THE 510(k) INVENTORY TOOL: A REGULATORY TOOL FOR USE IN MEDICAL DEVICE DEVELOPMENT

by

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DEDICATION

This work is dedicated to my son, Nathan ‘Nate’ Borek. A loving son and a beautiful soul who left us way too soon, he will always be missed greatly by those who had the privilege to know and love him.

July 17, 1995 – September 22, 2018 Forever23

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ABSTRACT

Designing and developing medical devices is a complex undertaking with significant opportunities, dependencies, and risks for the stakeholders. This capstone project explores the concept of developing a tool for the regulatory professional with a goal of improving both the quality of regulatory engagement in medical device development and product development efficiency, specifically in cases where the 510(k) FDA regulatory approval process is being used. This is accomplished by creating a checklist tool, the 510(k) Inventory Tool, utilizing published data about known 510(k) submission deficiencies and post-market device reports, then integrating these checklists into appropriate points in the medical device development process, leveraging traditional phase gate project methodologies. By exercising the 510(k) Inventory Tool within the medical device development process, the regulatory affairs professional would have a checklist tool to facilitate project team engagement, to generate stage-appropriate regulatory discussion, and to develop measured strategies for project risk mitigation during the development lifecycle.

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LIST OF ABBREVIATIONS

AI	Additional Information (*FDA Additional Information requests)*
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CFR	Code of Federal Regulations
FDA	Food and Drug Administration
FD&C Act	Federal Food, Drug, & Cosmetic Act
GMP	Good Manufacturing Practices
HDE	Humanitarian Device Exemption
HHS	Department of Health and Human Services
ICU	Intensive Care Unit
IVD	In Vitro Diagnostic
MDUFA	Medical Device User Fee Amendments
NSE	Not Substantially Equivalent
ODE	Office of Device Evaluation (FDA/CDRH)
PMA	Premarket Approval
QSR	Quality System Regulation
RTA	Refuse to Accept from FDA
SE	Substantially Equivalent
U.S.	United States

INTRODUCTION

FDA Regulation of Medical Devices in the United States

Although there are many markets for medical devices, with varying degrees of local regulation, the market in the United States (U.S.) is the standard-bearer for consumer protection, and as such, retains some of the most stringent regulatory requirements.

Medical devices used in the U.S. are subject to Food and Drug Administration (FDA) regulations. The FDA is a large federal agency of the U.S. Department of Health and Human Services (HHS). Within the FDA, three separate centers are responsible for the regulation of drugs, biologics, and medical devices/in vitro diagnostics: The Center for Drug Evaluation and Research, or CDER (drugs); the Center for Biologics Evaluation and Research, or CBER (biologics); and the Center for Devices and Radiological Health, or CDRH (medical devices/in vitro diagnostics).

Regulations governing medical products are based on the laws in the Federal Food, Drug, & Cosmetic Act (FD&C Act) and are part of Title 21, Code of Federal Regulations (21 CFR). Since it was enacted in 1938, the FD&C Act has had multiple amendments in order to expand FDA's ability to regulate and oversee safe, effective medical product development. Passage of the FD&C Act made medical devices subject to FDA determination of safety and effectiveness, but it did not include any requirements for premarket testing, review, or approval (Hutt 1996). It was not until the Medical Device Amendments of 1976 were passed that the FDA was able to set device standards, as well as require premarket clearance (permission to sell or market a device) and approval to market for some devices.

The 1976 Medical Device Amendments to the FDA regulations defined the process for obtaining FDA authorization to market a device via premarket approval and clearance through what is known as the device classification process (Kahan 2009). This risk-based classification process was established by the FD&C Act, section 513. The type and complexity of a medical device regulatory submission and the supportive data required is determined by medical device classification. Device classification is based on the degree of potential risk to the patient, as well as the regulatory controls necessary to provide reasonable assurance of safety and effectiveness (FDA 2014a). Medical devices are categorized as either Class I, Class II, or Class III, based on the level of regulatory control required to provide a reasonable assurance of safety and effectiveness (FDA 2018a). Class I devices have the lowest level of risk and lowest regulatory control. Class III devices, considered to have the highest level of risk to the user, have the highest level of regulatory control. Class II devices fall somewhere in between. Thus, devices are regulated based on the risk level, intended use, and indications for use. A successful regulatory submission for a medical device must provide the types of data the FDA (CDRH) will require to demonstrate the safety and efficacy of the medical device according to the level of risk when used in humans.

Regulatory Approval Pathways for Medical Devices

In general, the two most common regulatory submissions that companies submit to the FDA to obtain authorization to market a medical device in the U.S. are the Premarket Notification 510(k) or Premarket Approval (PMA) pathways. The PMA process is used to evaluate the safety and effectiveness for marketing approval for high-risk devices (Class III) used to support and/or sustain human life. The PMA pathway

requires submitting a complete set of data regarding technological characteristics of the device, as well as human data regarding safety and efficacy of the product. The PMA is the most stringent type of device marketing application required by the FDA (FDA 2014b). The Premarket Notification pathway is commonly known as "the 510(k)." This name comes from the actual section of the Federal Food, Drug, and Cosmetic Act, paragraph 510(k), where the process for Premarket Notification is described. There are three types of 510(k) submissions: Traditional, Special, and Abbreviated. The Traditional 510(k) submission is used for new devices where a predicate device has been identified. That is the focus of this Capstone Project.

Most Class II medical devices undergo clearance through the 510(k) Premarket Notification process. The 510(k) submission has lower data requirements than a PMA, lower fees to file, and generally shorter review times. To utilize the Traditional 510(k) regulatory pathway, a sponsor is required to demonstrate substantial equivalence (SE) to another legally marketed U.S. medical device which is identified as the predicate device in the submission. Substantial equivalence means that that the new device for which the 510(k) is being submitted is at least as safe and effective as the identified predicate device. The FDA defines a predicate device as a previously legally marketed Class I, Class II, or Class III device that is not subject to a PMA. The new device must have the same intended use and technological characteristics as the identified predicate device. If the new device has substantially different technological characteristics than the identified predicate, then adequate information/data must be submitted to the FDA in the 510(k) submission to support that the new device is as safe and effective as a legally marketed (predicate) device; therefore, there should not be additional questions of safety or

efficacy about the new device when compared to the predicate device (Kahan 2009). Under sections 510(k), 513(f)(1), and 513(i) of the FD&C Act, the FDA can determine that a new device is SE to the legally marketed predicate device, and the new device is then classified into the same class as the predicate device, subject to the same regulatory requirements (FDA 2014c). Figure 1 lists the key differences between the PMA submission and the 510(k) submission.

510k	**PMA**
Generally Class II Devices	Generally Class III Devices
Use of Predicate Device to demonstrate substantial equivalence	n/a
A clinical trial is not generally required (approx. 10%)	Clinical trial required
Review time can be as short as 90 days (though usually longer)	Review time average of one year or more
Standard Application Fee* - $10,566	Standard Application Fee* - $310,764
Small Business Fee* - $2,642	Small Business Fee* - $77,691

Figure 1. Differences between the 510(k) and the PMA regulatory submissions (FDA 2018b).

In addition to the PMA and the 510(k), alternate regulatory pathways are available for special case medical devices. The Humanitarian Device Exemption (HDE) is similar in form and content to a PMA submission, but there is an exemption from any effectiveness requirements. HDE is available for devices not used by more than 8,000 individuals in the U.S. per year and is intended as a mechanism to incentivize development of devices to treat or diagnose a disease or condition that affects only small

numbers of patients. If a device is novel or new, and has no predicate, the *de novo* 510(k) can be used. The *de novo* petition to the FDA is a request for the FDA to make a risk-based classification determination under section 513(a)(1) of the FD&C Act (Kahan 2009). To be considered by the FDA for *de novo* 510(k) status, a device must be of low to moderate risk (FDA 2012).

Medical Device Design and Development Process

The development of increasingly novel medical devices over shorter timespans is a positive trend for patients, since these innovations ultimately lead to a better quality of medical care. However, there are many associated risks to successful medical device developments in this environment. Regulatory risks exist because regulatory pathways are often uncertain and the regulatory environment is ever changing. Product risks not mitigated during the development cycle can lead to quality problems discovered after product approval. In fact, an FDA report on medical device quality identified that some of the greatest risks to the quality of medical devices occur during device design and development. The analysis of root cause data regarding development failures in this FDA report revealed that failures in product design and failures in manufacturing process control were the cause of more than half of all product recalls post-market (FDA 2011a). As illustrated in Figure 2, FDA regulatory requirements for medical devices span from product concept through ultimate product disposition.

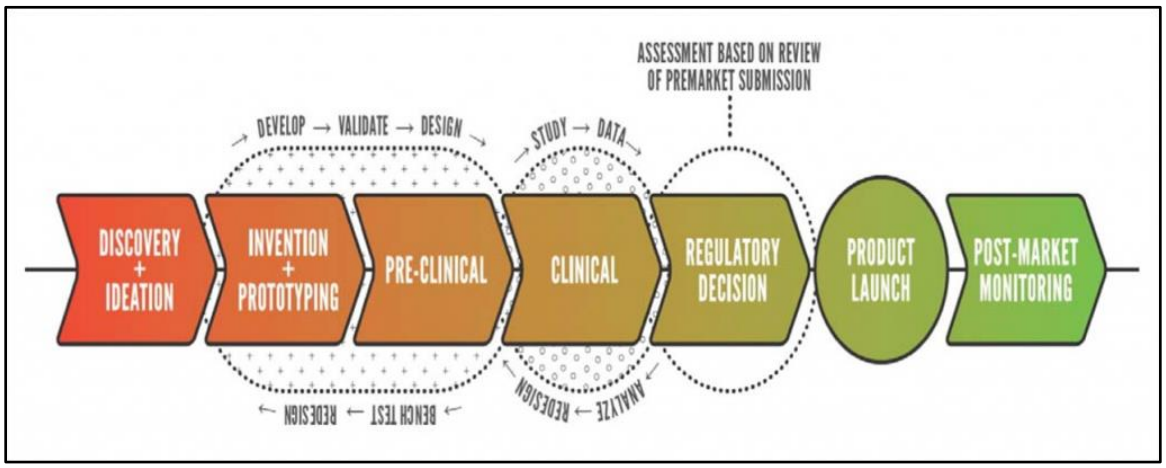

Figure 2. FDA regulatory approval process (FDA 2011b).

