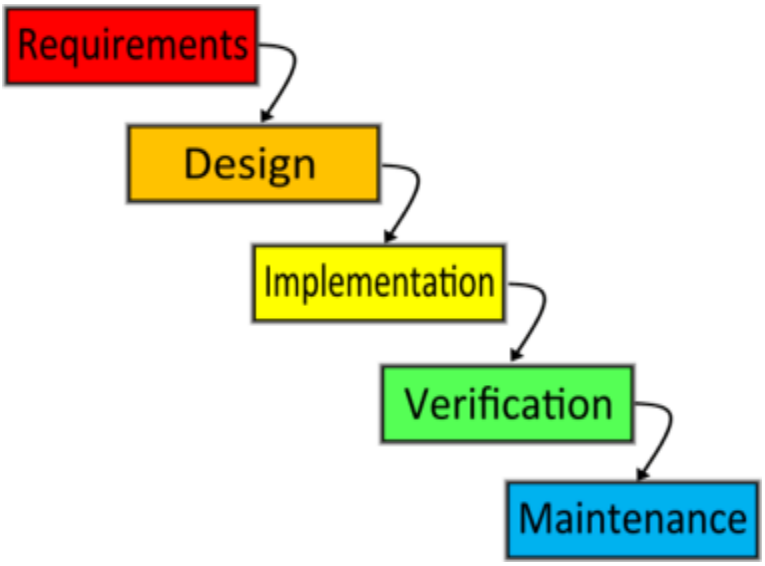

Figure 1. Waterfall Framework. Reprinted from Being agile while still being compliant, Collyer, K., & Manzano, J., 2013, Retrieved September 09, 2017, from

https://www.ibm.com/developerworks/rational/library/compliant-agile medicaldevice/index.html. Copyright 2013 by IBM, Reprinted with permission.

The diagram(Fig.1) shown above demonstrates the basic flow of waterfall model. It is a step by step process starts with requirements gathering, designing, testing, implementing and verification. If we talk about testing in waterfall then there are possibilities that during testing stage several defects and bugs can be detected and after the detection it should be resolved/fixed before the product is finalized. Once the product is done, the next step would be to create training guide.

Waterfall can negatively impact on project's timeline and cost if it's not properly managed. For example; Many times, it happens that company needs to finish the project in fixed time within determined budget limit, in this case quality of the product can be compromised. On other hand, in agile, budget can be monitored throughout the cycle and it can be tracked easily. Timing is the other significant factor, because in traditional approach testing is done near the end of the project. That gives the less time to identify and rectify errors. Agile is less risky, as testing is done during the sprints. It's always difficult to make changes to deliverables at later stages of production cycle.

On the other side, agile does not attempt to lock down the requirements at beginning. The requirements and design ideas will evolve at early stage, and more changes are discovered and learned during the process. Agile works by using user stories which are broken down into pieces as per the user requirements; which creates value to users, prioritize them and delivering them in one to three weeks short cycle that is called iterations. Requirements, design, development, testing are all part of the iterative process. There are no fixed phases and customer feedback are always welcome so that they can evolve and make changes, as shown in Fig 2. Agile focuses on evolutionary development, delivery and adaptive planning which encourages flexibility to make changes.

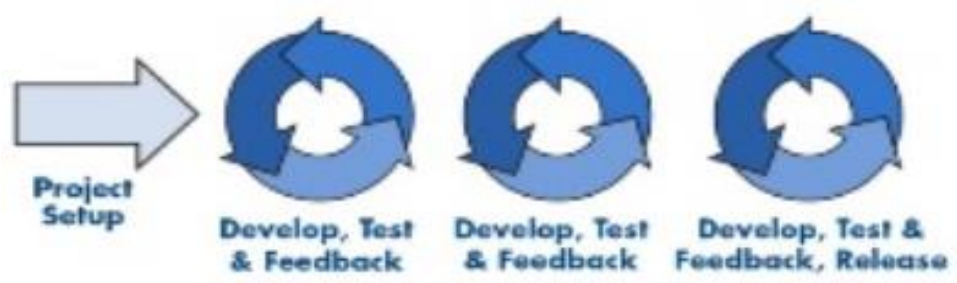

Figure 2. Iterative Process. Reprinted from Agile in an FDA Regulated environment, n.d., 2015, Retrieved September 29, 2017, From https://www.slideshare.net/pathf/e-book agileinanfdaenvironment. Copyright 2013 by Pathfinder. Reprinted with permission.

The benefits of agile over waterfall are:

- Agile helps to improve quality as testing starts from day one.
- Risk management process starts early in the process so, risk is reduced or in some cases eliminated
- It empowers the system that users and stakeholders experience the system which helps to highlight the errors earlier in the development stage.
- Get the clear picture of actionable items to correct the mistakes and navigate the process without having an error or doubt.

Let's assume that company is using waterfall approach for developing a software application then what would be their approach? In this case, the company would look up to the client. They will spend times with the customers to make sure scope and requirements are clear. Then development team will be working with customers and set up meetings to identify specifications until customer gives the information what they want in the product. Based on the specifications, team members would come up with the final design with desired features and applications. Then final design will be selected to implement in the project. Once design is finalized the team started developing the product. Once developer started to work on the

development part, then it would be difficult to change any design if customer wants to change. If customer really needs to change or add new requirements then entire process must start over from the beginning. And that could result in spending more money and time over the project completion. Testing will be done right after development work. During the testing if any bug or technical problem will be detected, tester needs to fix them. Once bugs are fixed and problems are resolved the final product will be move out to production. The next step would be product approval from clients and regulatory boards.

Now, let's take similar scenario in agile setting? In agile environment, the development team and customers will be meeting to identify scope of the project. Then development team will be working on developing a backlog of tasks. These tasks will cover all the user requirements from user feedback. The backlogs will be broken down into stories and features which would be a part of sprints. Each sprint will last for two weeks. While working on each sprint team members will meet regularly and discuss their progress. In daily stand up meeting all the team members will discuss the progress and problems that they are facing. If in between this procedure client want to add new feature then team will revise or introduce new tasks in next sprint. After completing all the sprints and getting feedback from the customers the product will be out to production and approval. During the project, sprint documentation and code repositories would be acting as required documents. The code repository could be a tool or website, where all the codes are written/uploaded.

Comparing the same scenario in different environment indicates that each methodology has their own importance and aspects to complete the project. It also highlights the fact that how these practices are different from each other. Agile has limited documentative approach. While waterfall is step by step and finish -to-start approach. Where, at every stage the documentations

are prepared. There are no over lapping of stages which gives the convenience to create the effective documents.

Research in multiple industries by experts and consultant in various regulated domains and industries authenticate to adapt agile practices; increasing evidence of effectiveness and productivity and 100 % compliance to customers, regulators ad market needs. Apart from limited documentation, agile totally focuses on team communication, performance and quality outcomes. And these all are the critical requirements for regulatory industries. So, in other words agile serves the purpose to what regulators want. Regulatory industry should adapt agile but due to strict documentation requirements agile approach could be customized the way regulators want and can be chosen wisely.

Challenges

Ali, Ronald, and Singler (2014, p. 43-45) identified 3 topics which provides holistic view of researched topic.

The regulatory complexity of software development. There are various guidelines like FDA and GAMP which are govern by the regulatory agencies. And these regulations must be followed by regulatory industries whether it is product manufacturing industry or software development industry. In agile where requirements are frequently changing, it would be difficult to maintain documentation. But regulatory industries such as Pharmaceutical industries have high cost projects and require high quality documentation. because of the high cost projects companies cannot afford tremendous changes to the system. Perhaps, it would be difficult to introduce new system in traditional environment where everyone is resistant to accept the change in methods and processes.

Difference between agile and documentative approach. The complexity of agility in regulated environment is; the documentative approach; required by FDA. Like medical device industries, pharmaceutical industries have many common mandates required by FDA. The fact is FDA doesn't mandate to follow waterfall methodology, so, if agile could help to generate quality documentation it could be an efficient methodology for pharmaceutical software development. There is a possibility to establish effective software development processes align with FDA guidelines. There are two prospective of documentation. Product and Project Documentation. Agile usually creates Project documentation and FDA requires product documentation. But the right development tool can create the product documentation flawlessly.

Lack of attempts to be an agile. Research shows developer and customer are satisfied by agile method hence it may not be suitable for larger functions. The solution to this is each organization must develop plan driven processes. Agile adaptation is a big step to take for large industries like pharmaceutics. Apart from functionality and processes there are few transformational challenges which involves several individuals. A notable transformational challenge would be change resistance. This plays significant role in transformation and adaptation of agile software development practices.

After deep analysis and observation from various articles we can say that It's a challenging for any regulatory industry that they need to abide to the several guidelines and regulations like FDA, GAMP and in some case HIPAA and ISO. After initiating a project, if work delays or team may need more resources to finish project timely. Then it would be difficult to hire new ones at the end of the project. It would be negatively impacted to money and time. Moreover, it could delay the project and company may not fulfil customer requirements timely.

Many times, team and team members are used to follow waterfall methodology. Then in this situation it would be difficult to keep them on track and make sure they understand the agile method fully and follow them. There is a resistance to adapt latest changes to the production environment. Due to lack of knowledge about the regulations and used to work in tradition environment; employees do not want to take a risk where they are not sure if the documentation requirement would be matched as per the guidelines.