However, product development requirements are not always managed in a manner that fully incorporates and considers the regulatory requirements at the right point in development—or at all. The regulatory approval process is integrated into the medical device development lifecycle; therefore, it is important that product development teams understand how to integrate regulatory development stages into the project plan and schedule across the stages of product development. The regulatory decision steps are unique to products in FDA development pathway and is not a step in a generic staged product development model. Figure 3 depicts a generic staged product development model with the corresponding regulatory stages of development.

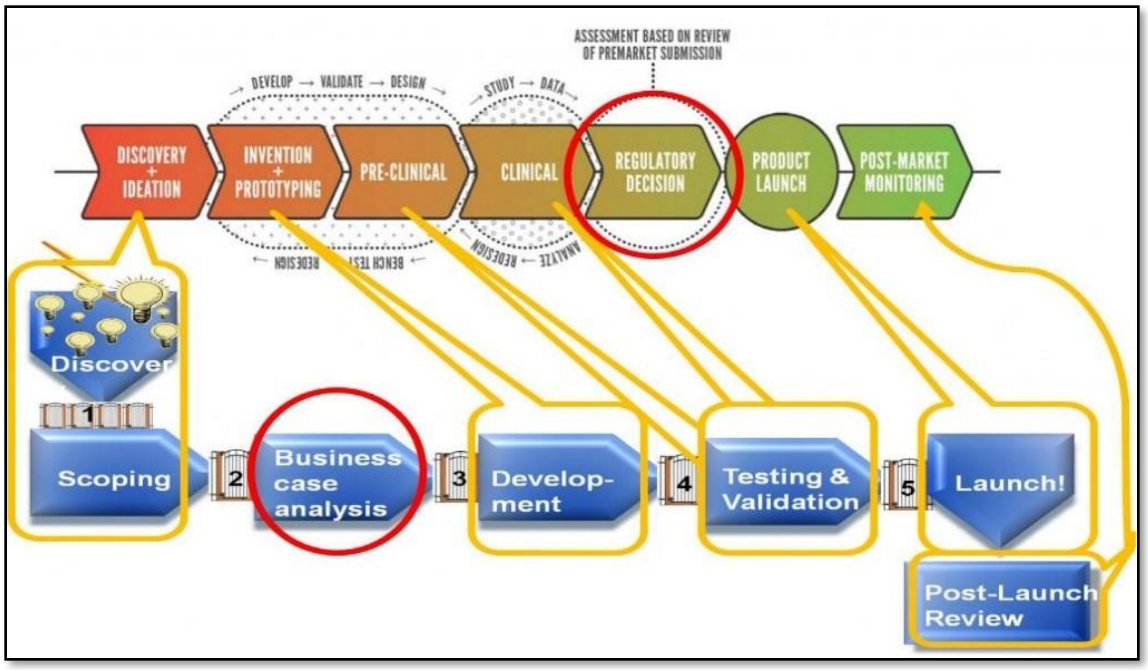

Figure 3. Medical device development pathway (Ross 2012).

Most new medical devices entering the market are Class II devices reviewed by the FDA via the 510(k) process. For every PMA application approved in 2013, about one hundred and forty 510(k)s were cleared (Gibbs 2014). Therefore, the odds are that a majority of project teams will be working on a Class II medical device and the regulatory affairs professional is coordinating project team progress towards the milestones of a 510(k) submission to the FDA. Effectively communicating regulatory guidance and advice, bridging gaps in understanding of regulatory requirements among team members, and consistently identifying regulatory risks throughout the project is important to regulatory success.

The Case for Development of Regulatory Tools

Designing and developing medical devices is a complex undertaking with significant opportunities, dependencies, and risks for the stakeholders. For the domestic

(U.S) market, ensuring that the design and development process is conducted in a regulatory-compliant manner is challenging because of the variety of devices, the global nature of the market opportunities, the varied business models, and the diversity of teams that are used in modern medical device product development.

Given the competitive nature of the industry and dependence upon rapidly evolving technologies like software, materials science, and electronics, medical device companies are hyper-focused on rapid product development cycles and cost efficiency to get their products to market and maintain a competitive edge. Traditional device companies are competing with non-traditional businesses for market share in domestic markets, and many of these companies, both large and small, sell into global markets with varying degrees of regulation and a variety of sales channels. Against this backdrop, product development teams often eschew "traditional" regulatory oversight in favor of product development velocity, which can lead to poorer 510(k) submission quality in the U.S. Since the FDA frequently points to issues with the quality of regulatory submissions as one of the primary reasons for delays in the FDA marketing approval process, developing a better approach to satisfying these regulatory requirements would logically improve the outcomes for these companies in the U.S. market.

Even in the best of conditions, when working as part of a medical device project team, regulatory affairs professionals are often challenged in keeping the team focused on the regulatory requirements and risks within a project. Regulatory affairs professionals must be able to focus the project team on the important requirements for a good, quality, complete regulatory submission, all while working within the constraints of a modern product development environment. This obligates a more focused and integrated

approach to engaging with the product teams, with guidance that balances regulatory risk management, and with rapid product development cycles.

This capstone project explores the concept of developing a tool for the regulatory professional with a goal of improving both the quality of regulatory engagement in medical device development and product development efficiency. This is accomplished by creating a checklist, or series of checklists, that leverages published data about known 510(k) submission quality issues, submission deficiencies, and post-market device surveillance reports, then integrating these checklists into appropriate points in the medical device development process, leveraging traditional phase-gate methodologies.

By establishing checklists built into the medical device development process from concept to full production, the regulatory affairs professional would have a regulatory project management tool to better engage with the project team, to generate stage-appropriate regulatory discussion, and to develop measured strategies and plans for risk mitigation with the project team. If the checklist tool mapped to the stages of product development, the checklists could support increased regulatory compliance at appropriate points throughout the development process and could increase the quality of the final regulatory submission. Ultimately, in theory, this would reduce delays or the lack of success in obtaining FDA clearance or approval to market, which is the primary goal of the medical device project team.

Rationale

Checklists can be used as tools to establish a standard baseline of performance by making clear the minimum expected steps in a complex process and by clarifying what needs to be completed. Checklists have proven effective for everything from aircraft

preflight safety to hospital ICU (Intensive Care Unit) practices, such as placing a central venous catheter line into a patient (Gawande 2007). The hypothesis posed for this research was that a 510(k) checklist or inventory of steps based on the phases of development for a Class II medical device working towards a 510(k) submission to the FDA would be an effective tool to consistently identify important regulatory deliverables, refine regulatory direction, and ensure that technical requirements are adequately addressed during medical device development. By integrating relevant regulatory tasks with product development activities in the development lifecycle, the use of a checklist tool would support clear, proactive management of regulatory risks at an appropriate point in the development process and would improve efficiency in reaching the project milestone of successful FDA 510(k) clearance. Research for this thesis sought to answer the following questions:

1. Can a 510(k) checklist tool enhance the predictability in the development process by helping teams understand the development phases and better identify the regulatory requirements in each phase of medical device development (based on a Phase Gate methodology)?
2. Can a 510(k) checklist tool aid in identifying regulatory issues earlier in medical device development projects?
3. Can a 510(k) checklist tool help teams identify regulatory issues that would reduce schedule and cost issues in device development projects?
4. Can a 510(k) checklist tool increase team knowledge of the requirements for creating a good, quality 510(k)?

5. Can a 510(k) checklist tool enhance the preparation of clear and complete submissions to the FDA, thereby reducing delays in the process to achieving 510(k) clearance?
6. Can medical device outcomes in published data that affect success of a product be tracked during development using checklists at each phase gate?
7. Do regulatory and program management professionals feel that use of checklist type tools are useful?
8. Do regulatory professionals feel that use of checklists could assist when working with small, inexperienced companies to better identify regulatory requirements at each stage and identify issues earlier in medical device development before a project has progressed through too many phase gates?
9. Are multiple checklists required?

MATERIALS AND METHODS

Materials

Research for this project involved gathering information and data from publicly available sources. Sources included published FDA data on FDA inspectional observations and white papers on 510(k) submission quality and NSE decisions, as well as general FDA information on medical device regulation. Publicly available industry publications on the Phase Gate methodology and medical device development were also used to acquire appropriate information and data. Each of the bulleted sections below detail the type of source category reviewed and the data that was extracted**.** Each section explains sources that were used; the associated data which was collected, aggregated, and represented in data tables; and how that data was utilized to flesh out the parts and sections of what became a completed checklist tool, the 510(k) Inventory Tool. The data was collected and then analyzed to determine if there were issues that were cross cutting across development and to determine if using the information in a 510(k) checklist tool would provide the type of information users needed to better inform development and 510(k) pathways and to avoid commonly found issues/pitfalls during medical device development. As much as possible, data was extracted from the sources and aggregated into tables of information which could be referenced during the checklist development process. These individual data tables are included in each section below:

1. **FDA 510(k) Review; Consideration of the Content and Format of the 510(k) Submission –** A review of information on the FDA website revealed that there is no available 510(k) format template provided by FDA for a Traditional 510(k). Though the required elements of the submission are listed and outlined in the regulations at 21

CFR part 807.87, they are not an instructional template on how to develop the appropriate content of a 510(k). Content of a 510(k) in a learning module at CDRH Learn on the FDA website, titled "The 510(k) Program," outlined sections of a 510(k) and details on the content description for sections of the 510(k) (FDA 2014d). The content of the 510(k) was extracted from the CDRH Learn module and listed in Table 1.