The problem with pharmaceutical industry is pharma cycle usually lasts for 3-5 years and software cycles are used to short ones. The problem with the waterfall is, it is quite difficult to gather requirements at early stage and finalize them. There are chances that requirements will change before reaching to the final phase. In that case agile would be an appropriate solution. The quality of project will be improved because testing starts from the day one of the project. Early feedback and improvements can be done at early stage of development processes.

The fact is FDA does not strictly mention that pharmaceutical industries must follow waterfall approach for software projects. Now, that stakeholder and management realizes that how agile is helpful and they are trying to make changes according to the standards. Agile presenting three principles risk management, quality management and software engineering which are proven superior to traditional methodology. If Diagnostic Grifols can adapt these strategies then any regulatory industries can customize agile approach to get better and qualitative result.

Agile Adaptation

Below are some high-level activities to focus to adapt agile successfully in pharmaceutical environment.

Table 1

Activities/Approach to adapt agile in pharmaceutical environment

Planning

- Gather Insights

  Agile principles and its interpretations

- Choosing and/or customizing agile approach
- Mapping regulatory activities to agile practices

  Benefits of customized approach

  Balancing conflicts

  Alternatives for conflicts

Requirement Management

- Documentation

  Importance of Documentation Requirement

  Define/Introduce quality stages to ease documentation

QA activities (Role)

- Training
- Communication
- Collaboration
- Flexibility
- Automation

The organization who wants to adapt changes to their ongoing processes need to do their research and gather insights of why these changes are required and is it necessary? The most

important question is how new techniques would be beneficial to produce qualitative products? Table 1 highlights the activities which are required to be analyzed before making any changes to the processes. The steps which mentioned in the table 1 are; to develop in detail understanding to know more about the agile practices. The first and most crucial step would be planning. Planning will include the fundamental approach to gather insights of the agile and its interpretations that how it's principles aligned with the regulatory requirements. The agile principles may be opposite to traditional approach but the qualitative principles of agile can be used in certain way to improve pharmaceutical processes. After having all the information on hand and having enough research on agile company need to focus on developing agile approach. If necessary, the agile approach can be customized in way that it fulfills the regulatory requirements of proper documentation. The next step would be the mapping of regulatory activities to agile practices. To match the regulatory requirement, mapping would be the next most significant step to work on by pharmaceutical industries. This is the phase where organization needs to come up with the customized solution that could be beneficial to the organization, and make sure to identify conflicts of having customized approach. And assessment should be done by presenting the solution for balancing the conflict.

Once the planning is done, organization needs to manage documentation requirements. Documentation is the most important requirement to any regulatory industry so, they should identify that which part of the cycle would cover the documentation approval and review process. Once documentation requirements are set the QA must work on next step. QA should concentrate on how they can help to ease agile adaptation in pharmaceutical environment. So, these are the high-level steps which can help to ease the adaptation process. Moreover, it helps to understand the requirements of what kind of approach or information is required and gathered before adapting

agile in any regulatory industries. Now, let's discuss each activity mentioned in table 1 and explore the possibilities of having agile.

Planning.

Table 2

Agile Principles and its interpretation to regulated activities

Agile Principles/Manifesto	*Interpretation*
Value individuals and interactions over processes and tools	Robust Processes
Working software over comprehensive documentation	Documents
Customer collaboration over contract negotiation	Processes
Responding to change over following a plan	Processes
Individuals and interactions	Roles

Source: A. Hajou, R. S. Batenburg, and S. Jansen. (n.d.). Determination of method description categories. Method æ; the agile software development method tailored for the pharmaceutical industry. Retrieved from https://slingerjansen.files.wordpress.com/2009/04/e36-method-c3a6-the-agile-software-development-method-tailored-for-the-pharmaceutical-industry.pdf

As discussed earlier that agile and traditional approach have many dissimilarities. They have different approach and principles. Agile has lists of principles which are totally different from traditional and at first it may indicate that these practices cannot be used in pharma industries and may not be accepted by the regulators. But the common goal for agile and regulators are to focus on quality of product. If we dive into the agile principles, they may serve common goal towards quality guidelines; which can be adapted in regulatory industries. The table 2 highlights the agile principles and its common interpretation in regulatory world. The interpretations can help to connect the dots between the agile and regulatory requirements. Moreover, it aids to know how

they can be adjacent to each other. The key agile principles mentioned in Table 2 are elaborated below, which can help to get in detailed information on agile principles.

Value individuals and interactions over processes and tools. The principle of Quality Assurance is to establish robust processes. Agile principles want to gather skilled people and working towards the same goal. The application of agile principle makes process more robust. Agile is to make continuous improvement when needed, that's what regulators want from manufacturer. Regulators want to make sure that every regulatory industry follow the guidelines and process. Agile and regulated industries have the same purpose. So, if we connect this requirement with the agile principles; agile can give us the effective and safe software.

Working software over comprehensive documentation. The purpose of documentation means industries are going to deliver the promising and safe software and following robust processes. Agile principles can help to contest documentation requirement during development process which could help to eliminate waste products and make sure valuable products can produced timely.

Customer collaboration over contract negotiation. The regulations mention that industries need to define design requirements for the activities like planning, design, coding and testing. It also requires that design requirements should include validation activities which shows the product adequacy to use. This may opposite to agile principles "customer collaboration over contract negotiation" But on other side, customer involvement can be a helpful tool to understand the user requirements. This means that customer's requirements can easily be included in design requirements. So, design requirements can be used to fulfill user needs and deliver satisfactory product.

Responding to change over following a plan. Next important requirement by regulations is development planning. Development document includes the standard of work and highlight process that should follow. Following the development document gives the assurance that process is followed and quality products are manufactured. While agile says the opposite that "responding to change over following a plan". It means agile supports the continuous improvement and changes in planning at various stages. And regulators agree the fact that documents need to be updated with the changes.

Individuals and interactions. For quality documents and processes agile core principle wants to have "individual and interaction" setting while working in a team. Regulators want organization where everyone in the team should have clarity of their job description and requirements. Regulators want to have quality product and agile principle supports this goal to achieve quality. The clarity and transparent communication between team members always help to complete the project timely.

Choosing and customizing agile approach.

The discussion above clearly reflects the benefits of agile in pharmaceutical industry. The agile principles covered all the requirements particularly providing robust processes. But the one more important and critical requirement is yet to be covered. Company also needs to focus on documentation requirements. the question is how documentation can be incorporated in agile environment? if company is planning to adapt agile practices. The company called Diagnostic Grifols have a solution to this problem. Diagnostic Grifols is a medical device company; which is one of the best regulated industries; who has become agile few years back and been successful in adapting agile practices. According to Collyer, K., & Manzano, J. (2013) "Organizations that work in any regulated fields could use a similar approach like Grifols. Agile practices are not only

compatible with regulated industries but can be implemented in ways that provide strong support for compliance with regulations". Grifols took several approaches to be agile and made few changes to the process. Fig 3 gives the idea that how Grifols customized approach can be used by any regulatory industries. Usually, regulated industries follow descriptive approach; where manufacturers establish their own development process and prepare documentation. And these documents clearly define the regulations and guidelines.

Mapping regulated activities to an agile development process.

The fundamental sequential process is start-to-start processes and pharmaceutical industries are used to follow this method. Here, Planning, Requirement analysis, Designing, coding, testing and software releases are sequential steps which should be mapped into agile process particularly in time boxed sequence of sprints. The mapping of regulated industries should be done to develop customized approach. As discusses earlier Grifols has emerged new time boxed activity called hardening sprint. This approach benefited Grifols to successful adapt agile in regulated industries. It encourages to make changes in typical agile environment. Taking Grifols as an example, any pharma industry can get inspired to take this approach.

The customized agile approach will have first iteration which will include plan of releases, design flow and identification of goal. This sequence of releases will be done throughout the product lifecycle. Succession of sprints lead to release. Fig.3 highlights the agile activities in regulatory industries. A sprint 0 will start with creating release plan, Product backlog and architecture design development. These documents will be reviewed in formal approval phase, which will be done before release planning started. After formal approval next step would be a release planning. The release planning includes the sprints planning, where team will be working on each story and/or product backlog. The product backlog consists of different stages such as

requirement specifications, designing and testing. For sprint planning, requirements are prioritized and requirement specifications will be updated during each sprint. There is possibility that at later stage requirements need to be changed or modified as per customer specification. So, at this stage we can say that the requirement specifications are informal documents where all the changes will be noted over the period of sprint planning. The informal documents will be prepared during each sprints or activities. But team members will have a chance to go through the changes and finalizing the changes during hardening sprints. These hardening sprints will be added in between the sprints and before releasing a software. So that final documents can be prepared in hardening sprint. The concept of hardening sprints has been used by Grifols; and these sprints are useful to accommodate regulatory document requirements in pharmaceutical environment. In between sprints these hardening sprints will be working as a synchronization of development and regulatory artifacts. Hardening sprint will be the area where all incomplete work will be done from regulatory aspects.

In this approach high level requirements should be approved first. The planning is to have brief scope of description but not having in detail information. This is the way when implemented features can be recognized. Next step is, these features should be approved by all the stakeholders. Decisions will be mentioned and described in the documents and TBD ‘To be defined” noted will be added to it. So, as further development progresses the changes will be added to it.