2. **FDA 510(k) Review Process - Consideration of FDA Refuse to Accept (RTA) Policy -** The FDA has instituted the RTA process which is intended to assure that the requisite pieces and parts of a 510(k) submission are present and correctly submitted. RTA is an administrative review by the FDA for inclusion of all applicable sections of the 510(k). The actual RTA process, outlined in an FDA guidance document, includes the checklist the FDA utilizes to check for the presence (acceptable) or omission (not acceptable) of elements in the 510(k). Elements that are not applicable to a device should be marked N/A by a sponsor. The FDA may accept omission of an item on the RTA checklist if the sponsor provides an appropriate rationale for something that is omitted. Sponsors who have submitted a 510(k) are allowed up to 180 days to correct deficiencies identified by the FDA in the RTA letter. (FDA 2018c). References to the RTA checklist sections for each section of the 510(k) are included in Table 1.

Table 1. Section outline, content description, and FDA RTA checklist section for each section of a 510(k) submission.

510(k) Section Title	FDA RTA Checklist Section
• Medical Device User Fee Cover Sheet (Form FDA 3601)	N/A
• CDRH Premarket Review Submission Cover Sheet (FDA Form 3514)	A2
• 510(k) Cover Letter	A8
• Indications for Use Statement (Form FDA 3881 recommended)	C16a
• 510(k) Summary or 510(k) Statement	A4
• Truthful and Accuracy Statement	A5
• Class III Summary and Certification (for Class III devices)	A6a
• Financial Certification or Disclosure Statement	A7a
• Declarations of Conformity and Guidance Documents (Form FDA 3654)	17c
• Executive Summary	N/A
• Device Description	B
• Substantial Equivalence Discussion	C
• Proposed Labeling	D
• Sterilization and Shelf Life	E and F
• Biocompatibility	G
• Software	H
• Electromagnetic Compatibility and Electrical Safety	I
• Performance Testing: Bench, Animal, Clinical	J
• Performance Characteristics (IVDs Only)	K
• Other	N/A

3. **FDA 510(k) Review - Consideration of FDA Additional Information (AI) Requests and Submission Quality Data -** Once a premarket submission has been accepted for substantive review, the lead FDA reviewer conducts a review of the submission. Within 60 days, FDA communicates with the sponsor either through interactive review (telephone calls, emails) or an AI request letter. The AI request is one of the ways the FDA will communicate with the sponsor applicant. An AI request to the sponsor places a review of the submission on hold and means no more review will take

place until the sponsor applicant addresses the FDA questions or provides the information requested. Through the AI, the FDA has a formal mechanism to identify information the reviewer is requesting to be able to continue FDA review of the submission (FDA 2014e). The FDA conducted a review of AI letters in 2010, with the goal to determine why total review time and the number of review cycles for 510(k)s had been increasing over time. They found that a principal cause was due to the poor quality of submissions. Poor quality submissions did not contain the necessary information for the FDA to complete a review, and companies failed to fully address the quality issues when they were raised by the FDA in an AI letter (FDA 2010). A published report on the FDA MDUFA (Medical Device User Fee Amendments) website detailed two separate analyses of AI letters that the FDA conducted. The FDA conducted an analysis of 100 AI letters sent for 100 out of 575 submissions for 510(k)s which had received an AI letter from the Office of Device Evaluation (ODE) between September 13 to September 24, 2010. During this period, ODE received 727 submissions of 510(k) applications for review. The 575 applications which received AI letters represents 79% of the total applications received for ODE review between September 13, 2010, to September 24, 2010. The FDA analyzed the 100 AI letters (n=100) for issues that indicated submission quality; from this analysis, the FDA created a list of 14 submission deficiency categories. They also created a list of subcategories of submission deficiencies that they believed were indicators of poor submission quality. The results of analysis found that 83% of the 510(k) submissions with an AI letter analyzed had at least one deficiency identified that was related to submission quality. In the same analysis of premarket review times, the FDA identified issues that may cause multiple review cycles to be performed (FDA

2010). Data on AI letters and submission quality issues are aggregated into data tables 2 through 4. The data for AI and submission quality issues is represented in Table 2 and includes a list of the top 10 submission quality issues.

Table 2. Top 10 submission quality issues for an FDA 510(k) submission.

Deficiency Category	**% Deficiency Category Cohort 1 (n=100)**
1. Performance Testing Inadequate	52%
2. Inadequate Device Description	52%
3. Predicate Comparison Missing or Inadequate	32%
4. Missing FDA Form 3654 (Documentation of Use of Recognized Standards)	30%
5. Problems with Indications for Use	26%
6. Instructions for Use Inadequate	26%
7. Failure to Follow or Otherwise Address Guidance Document(s) or Standards	24%
8. Discrepancies in Device Description or Indications for Use	22%
9. Software Documentation Inadequate	20%
10. Biocompatibility Information Inadequate	20%

A list of subcategories of submission deficiencies that the FDA believes are indicators of poor submission quality, aggregated in Table 3.

Table 3. FDA submission deficiency categories indicating poor submission quality.

Deficiency Category	Description
Inadequate Device Description	510(k) submission is required to have a description of what the device is intended to do • Reviewer must be able to determine from the submission what the device does. Documentation provided in the submission must support the intended use of the device
Discrepancies throughout submission (most often related to device description or indications for use)	Under the 510(k) pathway, the intended use and technological characteristics of the new device are compared to that of a predicate device • Indications for use statement must be consistent in all parts of submission. Reviewer must be able to determine if the device has same indications for use as predicate or if differences alter the intended therapeutic or diagnostic effect of the device compared to predicate
Problems with Indication for Use	510(k) pathway requires device to be found substantially equivalent to the predicate device • Predicate device must be identified in the submission. Device must have same indications for use as predicate • Any differences between device and predicate cannot alter the intended use of the device • Performance data submitted depends on indications desired • Indications for use statement clearly written and to allow the reviewer to determine if the methods used for performance study evaluate the device accurately to reflect intended use • Indication for use submitted not be subject to PMA
Failure to follow or otherwise address current guidance document(s) or recognized standards	Information to include in a 510(k) submission generally and for specific device types are contained in FDA guidance documents or recognized standards • Sponsor fails to follow current guidance. FDA considers submission quality poor, issues AI letter
Performance testing is completely missing (i.e., no performance data provided at all)	Performance testing is required for all traditional 510(k)s. • No Performance Testing submitted - FDA unable to evaluate if device performance is substantially equivalent to predicate
Clinical data (if required for certain device types) is completely missing; no clinical data provided at all	510(k)s for some device types require submission of clinical data to demonstrate substantial equivalence • Date from clinical testing outlined in device specific guidance is not included in the submission. • Clinical testing is outlined in a pre-IDE submission to FDA, but is left out of the 510(k) submission

FDA-identified top causes of multiple review cycles (top 10 identified issues) are listed in Table 4.

Table 4. Top 10 causes of multiple FDA 510(k) review cycles.

Deficiency Category
1. Performance Testing Inadequate
2. Failure to Follow or Otherwise Address Guidance Document(s) or Standards
3. Instructions for Use Inadequate
4. Inadequate Device Description
5. Predicate Comparison Missing or Inadequate
6. Problems with Indications for Use
7. Biocompatibility Information Inadequate
8. Missing FDA Form 3654 (Documentation of Use of Recognized Standards)
9. Software Documentation Inadequate
10. Biocompatibility Information Completely Missing and Missing Sterilization Validation

4. FDA 510(k) Review - Consideration of FDA Not Substantially Equivalent (NSE) Decision Data -

Submission quality issues can contribute to NSE decisions by the FDA. An NSE decision for a sponsor-applicant means that the device cannot be brought to market. In 2011, CDRH did an analysis of NSE decision data from 2005 to 2010 to gain understanding of the reasons 510(k) submissions end in an NSE determination. They came up with four main reasons for an NSE (FDA 2011c). Data aggregated from this CDRH analysis of NSE decisions from 2005 to 2010 lists the four main reasons for an NSE and is presented in Table 5.

Table 5. Reasons for NSE decisions made by FDA (CDRH).

Reason for NSE	Meaning
No Predicate	Suitable predicate device does not exist
New Intended Use	Intended use of new device different from the intended use of the predicate device
New Technology	Technology of the new device is not substantially equivalent to the existing technology of the predicate device
Lack of Performance Data	No performance data was submitted in the 510(k) submission. The data provided were inadequate. The data submitted failed to demonstrate that the new device performance was a least equivalent to the predicate device

This data shows that that a majority of NSE decisions are due to lack of adequate performance data. Performance testing was also found as a common category across the FDA 510(k) review data sets listed in Table 2, Table 3, Table 4 and Table 5.

5. **FDA 510(k) Development - Consideration of Medical Device Recall -** An analysis of medical device recalls conducted by the FDA Center for Devices and Radiological Health provided available data from Fiscal Year (FY) 2003 to FY 2012 for Recall Regulatory Violations (the associated FD&C Act violation) and reasons for recalls between FY 2010 and FY 2012. This data identified the top 10 regulatory violations, along with the top category for most serious Class I recalls for Class II devices. The same FDA analysis provided FY 2010 to FY 2012 recall case data (by recall causes assigned by the FDA). At least 14 of the sections in a 510(k) are directly linked to design controls (Speer 2017). Data for the top reasons for recall as detailed in the FDA 2012 report was extracted and used along with information from a 2014 FDA presentation (Ferriter 2014). FDA identified the top 3 reasons for recall were Nonconforming Material/Component (429 recalls), Software Design, Device (429 recalls), and Device

Design (425 recalls). FDA recall information and data are by recall cases assigned by FDA are presented in Figure 4.