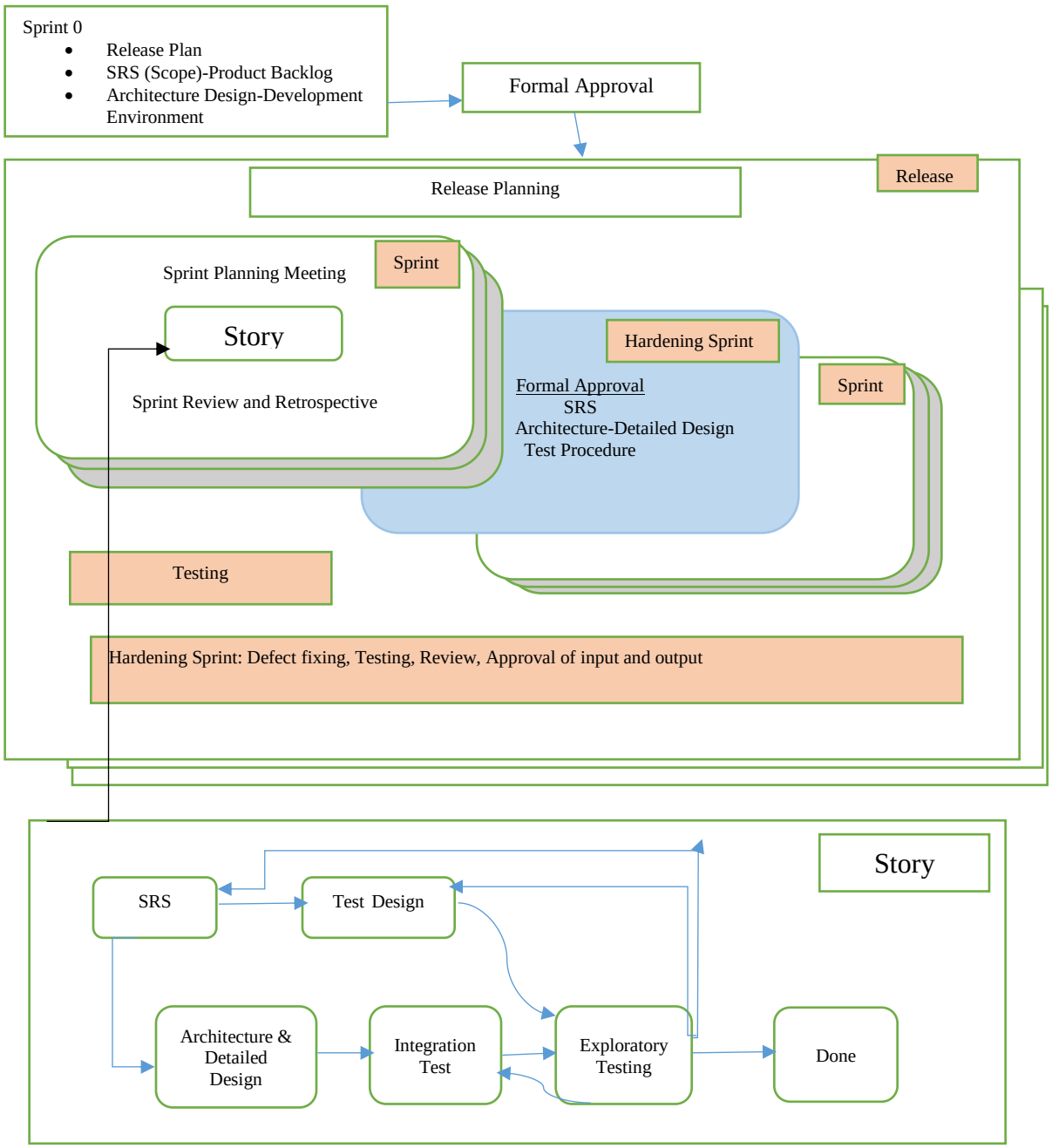

Figure 3. Customized Agile Approach. Adopted from Being agile while still being compliant, Collyer, K., & Manzano, J.,2013, Retrieved September 09, 2017, from https://www.ibm.com/developerworks/rational/library/compliant-agile medicaldevice/index.html. Copyright 2013 by IBM, Reprinted with permission.

To build the functionality into the system, during each sprint set of features will be selected. The limited amount of time would be spent on high level tests and informatory exploratory test. In this way, agile teams can work with each other and resolve communication gap. When exploratory tests are complete the synchronization tasks will help to deliver final tasks. Here, finish-to-finish approach can also help to achieve regulatory deliverables. Now, as regulators want a complete set of formal documents; hardening sprints would help to manage informal testing and iterative requirements.

Hardening sprint may help with following tasks:

- Formal testing will be done, and verification records will be created and documented.
- Synchronization activities will be done. Makes sure SRS, design documents are consistent with coding and test procedures.
- All this information will be documented so, formal approval and review cycle can be initiated.

Here, each release should be consisting of limited number of sprints that is not more than six. And hardening sprint should be initiated once at the end of the release. This helps to avoid accumulating technical and regulatory requirements.

Balancing Conflicts.

Developing a software requires elaborated requirements documented. In real life, it is very difficult to finalize all the requirements at early stage of development work. Requirements needs to be approved and reviewed by all the stakeholders but in real life it's difficult finalize requirements for complex system with the precision. The fact is, changes occur throughout the lifecycle and through different sources like customer feedback and audit. And if requirements need to change then employee needs to rework on decided requirements. On the other side, there are

certain system features that should be defined and it is defined by other than the development team. The customers may have set of the features that they want in the system because they are the one who are using the product. And additionally, there are existing functionality that may not be changed. So, in this case without initial input and effort requirements cannot be finalized. For success of the project product requirements should be properly addressed and identified. Let's assume that developer and tester working parallelly on writing test procedures and implementation. If at later stage, developer find lack in detail or contradictory requirement then developer should go back to requirements, make changes or create new requirements. After creating them, it should be reviewed, finalized and approved from the stakeholders. So, here, all the test procedures should be written again or rewrite old one.

Collyer, K., & Manzano, J. (2013) highlighted three alternatives for balancing these conflicts:

- Just enough design input rather than completing design input (High level design requirements with informal documentation)
- Unlike waterfall approach the activities that take place sequentially can take place in parallel. So, it would be finish-to-finish relationships rather than finish-to-start ones.
- Introducing synchronization point between design input and output. (Time boxed synchronization point includes in detail design specification and formal documentation approval)

Requirement Management.

In agile process, documentation can be updated per iteration. Other documentation can be updated while software is under testing environment. Possible documentation practices mentioned below can be taken into consideration while adapting agile in pharmaceutical environment. All

documentative deliverables mentioned below are inclined to quality management System and Software development life cycle.

Table 3

Deliverables produced from Hardening Sprints

Iterative activities	*Documentation Deliverables*
Release Planning	Update Project Plan
Architect Analysis Compose Estimate Future Stories Story Design User Story-Design evaluation Story design approval	Update system architecture and system protocol Add to Requirement Document and traceability Matrix
Write- Test-Develop	Update Design Document and Traceability
Demo	Document Design Review
Acceptance testing	Update Test report and test suite
Retrospective	Update Software Development Plan

Source: Pathfinder. (2015). [Documentation updated during course of a development iteration]. Agile in an FDA environment. Retrieved from https://www.slideshare.net/pathf/intro-to-agile-in-an-fda-environment.

The documents which are created during traditional approach are equally important and produced during agile practices as well. During agile cycle these documents may or may not be generated at a time. To ease the documentation process hardening sprints are introduced in customizing agile practices. The hardening sprints will be the time boxed activity where all the documents requirements are reviewed and finalized. This will be the formal procedure where team

will be working on documentation mentioned in Table 3. The table indicates documentation will be updated and reviewed to cover iterative activities performed during sprint or release planning with the outcomes. These documents may informally produce and during the each stage these documents included the progresses done during the sprint cycle. The hardening sprint is the point where team members can review data/information mentioned in the documents against the data produced by the system. The principle of agile is flexibility and there is a possibility to change in story or design requirements. So, changing in requirements can confuse the other stakeholders who are not directly working on the project or not a part of the development team. So, the goal is all the team members will be working together and document their progress. But, as mentioned earlier hardening sprint will be used to document final requirement or testing or design review.

The list of documents mentioned in Table 3 will be before products are released. For various iterative activities allotted documentations are prepared. During the sprint planning if any change to requirements and design occur then design documents and requirement specification will be updated. After completing the writing, testing and developing design- design documentation will be review and updated. Moreover, updating test documentation will include acceptance test results. The documents related to release planning, demo and retrospective activities will be covered in hardening sprint allotted before release. So, these documents can be used as a reference for future projects. So, in summary, any unexpected changes occur during the sprint planning they will be covered in hardening sprints to make sure all the changes are documented properly with the completion of final review and formal approval.

Quality Assurance.

Apart from documentation, clarity on regulatory requirements would be the most critical factor the team has to work on. Before providing guidance to everyone, research should be done.

The very important stage is gather the information on what message needs to convey and what are the pre-determined facts, myths and misconceptions exists among teams and team members. According to those information relevant, useful information should be gathered and strategies should be established. If agile is being used in regulatory environment, the team seeks agile testing methodology to speed up process while quality will always be the priority.