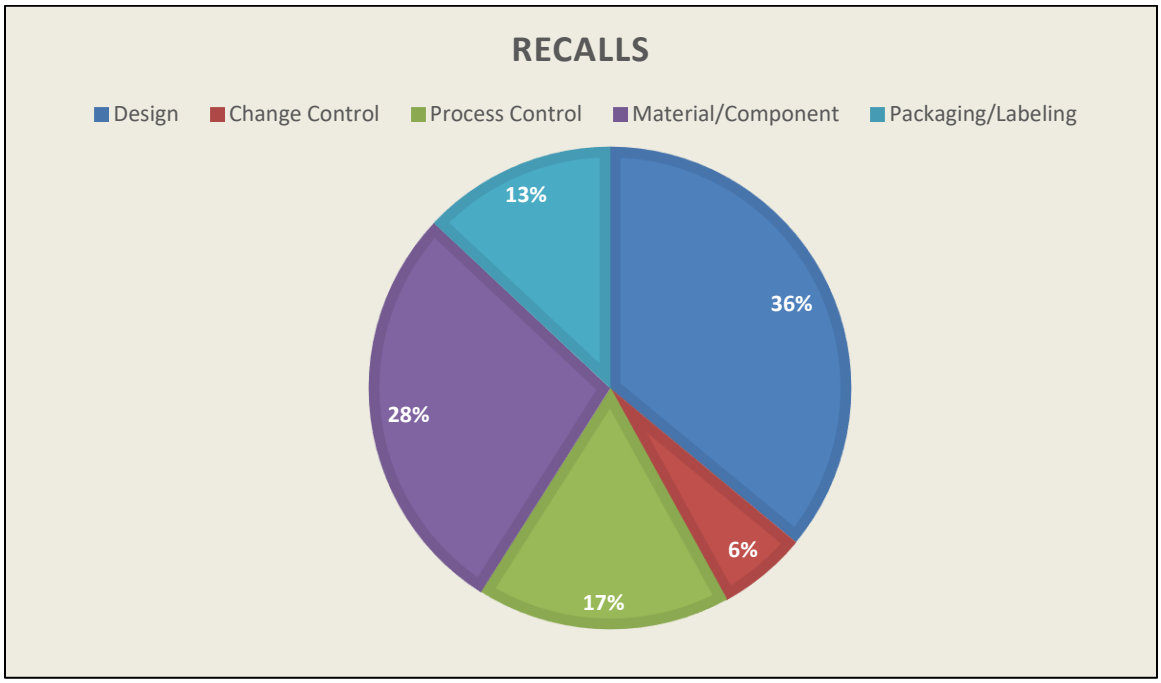

Figure 4. FDA review of FY2010 to FY2012 recall case data.

6. **FDA 510(k) Development and Consideration of FDA 483s (Inspectional Observations) for Design Controls Violations -** Medical device products cleared to go to market under the FDA 510(k) clearance are subject to the FDA Quality System Regulation (QSR) found in Title 21, Part 820 of the U.S. CFR. The QSR is also commonly referred to as Good Manufacturing Practice, or GMP. Design Controls at 21 CFR Part 820.30 is the only aspect of device QSRs that must be adhered to premarket during development. The FDA does not issue certification for GMP compliance, but instead conducts inspections to verify quality system compliance. The FDA provides publicly available data on the regulations cited on 483s generated within the FDA's

system. Data is available by fiscal year and divided by product type (e.g., drugs, biologics, devices, etc.) in Inspectional Observation Summaries. While not a comprehensive listing of all inspectional observations, looking at the FDA data does clearly illustrate the number of times a particular regulation is cited as an observation on an FDA Form 483 and shows a trend toward design control citations being first, second, and third most frequent citations over the 5 years of data reviewed (FDA 2018d). Data from the FDA Inspectional Observations is aggregated into Table 6 (FDA 2018).

Table 6. FDA 483 (Inspectional Observations) data showing most frequent citations.

Year (FY)	Total Number 483s per FY	Total Number Regulations Cited	Total Number 820.30 Citations	% 820.30 Citations	1st Most Frequent 820.30 Citation	2nd Most Frequent 820.30 Citation	3rd Most Frequent 820.30 Citation
2017	1030	200	27	13.5%	820.30(i) Design Changes – Lack of or Inadequate Procedures	820.30(g) Design Validation – Risk Analysis Not Performed or Inadequate	820.30(a) Design Control – No Procedures
2016	934	213	27	12.6%	820.30(i) Design Changes- Lack of or Inadequate Procedures	820.30(g) Design Validation – Lack of or Inadequate Procedures	820.30(a) Design Control – No Procedures
2015	1008	232	28	12.1%	820.30(i) Design Changes – Lack of or Inadequate Procedures	820.30(g) Design Validation – Lack of or Inadequate Procedures	820.30(g) Design Validation – Risk Analysis Not Performed or Inadequate
2014	972	241	30	12.3%	820.30.(i) Design Changes – Lack of or Inadequate Procedures	820.30(a) Design Control – No Procedures	820.30(g) Risk Analysis Not Performed or Inadequate
2013	1099	243	30	12.3%	820.30(i) Design Changes- Lack of or Inadequate Procedures	820.30(g) Design Validation – Lack of or Inadequate Procedures	820.30(a) Design Controls – No Procedures

7. **Publicly Available Sources of Data – Additional Data on the 510(k)**

Submission - Additional material to provide data on potential issues during the 510(k) submission process were sought from publicly available sources of data. This data

provided clarity on impacts of FDA requirements for 510(k) submissions. The way project teams understand these requirements can have an impact on the project schedule and timeline. Two primary points in the 510(k) submission process where the project team can encounter significant delay or halting to the schedule are in the FDA RTA process and the AI letter. Receiving and having to respond to an AI can greatly impact the path to achieving successful 510(k) clearance. Common issues that result in an AI as defined by public sources of data were analyzed (Seiple 2016). This data was aggregated into Table 7.

Table 7. Common 510(k) submission issues resulting in FDA AI requests as identified by industry research.

AI Category	510(k) Review
Inadequate Device Description	FDA can't determine if device properly evaluated during review.
Submission Discrepancies	Important to ensure information is consistent throughout 510(k).
Product Name	Ensure the product name consistently throughout submission
Failure to Follow or Address Guidance Documents or Standards	Failure to follow current guidance or meet relevant standards for the device, without explaining why in the 510(k) submission will often result in FDA request for AI request.
Inadequate or Missing Performance Testing Data	FDA reviewers cannot determine substantial equivalence between a device and the indicated predicate device without performance testing data/information.
Usability Report	Usability Report issues occur when device testing was not conducted as described in the FDA guidance document(s).
Risk Management	The consensus standard for risk management in the U.S. is ISO 14971:2007 requiring a Risk Management Plan, a Risk Management Analysis, and a Risk Management Summary Report. Risk analysis is complex and requires team attention to detail.
Missing Clinical Data and Forms	Some 510(k) submissions must include clinical performance data. Clinical documentation/forms are often are missing.

Sources consulted provided data for the average times to reach 510(k) clearance beginning in the year 2000 and across a five-year period between 2012 and 2016, as well

as the average timeframe to get to 510(k) clearance by the category of device type (Emergo 2017). Since 2000, there has been a general trend of the FDA requiring ever more stringent testing and increasing amounts of clinical evidence, resulting in it taking longer for a 510(k) clearance to be obtained for a device to go to market. This is particularly true for certain categories of devices, such as anesthesiology and hematology devices and the average for all device types is 177 days Between 2012 and 2016, the shortest amount of time to clearance was 168 day in 2012. The longest amount of time was 178 day in 2014. The average number of days across the 5-year period was 173 days. This data is aggregated into Table 8.

Table 8. Number of days to obtain 510(k) clearance.

Year	**Number of Days to Obtain FDA 510(k) Clearance**
2012	168 days
2013	170days
2014	178 days
2015	172 days
2016	177
Average Number Days for 5 Year Period	**173 days**

Data for time to 510(k) clearance by category of device type was aggregated into Table 9.

Table 9. Length of time to obtain FDA 510(k) clearance by device type.

Device Type by Medical Specialty (Classification Regulation Citation 21 CFR)	Number of Days to Obtain FDA 510(k) Clearance
All Devices (Parts 862-892)	177 days
Immunology (Part 866)	250 days
Hematology (Part 864)	247 days
Anesthesiology (Part 868)	245 days
Dental (Part 872)	218 days
Chemistry (Part 862)	211 days
Physical Medicine (Part 890)	182 days
Cardiovascular (Part 870)	179 days
Gynecological (Part 884)	171 days
Surgery (Part 878)	171 days
Ophthalmic (Part 886)	170 days
Obstetrical & Ear Nose & Throat	167 days
Toxicology (Part 862)	163 days
Orthopedic (Part 888)	153 days
Microbiology (Part 866)	144 days
Gastroenterology & Urology (Part 876)	131 days
Radiology (Part 892)	112 days

Northwestern University researchers surveyed medical device industry respondents from both large and small companies about the FDA 510(k) process. The objective of the study was to obtain specific information about what works well in the 510(k) process and what could be potentially improved from those engaged in medical device development. The researchers conducted a survey with 86 questions across a total of 356 participants. Respondents had a range of experience, from as little as under 2 years to more than 20 years of experience working the 510(k) submission process. Respondent experience was also across a broad category of device types. Fifty-seven percent of respondents stated that the requirements for FDA 510(k) submission were unclear/uncertain, with over half of respondents stating that if the FDA were to make changes to the process to obtain 510(k) clearance, predictability of the process should be

one of the primary metrics used by the FDA to evaluate the overall performance of a revised 510(k) process. Thirty-nine percent of respondents stated that they could have improved their initial 510(k) submission, and twenty-six percent of respondents stated that FDA review questions should have been anticipated by the company (Linehan 2011). Figure 5 illustrates the number of respondents in the Northwestern University study stating that regulatory requirements were either important or very important to their business decision to pursue a major investment in a new medical device product.