For quality Assurance team waterfall is the common approach to use but now QA teams are looking for agile approach for testing to speed up processes and make sure quality remains the priority. As discussed earlier the rigid mindset would be the biggest challenge in transitioning process. To eliminate this challenge the better understanding of new practices could help to plan in a better way so team can successfully understand the shift with limited effort. There are six ways that QA can ease this transition from waterfall to agile, mentioned below.

Training.

Without any training to employees, if company wants them to work directly on the project it can be total disaster. Without any guidance on the new practices, transition from waterfall to agile can result into a failure. Company cannot assume that staff can easily adapt the changes and can work smoothly without any knowledge of what are the changes to the system. For that company needs to hire an expert and has to provide the training to the staff. The training session would help to understand their roles in the system and make sure their contribution match agile values. The company has to look for other options such as online articles, blogs and institutions they are happy to provide their guidance. There are number of providers available out there who can help to improve team's capability and provide their guidance to support agile.

Emphasis change of thinking.

Organizations can help to realize the importance of new practices but old way of completing their tasks could be disruptive to adapt new changes. For team, it may be challenging to forget old practices and stay focused new practices, as they are used to work in that manner. But by concentrating on benefits of agile could help them to be committed to agile and make this transition easier. Developers and engineers must have adapt agile concept that they have to extend their practices and initiate collaborative approach over traditional approach. Moreover, training should emphasis on quality driven processes so that coordinated mind can work together towards same goal.

Communication.

When moving to agile communication plays very important role in development and testing activities. In agile it is important to keep everyone on same page. Communicate well with them, ask about the feedback and share solution to that. Moreover, in this kind of situation it is necessary to come up with the potential solution and make quick decision. So, establishing a clear line of communication and sharing would help team to keep up with the changes and support in activities in order to complete the project.

Collaboration.

Collaboration is the next important thing that team should be focusing on. Transition from tradition to agile would be difficult if team members are not working together. It makes transition easier and help to understand the importance of agile. Collaboration can make them understand the new practices, introducing the involvement of testers in development work help them to gain better understanding of agile methodology. Tester can easily determine the levels of testing. The involvement of customer in testing can also be a part of the collaboration activity. Engaging

customers in testing would help to ensure that requirements and functionality matched the standards. On other hand this kind of activities can take more time but adaptation of this practices in earlier stage will help to ease transition to agile. Through collaboration team members can assimilate their ideas to establish the best results of reaching developmental goal. Hence, delivering the best product in the market and best value to the business.

Flexibility.

Flexibility is as important as other factors mentioned above. Over emphasis procedure can ruin creativity while minimizing the importance of process can affect the quality of product. The key to make solid development platform is to facilitate the innovation while equally ensures performance goals. Development team needs to work together on processes that encourage the innovative ideas and quality functionality and that can be achieved through team interactions. Through the interactive approach balancing between strategic process and managing circumstances could result into outstanding results.

Focus on end product.

There are possibilities that during development or implementing cycle there are concerns and issues. If is not solved quickly can delay the software build. In this situation incremental agile gives the flexibility to accommodate changes without any delay. Agile is responding to change over established procedure. Agile helps to reduce risk and facilitate decision making. It also allows to interact with business stakeholders to participate in progress. Agile emphasizes on improving process and ideas than process plan. Agile focuses on continuous planning for successful deployment. The company uses the agile for The development projects are tend to more successful than using waterfall. The transitions require the organized planning that team needs to focus on targeting key issues, purposed and projected outcomes. Prior to transition, engage project sponsor

and utilize development and QA. Acquire experienced coach or trainer and start with the small team and projects that may inspire early successes.

Integrate tool.

QA can able to help in transition if they have the right tool available. Agile team will get benefit from the test management software, where every team member can work on same tasks at once. They can see the changes in real time. This will helps to team to track the changes and observe the modification as well. Through right tool teams can easily collaborate. This type of tools help QA to support the agile practices and leave waterfall testing behind.

Automation.

When stakeholders begin to strictly set the project schedules and have high expectation for deliverables, agile and automation go hand-in-hand. Depending on each projects and its requirement, selecting and investing right automaton process and tools are very much important. An automation could help to reduce the time to market. Automation produces constant workflows and eliminates the most redundant efforts. It also helps to increase visibility into integrating business, production domain and interests in a collaboration.

In pharmaceutical environment the traceability matrix connects requirements, architecture, design, implementation and testing. So, any changes to previous phase would be difficult to accept. But when this method changes to interactive process then initially it would be difficult to cope up with these changes where production of documentation would be the necessary requirement. This documentation will be inspected by an auditor. So, in this scenario selection and use of suitable tool can help to accommodate these changes. The tool can help to manage traceability cycle in consistent way. That could be valuable addition to make transition easier and trackable. Requirement, architecture, design and testing are important phases and for that clear formal

documents ate required to be produced and maintained to meet regulators' expectations. This is where these tools can become more relevant.