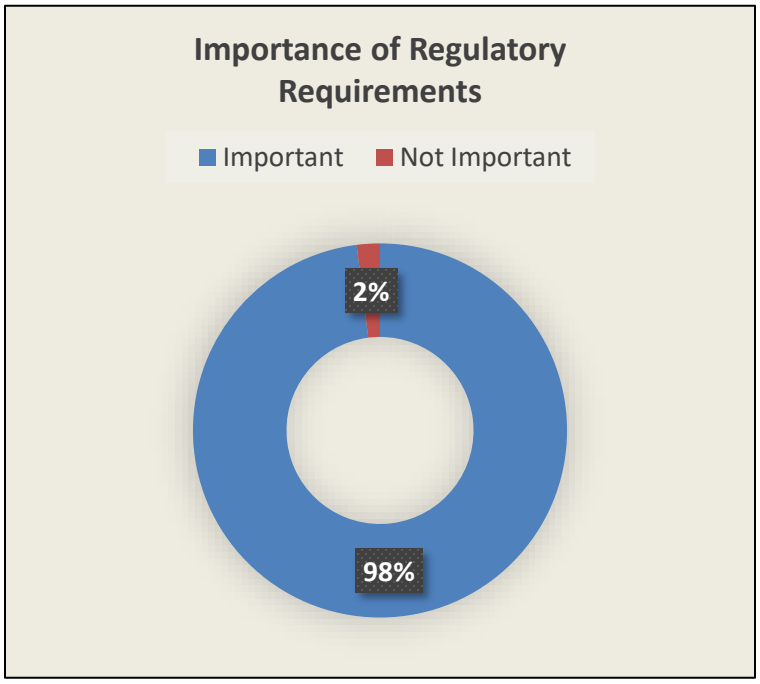

Figure 5. The importance of regulatory requirements in the development process (Linehan 2011).

8. **Phase Gate Methodology for Medical Device Development -** In 2009, a team at Stanford University published results from an in-depth analysis that reviewed existing Phase (Stage) Gate models for medical device development commonly used

across medical device development. By conducting in-depth interviews with more than 80 seasoned medical device experts, and by performing analysis of the generally accepted best-practices of medical device development, the Stanford team created a new and comprehensive model of the Phase Gate process to uniquely capture all aspects of device development (Pietzsch 2009). This analysis advocated that Phase Gate methodology be widely used to manage new product innovation as a model of product development that manages the effort from product concept to product launch through various "phases" of medical device development and "gates" of decisions. The goal of utilizing a Phase Gate process is to get the right product developed more efficiently with fewer issues and at a controlled cost level. This correlates with the objective of this Capstone Project; to provide the type of information users needed to better inform development and 510(k) via a checklist tool. The framework of the Phase Gate methodology discussed in the Stanford University analysis (Phase Gate approach consisting of five major phases/decision gates) was utilized as the template for the 510(k) Inventory Tool. Figure 6 provides the five generally accepted phases of medical device development per a phase gate methodology with a description of each phase.

Phase of Development	Description of Phase
Phase 1	**Initiation, opportunity, and risk analysis**
Phase 2	**Formulation, concept, and feasibility**
Phase 3	**Design, development, verification, and validation**
Phase 4	**Final validation and product launch preparation**
Phase 5	**Product launch and post-launch assessment**

Figure 6. The five major phases of medical device development (Pietzsch 2015).

Figure 7 presents the phases in a slightly different manner and illustrates the description of the five phases of phase gate focusing on the development process steps.

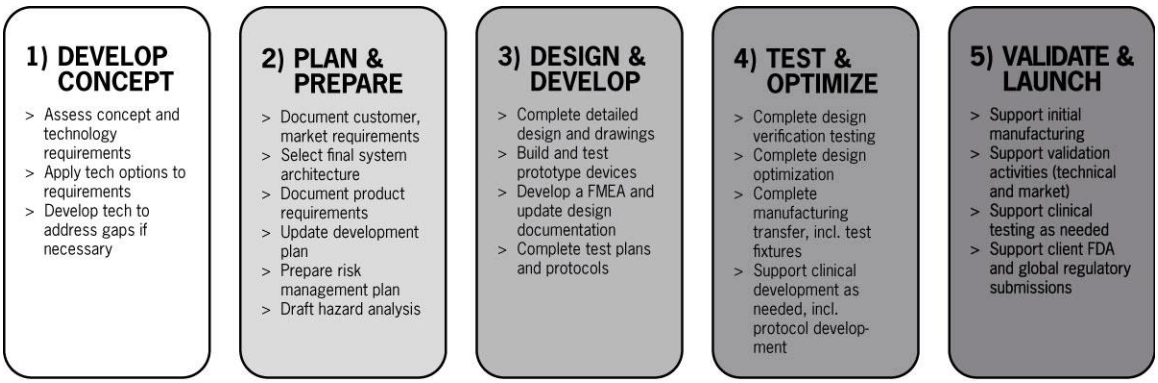

Figure 7. Phase gate development pathway for medical devices.

To see how FDA regulatory requirements overlay with the typical generic steps of the Phase Gate model of product development when applied to medical devices, refer to Figure 3 on page 15.

Methods

Research for this project consisted of consulting, aggregating, and analyzing data from publicly available sources on information about 510(k) development and medical device development. Research and data obtained led to a concise list of consistent categories that may contribute to lengthy 510(k) review cycles and can lead to a product not achieving the goal of marketing clearance. The research categories were analyzed to determine if they provide good information and categories to include in a checklist tool. For inclusion, each was analyzed to determine impact to the following:

1. Providing information for each phase of medical device development defines/expands knowledge of specific activities within that phase.
2. Providing additional information on important parts of a 510(k).
3. Impact to creating a good quality 510(k) submission.
4. Information that could help mitigate 510(k) submission delays and delays in the schedule due to issues during FDA review of the 510(k) submission.
5. Information that could mitigate issues with obtaining 510(k) clearance.

Section 1 through Section 8 below detail the method of analysis to determine which data items should be utilized to create the 510(k) Inventory Tool, the final checklist product. Section 9 and Section 10 describe how the 510(k) Inventory Tool was templated, created, and tested. The completed 510(k) Inventory Tool Checklist product that was created and tested is multi-section word document of aggregated checklists.

1. **510(k) Content and Outline –** Using available sources, a 510(k) section outline and content description was created. Providing this standard outline as part of the 510(k) Inventory Tool serves to provide project teams with a concise template for sections of the 510(k).

2. **FDA 510(k) Review Process and Consideration of FDA RTA Policy** - The RTA process provides useful insight into FDA expectations about what the reviewers expect to receive as part of a 510(k) submission. The information on RTA is also useful as background on the types of issues that might arise if a sponsor does not carefully check to ensure they have considered all the necessary information the FDA uses to accept a 510(k) into review. This data provided useful information to consider when creating the 510(k) Inventory Tool product.

3. **FDA AI Requests and Submission Quality Data -** Submission quality issues increase the number of review cycles that a 510(k) must undergo and thereby have a big impact on project schedules, often causing significant delays to the schedule. Increasing awareness of the issues that cause problems with 510(k) submission quality among project teams is important. From the available data, the top deficiency categories were aggregated to come up with the three most likely issues to cause quality issues in submissions. These common categories across submission quality and submission deficiencies were issues with performance testing, device description, and intended use/indications for use. Information on known submission quality issues that the FDA sees, as well as triggers for AI letters, are also useful for creating the 510(k) Inventory Tool. These categories of issues that contribute to poor submission quality were

considerations for the types of information included in the sections of the 510(k) Inventory Tool, as well as the information used to create the appendices.

4. **FDA 510(k) Review and Consideration of FDA NSE Decision Data -** These sets of data were important to consider for creating the 510(k) Inventory Tool since they provided information on issues that could potentially cause receipt of an NSE from FDA and inability to get the device to market. NSE data pointed to the importance of a sponsor understanding requirements for performance testing and developing/submitting good quality performance data to FDA in a 510(k). The importance of performance data to 510(k) development also showed up in analysis of submission quality data. This provided rationale for the inclusion of an appendix section in the 510(k) Inventory Tool for Performance Testing as well as ensuring inclusion in the various Phase sections of the 510(k) Inventory Tool.

5. **FDA 510(k) Development and Consideration of Medical Device Recall-** FDA analysis from 2012 found that the top 10 regulatory violations were all related to Quality System Regulations (QSR, 21 CFR Part 820). For Class II devices, which are generally subject to 510(k), the top category of violations for the most serious type of recalls (Class I recalls) were due to Design Control and related subpart violations (Design Controls are part of the QSR, 21 CFR Part 820.30). FDA review across FY 2010 to FY 2012 recall case data (by recall causes assigned by the FDA) identified the top three reasons for recall were Nonconforming material/Component (429 recalls); Software Design, Device (429 recalls); and Device Design (425 recalls) (FDA 2012). Because the analysis of existing FDA recall data pointed to importance of compliance to the Design Control Regulations (21 CFR Part 820.30) during the medical development process, the

510(k) Inventory Tool was developed to include Design Control requirements in each relevant Phase of the development process. Design controls provide the documented evidence developed throughout the product development process to provide evidence that the device is safe and effective. This process feeds directly into development of the content of the 510(k) and becomes important criteria for project teams to monitor. Therefore, it was an important category of information to include in the 510(k) Inventory Tool.

6. **FDA 510(k) Development and Consideration of FDA 483s (Inspectional Observations) for Design Controls Violations -** The top three 483 FDA Inspectional Observations citations were consistent in the data obtained and analyzed. The top three citations were 820.30(g) Design Validation (inadequate or no procedures; risk analysis inadequate or not performed); 820.30(a) Design Controls (inadequate or no procedures); and 820.30(i) Design Changes (inadequate or no procedures). A snapshot of the aggregated data for years FY 2013 through FY 2017 illustrated the importance of ensuring compliance to Design Control (21 CFR Part 820.30) during medical device development because every year an average of 12.5 percent of regulations cited on 483s were due to 820.30 Design Control compliance violations. This data supported the importance of including substantial details for Design Control (21 CFR Part 820.30) requirements in each separate checklist section of the 510(k) Inventory Tool. Including appropriate Design Control information in the 510(k) Inventory Tool ensures that Project Teams will pay appropriate attention to this critical element during the process of development of the product and 510(k) submission.