There is no way to eliminate or reduced quality documentation. So, the best approach could be incorporation of activities in agile to encourage more regulated industries to make changes to traditional environment. Providing customized agile approach with proper documentation and quality practices can inspire the researchers and scientists to do more research.

Discussion and Future Study

Research of the agile practices indicate a potential to make development more efficient by reducing the distance between customers, developers and testers. This is the true even in regulatory domain. By using short cycles and frequent integrations, progress can be tracked easily but review of its impact can be difficult to analyze by inexperienced users. Big challenge is to find an effective way of working on required documentation in an incremental way and creating and updating those documents only when it is required, possibly using automated tools. The heavy requirement of documentation will make the work less agile. The thesis clearly shows that even agile and regulatory principles seem to collide with each other, they reinforce each other as well.

The research has been done using definitive process and gathered all the data to generate required results related to this research. The research is done by using various articles available online, but no articles mentioned the descriptive and practical agile approach that could be used. Theoretically, research articles covered possible ways to adapt agile but practically there may be limited amount of regulated industries available that are using agile in a productive way. After establishing customized approach from Grifols case study, it clearly indicates that other regulated industries can take their approach for advancement.

There is one element that is open for discussion is validity of this approach. Well, the research paper includes the processes and practices used by the software and other industries. Though pharmaceutical software industries are working hard to establish quality produces and observe the same process used by the software industries but the requirements are quite different. The goal for both the industries are may be to have working software but the principles are different where pharmaceutical industries want to focus on quality documentation as well. So, the industries has to come up with the different approach like Diagnostic Grifols did. The thesis clearly concludes

the solution to get customized approach with the time boxed activities called hardening sprint to review and finalize the documentation requirements as per the regulatory norms. The approach is the primary step to adapt agile and Grifols has gained success by adapting this approach. Not only they initiated this change but regulators has approved this approach as well. They set an example that any regulatory industries can adapt this change but for that regulatory industries have to take a step towards to it, by providing a training to employees and changing their mindset.

Like pharma industries govt or other regulated industries may have quality documentation as crucial requirements. The solution approach mentioned in this thesis could be useful to other industries as well. An allotment of hardening sprint makes documentation process easier to manage. May be other industries have different regulatory requirements but for the documentation this could be the ideal agile approach, if industries are looking for agile solution.

It's a strange that why other articles and research paper did not include the required solution to adapt agile or ease adaptation. The solution mentioned here may encourage the other industries and researchers to do more research in this area and may help them to establish customized agile approach as per their requirements and suitability.

Further Research

Kim, Maria, and Casper's (2016) study covered future research agenda which included topics that were not clearly described in articles/data found on the web. (p.106). The future research agenda suggested that surveys are needed where companies has already adapted agile practices

The pharmaceutical industries is not the only industry that require proper documentation in software development setting. So, to get more information on this topic research can be done by searching articles and/or results from other documentative industries such as the governmental, aerospace or aircraft industries. The goal of this study is to cover insights of agile approach. But

specialized study would be done especially its focused-on documentation practices and its implementation. The study also can include its ability to implement in the working environment and gathered information that how valuable this process can be in real world at quality prospective. Moreover, there is a need of having more descriptive process or software development method which implicates the variabilities of software development methods and fulfills the principal regulations regarding software development within pharmaceutical industry.

Conclusion

This research thesis has outlined agile development approaches and their applicability to pharmaceutical software development industries. It has also highlighted the fact that how well-regulated industries can adapt agile practices. Any regulated industries can use similar approach. The research thesis shown that the customized agile practices can be implemented in ways that provide robust support for compliance with regulation with active QA participation in adaptation process. This approach can help to form promising results in productivity and compliance. The research paper came up with some significant answers that there is no way to create less documentation and perform less quality assurance related activities. Agile is the unpleasant research of study for scientists and that could be the reason to have limited number of articles available on adapting agile methods with in pharmaceutical industries. An innovative route of agile approach can help to attract more pharmaceutical industries to embrace changes to traditional approach, where new practices has the strong features of agile development practices inclusion of regulated activities.

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Appendix

Acronyms and Abbreviations

FDA	Food and Drug Administration
QA	Quality Assurance
GAMP	Good Automated Manufacturing Practices
ICH	International Conference on Harmonization
ISO	International Organization for Standardization
HIPAA	Health Insurance Portability and Accountability Act
TBD	To Be Defined
SRS	Software Requirement Specification
SOP	Standard Operating Procedure