7. **Additional Publicly Available Sources of Data on the 510(k) Submission -** Analysis of data that have been published in industry articles and other sources supported the idea that the complexity of the 510(k) process is a challenge for most teams. Key issues found through analysis of public data sources include: Clarity of requirements for the preparation and submission of a 510(k), predictability of the process, and anticipation that the FDA will review questions before making the submission. This data substantiated a key assumption for creating the 510(k) Inventory Tool: Increasing complexity of developing the 510(k) submission is a common problem for all project teams and using a checklist tool like the 510(k) Inventory Tool should help teams develop 510(k) submissions that more consistently meet FDA requirements.

8. Analysis of Phase Gate Method of Medical Device Development - Information and data analysis on the Phase Gate Methodology supported that use of the methodology can increase efficiency in the development process and formalize the interrelationships between the expert communities (supporting functional groups), such that problems and risks could be identified and addressed at appropriate points in the medical device development cycle. A key goal of this research was finding a method to create a checklist to ensure that FDA regulatory requirements are satisfied during development. Another goal was to ensure that any potential issues are addressed by the project manager and expert communities at appropriate points within the development cycle to improve the probability of success of the overall project and to minimize overall project cost. Since the requirements of traditional engineering development activities, as well as the FDA regulatory requirements and regulations under which medical devices are developed and approved, fit across the Phase Gate process, use of this methodology

was analyzed and leveraged as a model for the 510(k) Inventory Tool. The 510(k) Inventory Tool was created in a template that utilized each of the five generally accepted phases of medical device development, along with a description of each phase and checklist items that provide regulatory and project checks in each phase. By injecting appropriate regulatory checks into the Phase Gate development process through the 510(k) Inventory Tool, the efficiency of the process can potentially be improved. Additionally, the use of the 510(k) Inventory Tool modeled on the Phase Gate process provides a tool to potentially reduce the time-to-market for medical devices, making it a highly valuable tool for development teams, especially inexperienced teams.

9. Creating The 510(k) Inventory Tool -Research into the Phase Gate process provided a development reference framework around which to develop an "inventory" of steps and requirements across the phases of medical device development. Analysis of this model provided a basis upon which to develop the 510(k) Inventory Tool. The Tool is comprised of regulatory item checklists around the stages in each Phase and Gate to ensure that all team members understand the regulatory requirements at each phase of development.

Each section of the 510(k) Inventory Tool was based on a phase of development from the Phase Gate methodology. A total of five phase sections are included in the 510(k) Inventory Tool. Each section lists all steps that the project team needs to consider in order to meet 510(k) submission requirements during development in that phase, along with the typical exit criteria or "gate." The checklist format was included to assist teams to consider if they had completed required deliverables before moving through a decision gate.

The 510(k) Inventory Tool was formatted into a multi-section Word document. Consideration for what to include in each section of the document was first done according to the standard information for that Phase/Gate according to the Phase Gate methodology. Research from this project identified categories of information known to continually cause poor quality of FDA submissions, delays in schedules, NSE decisions, and potential for recall of a product once marketed. Since it is useful for a project team to be aware of 510(k) submission quality issues or submission deficiencies and to utilize this knowledge to avoid common pitfalls in creating a 510(k) submission, the 510(k) Inventory Tool document was developed to include significant input on the most common submission quality/deficiency categories. These critical development and regulatory activities and requirements were identified in each phase of device development when applicable to successful completion to that phase.

Data identifying steps in the development process or regulatory process that delay or cause issues with the FDA 510(k) review were analyzed to determine which had the highest percentage of frequent causality to delay or cause non-receipt of marketing clearance. These identified issues became structured appendices in the 510(k) Inventory Tool, with the intent to provide users with additional sources of more in-depth information about these important information categories. The topics of these three appendices are performance data, intended use/indications for use, and device description.

10. Testing the 510(k) Inventory Tool - The completed 510(k) Inventory Tool was tested by providing the document to product managers, project officers, and regulatory affairs professionals who work as part of medical device development teams

across industry and the government. The 510(k) Inventory Tool was provided to reviewers with a training slide-set that explained the background of this Capstone Project, a list of instructions, and a set of survey questions that users were asked to answer and return to the author by email. The survey questions were specific to the utility of the tool relative to their work, what potentially worked with the tool, what they liked about the tool, what they didn't like, and if they thought there were improvements that could be made in the instrument. The survey questions are in Appendix 1. Individuals had varying years of experience working on development of different types of medical devices. The individuals surveyed also came from different educational levels: PhD, MS and BS. Survey participants were chosen to have diverse backgrounds, not only including regulatory affairs, but also project management, engineering, and quality. Participants were also chosen with differing years of experience to ensure that those with both experience and inexperience in medical device development were captured. Experience of participants who were Project Managers ranged from a recent biomedical engineering graduate who has just started working in product development within the last two years to an individual who has over 25 years of experience in product development. Regulatory affairs professionals surveyed had similar varied ranges of level of experience. Regulatory participants ranged from an individual who recently completed a regulatory affairs fellowship, and thus had minimal regulatory experience, to a seasoned professional with over 20 years-experience in regulatory that included time working as a medical device reviewer for FDA/CDRH. Responses were blinded when received by email, so that the author did not see which participant had sent the answers to the survey. To maintain the blind, the data was aggregated by a third party. This was done to prevent

any potential bias about responses since all survey participants were known to the author (having worked with all these individuals at some point over the last 10 years). Overall, the goal of the data set analysis was to determine if there was a positive reaction to the 510(k) Inventory Tool as a development tool. And, to determine if participants believed that there may be some utility of the 510(k) Inventory Tool as a regulatory tool to support better developed, better quality 510(k) submissions.

RESULTS

The 510(k) Inventory Tool document was created using the information and data gathered. The tool was templated using a publicly available Microsoft Word business checklist template which was modified. The template was chosen because it was in a checklist format with collapsible sections when the document is open. This allows users to think through items as a checklist (even if not technically checking each item off) as well as to open just the section being used while leaving the other sections of the document closed. The document was created to have each Phase as outlined in the Phase Gate methodology be a separate section in the document (Phase 1/Gate 1 – Initiation, Opportunity, and Risk Analysis; Phase 2/Gate 2 – Formulation, Concept, and Feasibility; Phase 3/Gate 3 – Design, Development, Verification, and Validation; Phase 4/Gate 4 – Final Validation and Product Launch Preparation; Phase 5/Gate 5 – Product Launch and Post-Launch Assessment). Each of the separate checklists divided by Phase provides a synopsis of the activity in that phase, as well as a list of items to be considered. The lists in each section establish a standard baseline of performance suggested by research and contain the elements that should be completed during each phase of development (at the minimum). Since research showed that it is common for teams to miss important data or testing required for a quality 510(k), the document structure was designed to support proactive management and monitoring of regulatory and quality tasks and risks to provide a method to communicate and define these requirements to all team members. Each phase or gate section of the inventory was developed for a specific development phase and included the gate review criteria that the project team should evaluate and consider before moving on to the next phase of development. Reviewing or completing

item checklists should ensure that all team members understand the regulatory/quality requirements at each stage of development. To support proactive use by teams, a brief introductory section was included at the beginning of the document. Appendices that elaborated on areas shown by research to be common problem areas across typical medical device development projects were included as separate, collapsible sections to provide expanded information on those topics. The 510(k) Inventory Tool document was not included within this paper, but is available from the author upon request.

510(k) User Survey and Survey Results

To obtain actual user feedback on the final version of the 510(k) Inventory Tool, the document was sent out to a panel of users, along with a short survey. The user panel was a cross section of representative users from program management, regulatory, and quality functions with various educational backgrounds (science, engineering), educational levels (BS, MS, PhD), and experience levels (two years to more than twenty-five years of experience). Each user was presented with a power point presentation that described the background on this Capstone Project and the goal of creating the 510(k) Inventory Tool. Reviewers were asked to look through the tool to familiarize themselves and then answer a set of survey questions that had been provided. Survey Questions are provided in Appendix 1.

Sixteen users agreed to review the 510(k) Inventory and provide feedback. Out of the sixteen users the tool was sent to, eight provided fully completed surveys and feedback. Since the users and their individual backgrounds were known to the author, the data from the users was blinded when received to prevent any bias about the answers

provided. The data was aggregated by responses to questions to be analyzed. This was completed by an individual other than the author also to prevent any introduction of bias.

To obtain a baseline on the importance of regulatory requirements to survey participants in their current work, users were asked a series of questions about their overall current business processes. All users stated that regulatory requirements are very important or important to their current business processes (four users stated very important, four users stated important). Additionally, a majority of those surveyed stated that they felt the tool could assist the teams they work with to better identify regulatory requirements and potentially identify issues that impact schedule and cost during device development. Seven out of eight users stated that having the regulatory process well defined is important to the success of development and getting a product launched and fielded (seven out of the eight participants stated very important or important).

Because some people dislike the entire concept of checklists, it was important to understand if those reviewing the tool had any inherent bias against using the instrument. Among options for other answers, respondents were given the opportunity to check a box stating outright that they didn't like checklists on several of the questions in this section. However, no one checked this option. All surveyed stated affirmatively that they thought checklists can be useful to help achieve project goals. All respondents also answered in the affirmative that a checklist or a similar tool can be used to enhance predictability in the development process when used across phases of development. However, not all respondents were entirely sure that checklists could be useful for doing a 510(k) submission. Just five users stated yes to this question and three stated maybe. Results for user feedback for checklists are listed in Table 10.

Table 10. Results of user feedback on checklists.

Question	Yes	No	Not Sure	Comments
Do you think checklists are useful to help achieve product goals?	8	0	-	Users given option to answer they don't like checklists. Zero users checked this box.
Do you think use of checklists or a similar tool can enhance predictability in development or help teams understand development phases and regulatory requirements in each phase?	8	0	-	Users given option to answer they don't like checklists. Zero users checked this box.
Do you think checklists enhance the preparation of clear/complete FDA submissions?	5	-	3 maybe	Users were given option to answer that they don't like checklists. Zero users checked this box.

Within the survey, users were asked about their overall knowledge of the 510(k) process. Majority of respondents stated they were very clear about requirements for a 510(k) and the types of issues that can potentially affect submission quality. Most respondents relayed that they have experienced issues or problems during their work that they can attribute to the teams struggling to address FDA requirements during the development. They felt that using a tool like the 510(k) Inventory Tool would help them better address FDA requirements and would generally have helped them increase their knowledge of the requirements for creating a good 510(k) submission (Table 11). Response to the 510(k) Inventory Tool content was generally positive, with most users feeling that it was a comprehensive tool that could add value when used with a project team. User responses to the specific questions about the tool are listed in results Table 12.

Table 11. Results of user's overall knowledge of the 510(k) process.

Question
How clear are the requirements for preparation/submission of a 510(k)?
Before tool review, were you aware of how submission quality can affect FDA 510(k) review?
Did the tool help increase your knowledge of requirements for a good 510(k)?
For products your team has worked on, have you had issues properly addressing FDA requirements during development?
If you have had issues in developments, do you feel the tool would have helped your team better address FDA requirements?

Table 12. Results of user feedback on the 510(k) Inventory Tool.

Question	Yes	No	Not Sure
Tool can assist team to better identify regulatory requirements at each phase.	7	1	-
Tool could assist team to identify regulatory issues that impact schedule/cost of project.	7	0	1
Tool could assist team know what items contribute to 510(k) submission issues.	7		1
Tool would be useful when working with small, inexperienced companies.	7	1	-
Are you clear on the requirements for preparation and submission of a 510(k) (based on current level of understanding)?	7	1	-
Before reviewing the tool, were you clear or mostly clear about how submission quality can affect FDA 510(k) review?	8	0	-
Did the 510(k) Inventory Tool help increase your knowledge of requirements for a good 510(k) submission?	6	2	-
For products you've worked on, has your team had issues addressing FDA requirements?	7	1	-
If you worked on a team that had issues, do you think that the 510(k) Inventory Tool would have helped your team?	5	2	1 -Possibly with edits

510(k) Inventory Tool Survey Narrative Comments

Some of the survey questions required respondents to provide written, narrative answers/comments to a specific question. Each question is listed below with the aggregation of the overall response to the question. Narrative responses were extracted from each survey into a separate document for analysis and the actual full text of the answers/narrative comments are included in Appendix 2

What user respondents liked or found useful with the Inventory Tool Concept – Aggregation of comprehensive information

Reaction to the concept of the tool by users seemed generally favorable. When asked what they liked about the 510(k) Inventory Tool as a concept, users stated that the tool was comprehensive and relatively easy to understand. They liked that the tool provided a lot of practical information to 510(k) requirements. The aggregation of information about the steps in regulatory, manufacturing, and development processes into one place seemed to be something users viewed as a good approach that might be helpful to both experienced and inexperienced users. Inexperienced users felt that the 510(k) Inventory Tool would be extremely helpful to make sure that everything required for a good submission is considered throughout the development cycle. Experienced regulatory users felt that they could modify the tool to suit their specific needs. One user called the tool a "one stop shopping" approach. Another respondent specifically stated that use of this type of tool may lead to better discussion in a team about development decisions and requirements, which was a specific objective of the project. However, some felt that while the tool would be good for an experienced and moderately

experienced company to use this as a tracking matrix, it may prove more difficult for inexperienced companies to use.

What user respondents didn't like or didn't find useful with the Inventory Tool Concept: Length of the tool

While users mentioned that they liked that the tool was informative and comprehensive, they felt that the length of the tool was a problem. Generally, it seemed that the length made users feel that the tool may potentially be cumbersome to use or might be overwhelming for inexperienced users. One user stated that it provided a good base document that an experienced person could modify to suit individual needs.

User suggestions for improving the Inventory Tool Concept to make it more useful in their work: Addition of specific content

Interestingly, though the primary complaint about the document was the length, when asked for suggestions on how to improve the document, most users suggested ***adding*** specific content. This seemed counterintuitive as it would make the overall document even longer – which was what their primary complaint was about the tool. Only one user suggested cutting the size of the document down. Users suggested adding the following types of content to the 510(k) Inventory Tool:

1. Provide examples within the tool.
2. Add descriptions and some criteria for go/no-go decisions during development.
3. Add links to FDA guidance documents in the tool.
4. Provide information on how to bring the team to agreement on product characteristics, such as including Target Product Profile information as part of the tool.

5. Add a Table of Contents to the tool to make it more user-friendly.
6. Provide information on products that may have requirements that go beyond the 510(k) process. For instance, include how information on how this tool could work or be used for development of a combination product.
7. This tool would be helpful for any premarket submission preparation. So, the tool could be expanded to mention *De Novo* medical device submissions to the FDA. (Note – Here this user is referring to *De Novo* device submissions which are a common FDA submission for novel devices of low to moderate risk where there is no predicate device.)
8. Some wording could be included to make the tool more applicable to IVDs, such as "analytical testing." (Note – Here this user is referring to In Vitro Diagnostic medical device products.) Breaking the check lists into more independent lists so they could be used more independently.
9. Highlight the subsections that are part of any 510(k), and point out the sections that may not be required, such as software validation for a device not requiring software, etc.
10. Add discussion about risk in stage 1 to specifically examine the market risk that potentially none may need this device; therefore, it may not need to be developed.
11. Emphasize the importance of the FDA pre-submission process to companies and to involve regulatory support early in the development process.
12. Supplier collaboration and Quality Agreements. Emphasize how important planning for this is and touch on it earlier in the document. Many Manufacturers get ready to

manufacture and then discover they can't obtain the materials or that the quality of materials is lacking. This causes issues with the project timeline/success.

DISCUSSION

Almost half of all activities and decisions in the medical device development process are affected by regulatory requirements. Error and deficiencies in an FDA 510(k) submission for a sponsor-applicant can mean that the project schedule is delayed or even ultimately that the device cannot be brought to market. The questions posed for this Capstone Project were as follows:

1. Are there categories of consistent and common causes of errors and deficiencies in 510(k) submissions across typical 510(k) medical device development projects?
2. Could a checklist or tool be developed for use by medical device product development teams that would be useful to help these teams have a better awareness of and ability to track device development and regulatory requirements throughout the development process so that teams could more easily avoid the typical issues that cause errors/deficiencies in a 510(k) submission?
3. If this tool were developed, would users like this type of tool, and do they think using such a tool would assist in a successful 510(k) submission to the FDA?

Initial research into FDA and publicly available data gathered in this project demonstrated that there are consistent and common causes of errors and deficiencies in 510(k) submissions which could be addressed using standardized tools and processes. This supported the development of the proposed 510(k) Inventory Tool, a checklist incorporating key causal attributes related to those errors, to be reviewed during the typical phases of development to better address these deficiencies. Once developed and tested on a small group of users, the concept of the 510(k) Inventory Tool was found generally favorable. The evaluators indicated that this type of tool could assist the teams

they work with to better identify regulatory requirements and potentially identify issues that impact schedule and cost during device development. Users noted that they appreciated the comprehensiveness of the tool. However, concern was raised that it may be cumbersome or overwhelming to use, especially for those less experienced in the medical device development process. The reactions of the respondents to the use of this proposed checklist are indicative of both the commonality and complexity of medical device development as it relates to regulatory compliance. Survey respondents noted that the complexity of the tool may limit the utility of a checklist, yet no one argued for simplification with respect to content, since there are many regulatory aspects to consider within the development process, and many of them are dependent upon the product type and intended use.

The objective of the 510(k) Inventory Tool is to ensure that the appropriate regulatory considerations are being contemplated at the appropriate point in the development lifecycle. Additional work could be done to more closely map the regulatory requirements in the checklists to customize the tool for specific types of products. This targeted approach by product type may improve checklist utility. For the purposes of this study, a generic medical device development Phase Gate methodology was proposed (refer to Figures 6 and 7), which obligated a checklist with substantially more complexity to cover wider product variance. Establishing more product type specific Phase Gate development lifecycles that are narrowly tailored to specific device types would allow the 510(k) Inventory Tool to be decomposed, improving its utility to project teams, and making it less unwieldy for the user. This should be contemplated in a future version of the tool. The 510(k) Inventory Tool could also be converted into a

training aid for teams, particularly inexperienced teams, to use in an interactive setting to teach them more about the regulatory requirements they should be aware of during the medical device development process.

Effective product development teams bridge the gap between inventor and invention to a commercially viable product. Focus by product developers on the problematic sections of a 510(k) at the appropriate point in the development process will improve the economic efficiency of the development effort, reduce the lengthy cycles of review, and improve the product time-to-market. In theory, the 510(k) Inventory Tool would assist the project team in focusing on the activities required at each phase of development for a medical device that will undergo premarket review for which a 510(k) submission is being drafted. Understanding the development requirements at each phase, and ensuring those requirements are addressed as appropriate, would resolve areas that are problematic with FDA submissions and approval, and would increase predictability of interactions with the FDA during the review cycle. Though the 510(k) Inventory Checklist developed as part of this project only partially met these goals and needs, it was a first effort. With some incremental targeted work, it could become a valuable component of the medical device development lifecycle and improve the efficiency of 510(k) submissions across a wide range of medical device products.

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APPENDIX

Appendix 1

This appendix is the 510(k) Inventory Survey Questions sent to users in the user survey of the 510(k) Inventory Tool.

SECTION 1 - Please Answer A Few Questions About the 510(k) Inventory Based on Your Review

1. Does your organization currently use an established Phase Gate approach to design and development or a similar process?
    a. YES ☐
    b. NO ☐
2. Did you think about medical device design and development and regulatory requirements in terms of product development phases before you read this Inventory?
    a. YES ☐
    b. NO ☐
3. Do you feel this tool could assist the teams you work in to better identify regulatory requirements at each phase or identify regulatory issues earlier in medical device development projects?
    a. YES ☐
    b. NO ☐
    c. NOT SURE ☐
4. Do you feel this tool could potentially help teams identify regulatory issues that would reduce schedule and cost issues in device development projects?
    a. YES ☐
    b. NO ☐
    c. NOT SURE ☐
5. Do you think that the list of items in each phase and items in the Appendices that can contribute to 510(k) submission issues would be more fully considered by your project teams if you had the 510(k) Inventory Tool to distribute to your team members as a guide?
    a. YES ☐
    b. NO ☐
    c. NOT SURE ☐

6. Do you think that when working with small, inexperienced companies this type of tool would be helpful?
    a. YES ☐
    b. NO ☐
    c. IF YES, can you provide me with a few comments regarding why you think the tool might help inexperienced companies?
7. If you answered "NOT SURE" for question numbers 3, 4, or 5, is it because you're having difficulty understanding how you would apply this tool in your current work?
    a. YES ☐
    b. NO ☐
8. Please provide comments on:
    a. What you like or find useful with the Inventory Tool Concept.
    b. What you don't like or find useful with the Inventory Tool Concept.
    c. Suggestions for improving the Inventory Tool Concept to make it more useful for your work.

SECTION 2 - Please Answer a Few Questions About Your Overall Knowledge of the 510(k) Process

1. How clear do you feel the requirements are for preparation and submission of a 510(k) (based on your current level of understanding)?
    a. VERY CLEAR ☐
    b. MOSTLY CLEAR ☐
    c. NOT CLEAR AT ALL ☐
2. Before reviewing the introductory slides, were you aware of how submission quality can affect FDA review of a 510(k)?
    a. YES ☐
    b. NO ☐
3. Did the Inventory Tool help increase your knowledge of requirements for creating a good quality 510(k)?
    a. YES ☐
    b. NO ☐
4. For products you have worked on, has your team had issues addressing the FDA's requirements properly during the development process?
    a. YES ☐
    b. NO ☐

5. If you answered yes to Question 4, do you think using a tool like the 510(k) Inventory Tool would have helped your team better address FDA requirements?
    a. YES ☐
    b. NO ☐
    c. SOME ☐
    d. POSSIBLY, BUT ONLY WITH SOME CHANGES/EDITS TO THE TOOL ☐

SECTION 3 - Please Answer a Few Questions About Your Current Business Processes

1. How important are regulatory requirements to business decisions in your organization to make an investment in supporting development of a new product?
    a. VERY IMPORTANT ☐
    b. IMPORTANT BUT NOT CRITICAL ☐
    c. NOT IMPORTANT AT ALL ☐
    d. NOT CONSIDERED ☐
2. In your organization, and for the specific technological developments you have worked on, how important do you feel having the regulatory process well defined is to success of the development and getting a product launched/fielded?
    a. VERY IMPORTANT ☐
    b. SORT OF IMPORTANT BUT NOT CRITICAL ☐
    c. NOT IMPORTANT AT ALL ☐
    d. NOT CONSIDERED ☐
3. What types of tools or processes do you currently use to ensure that regulatory requirements are adequately addressed in the product development lifecycle at your organization?

SECTION 4 - Please Answer a Few Questions About Your Opinions on the Use of Checklists

1. Do you think that the checklists are useful in the process to help achieve project goals?
    a. YES ☐
    b. NO ☐
    c. I DON'T LIKE TO USE CHECKLISTS ☐

2. Do you think we can enhance predictability and enhance our development process by helping our teams understand the development phases and the regulatory requirements in each phase by using checklists or a similar tool across those phases in our developments?
    a. YES ☐
    b. NO ☐
    c. MAYBE ☐
    d. I DON'T LIKE TO USE CHECKLISTS ☐
3. Can we use checklists to enhance the preparation of clear and complete submissions to the FDA?
    a. YES ☐
    b. NO ☐
    c. MAYBE ☐
    d. I DON'T LIKE TO USE CHECKLISTS ☐

In the space below, please feel free to provide additional comments on the 510(k) Inventory that you'd like to share with me.

Appendix 2

This appendix is the 510(k) Survey Results and includes narrative Comments and full text of feedback received from survey users on the 510(k) Inventory Tool

Section 1 Question 8

A. What you like or find useful with the Inventory Tool Concept:

1. The issue I am facing with this tool as written is it would not benefit the people in an inexperienced company because the tool just scratches the surface of product development. An experienced and moderately experienced company could use this as a tracking matrix. It would have helped if you would have provided some examples of the terms being used. While you manage to outline the stage gate process, it may have been easier to follow if there were examples of the process. Also, while implied, you have not emphasized the importance of review of each stage and the importance of no-go criteria selection at each stage. Typically to pass through stages, developing regulatory strategy and additional steps would require money, and the money is going to dictate the studies and critical path of development. Those are some of my thoughts, but since I believe in this effort, I can use this in my work and make improvements, so it is a good starting point.
2. I like that it is “one stop shopping.”
3. The tool is comprehensive and relatively easy to understand. I find this tool extremely useful. This provides a good overview of the required steps in the regulatory, manufacturing, and development process. It also makes you think about all the different aspects over and over again as an iterative process, allowing for constant improvement. Finally, it ensures that you discuss your device and

everything with the FDA, so there is a general agreement with your development decisions and validation requirements.

4. The explanations at each phase provide a lot of information that helps people unfamiliar with the full FDA process understand each phase better.
5. Tool provides practical approach to 510(k) requirements, clarifying in one single place what needs to be done.
6. Checklists are clear and comprehensive to ensure nothing is forgotten.
7. The tool is very comprehensive.

B: What you don't like or find useful with the Inventory Tool Concept:

1. Yes, as mentioned above, as an experienced regulatory person, I feel I can use this tool because I can modify it to suit my needs.
2. It is very informative and comprehensive in its approach, but it is much too long and cumbersome to try to get through. It might be helpful to include references to the FDA guidances, etc. per section, although that would make the tool even longer.
3. While it's great that it provides a lot of information, I think that could also be a deterrent for some because it's fairly overwhelming when you first open it up.
4. I did not see where it mentioned creating a target product profile so all the key stakeholders could agree on the characteristics of the final product. Maybe it was called something else in the document.

C: Suggestions for improving the Inventory Tool Concept to make it more useful for your work:

5. Provide examples, add description and some criteria for go/no-go. Also, while you have included reimbursement at stage 2, you may have to ask who will.How can I fund the activities in each stage as a criteria?
6. You have included publicly available information on 510(k) submission. While all the subsections may not be important, you may want to highlight the subsections that are part of any 510(k) and point out the sections that may not be required, such as software validation for a device not requiring software etc.
7. Add a Table of Contents to make it more user-friendly. It might be easier for the user if the checklists were to be combined and in one appendix.
8. Maybe someone with a better background in regulatory science may be able to improve the checklist, but from my perspective, it is great and covers everything you need to consider in the development process.
9. Provide information on products that may have requirements that go beyond the 510(k) process. How could this work for a combination product, for example.
10. I think that if you are able to create a smaller checklist from the 30 page document so that the PM can make sure to hit all of the key points within regulatory without needing the full document. And then they can use the full document as reference.
1. I think the tool could be expanded to mention *de novo* submissions. Many of the requirements are the same and *de novos* are also Class II. In fact, this tool would be helpful for any premarket submission preparation. Also, some wording could be included to make the tool more applicable to IVDs, such as “analytical testing.”

2. I think that an accompanying e-learning module would help companies not familiar with the process understand it better.
3. Perhaps breaking the check lists into more independent lists so they can be broken down and used more independently.

Section 1 Question 6 C:

Do you think that, when working with small, inexperienced companies, this type of tool would be helpful?

1. Many small companies have little to no experience in development, much less device development. This would be extremely helpful to help them begin thinking about an overall strategy and decision points regarding what needs to be done, considered, and when.
2. There are a vast majority of different things to consider while designing medical devices. This checklist provides a good overview of everything that must be considered that a small inexperienced company might not think about.
3. Tool would help small companies be more efficient in understanding and addressing regulatory. Tool allows for the development of a more streamlined efficient approach to identifying and meeting requirements.

Helping with a road map a for product progression through the 510(k) process, as well as organize and plan.

Section 3 Question 3:

Please Answer a Few Questions About Your Current Business Processes:

1. Our regulatory support is a big help and assists in crafting regulatory requirements within contracts that are let out. Including creation of the FDA DID (Data Item Deliverables).
2. I currently work for a CRO and also do consulting to DoD – we utilize established processes in both organizations and rely heavily on FDA/EMA guidance, Trace matrices, Documentation, QMS Regulatory Strategy Documents and checklists.
3. Emphasize importance of pre-submission process to companies; involve regulatory support early in the development process.
4. We do not have tools. Only subject matter expert expertise guides the processes.

Section 4, Question 4:

In the space below, please feel free to provide additional comments on the 510(k) Inventory Tool that you'd like to share with me:

1. You may want to look at a few types of devices, with electronics, without electronics, with software, without software, devices, diagnostics, in vitro diagnostics provide some examples or considerations for each type of devices within stage gate requirements. Each of these devices may have a lot or no steps or considerations in each stage of development; therefore, it should provide you with some test cases for information the user of this document may want to think of during their development. Also, you talk of risk in stage 2,3 and 4. I feel you should be talking about risk in stage 1, and it may be the risk that no one need this device (most of the devices we develop in the army fall into this category). The risk and reimbursement should be a consideration in stage one.

2. As someone who has little experience with the FDA, this checklist is extremely helpful in making sure everything that is required for a good submission has been considered prior to submission and throughout the development cycle. It will certainly improve my evaluations of products, companies, and proposals. It will also improve the types of things I require when writing RFPs in the future.
3. For Phases 3 and 4, you mention Supplier collaboration and Quality Agreements. I recommend you discuss even earlier how important planning for this is. Many Manufacturers get ready to manufacture and then discover they can't obtain the materials or the quality is lacking and this causes issues with the project timeline/success.