# Highlighting Challenges in the New Combination Product Regulatory Landscape:

## What Industry is Doing About 21 CFR Part 4

Industry Survey Completed November 2015

### HIGHLIGHTS

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# Executive Summary

Growth in the drug-device combination product marketplace, driven by new innovation, is expected to reach $115B by 2019.[1]

It is clear that the Combination Product revolution is underway, but the impact of the new Combination Product regulations (21 CFR Part 4) on industry is not as well understood. The ability to effectively interpret, implement, and execute in response to the new regulations has the potential to separate the category leaders from the rest of the pack. In order to act on this opportunity, most Combination Product manufacturers have been proactively taking steps to be leaders and not laggards in responding to the regulations.

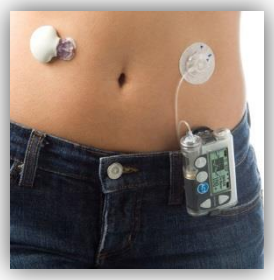
This EdgeOne Medical report brings together the views of 33 experienced Combination Product professionals involved in Regulatory, Quality, and R&D functions of some of the world's most respected large and emerging BioPharma and Biotech firms that are developing Combination Products. The report brings to light several common challenges facing organizations as they respond to the recent FDA regulations on combination products, as well as insights on where they are in the process of achieving full compliance to the new regulations.

1. Top challenges for companies fall into 3 categories: Organizational (lack of awareness and experience), Operational (unproven and incomplete Quality Management System (QMS) and Transactional (remediation & handling of off-the-shelf (OTS) devices)
2. Companies rated their Quality Management System (QMS) and Design History Files (DHF's) as 50% and 40% compliant, respectively, implying that there is still a lot of work to achieve full compliance.
3. Senior Management is perceived to have a very low understanding of the impact the new combination product regulations have on product development.
4. Almost 60% of large companies indicated that the device constituent is being introduced into the drug or biologic program too late , causing issues and compromises.
5. Companies continue to outsource, with highest level of outsourcing engagements occuring in Manufacturing and R&D relative to other funcional areas - Regulatory, Clinical and Quality.

This report serves as a discussion guide and a measuring stick to help your firm gauge where you are in this journey.

[1] Citation – Transparency Market Research, Drug Device Combination Products Market (Drug Eluting Stents, Infusion Pumps, Photosensitizers, Orthopedic Combination Products, Wound Care Combination Products, Inhalers, Transdermal Patches, Intraocular Implants and Drug Eluting Beads) - Global Industry Analysis, Size, Share, Growth, Trends and Forecast, 2013 - 2019 , 24Dec2013.

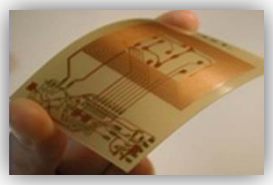
# Why So Much Interest in Combination Product Regulations?



The combination product space is a rapidly growing and exciting, dynamic and evolving landscape. The drug-device combination product marketplace is expected to reach an estimated global value of $115B by 2019 with the primary driving forces being a desire for minimally invasive devices and an aging population with chronic diseases.[2] These drivers have produced innovations such as patches for transdermal delivery of drugs, surgical meshes with antibiotic coatings and ambulatory infusion (patch) pumps.

The innovation that has produced these products has in many respects out-paced the regulations that govern combination products until 2014 when new combination product regulations were issued by the FDA. The new regulations address the intricacies involved in designing, developing, classifying, and evaluating combination medical products. In this survey report we highlight common exposures that are important to address in order to bring the combination products successfully to market.

The shift from the historical norm of devices constituting the primary component of combination products to the current trend of the drug (or biologic) providing the primary mode of action (PMOA)[3] has added to the complexities facing manufacturers. In 2014, the majority of combination product applications to the FDA were Original IND's (51%), followed by Original 510(k)'s (21%) and Original IDE's (17%)[4]. In addition, by some counts, roughly 30% of all new drug/biologic products in development are being paired with a device constituent, and this is projected to increase during the coming years.[5]



Not surprisingly, the capability to efficiently and effectively navigate regulatory frameworks in this changing paradigm often becomes a key challenge and a potentially important competitive advantage for manufacturers. This leads to one of the most common questions that we, EdgeOne Medical, receive from our clients…"What are other companies doing?"

To help provide answers to this question, we surveyed individuals from several combination product manufacturers about how their companies were responding to the FDA final rule (21CFR Part4) and its latest draft guidance issued in January 2015 on "Current Good Manufacturing Practice (GMP) Requirements for Combination Products."

The report is presented in two sections, the first providing an assessment of how organizations are interpreting, implementing and executing the regulations, and the second analyzes organizational best practices and challenges

[2] Citation – Transparency Market Research, Drug Device Combination Products Market (Drug Eluting Stents, Infusion Pumps, Photosensitizers, Orthopedic Combination Products, Wound Care Combination Products, Inhalers, Transdermal Patches, Intraocular Implants and Drug Eluting Beads) - Global Industry Analysis, Size, Share, Growth, Trends and Forecast, 2013 - 2019 , 24Dec2013.
[3] Citation – FY 2013 Performance Report to Congress for the Office of Combination Products.
[4] Citation – FY 2014 Performance Report to Congress for the Office of Combination Products.
[5] Source: Combination Products- Navigating Two FDA Quality Systems, Microtest White Paper, 2007

## THE SHAPE OF THE COMBINATION PRODUCTS MARKET

### Rising...

- incidences of chronic pain-causing diseases, prostate and colorectal cancers, diabetic retinopathy, and cardiovascular diseases
- aging population
- demand for minimally invasive procedures
- number of interventional cardiologists

Encouragement for **DRUG-DELIVERY IMPLANTS** by government & non-government organizations

**innovation** advances (e.g., biodegradable drug-delivery technologies)

*Site of care shifting from hospital/clinic setting to home*

**EVOLUTION** from diagnosis & treatment to prediction & prevention

**BUSINESS INTERESTS**

- alliances between medical product manufacturers and technology firms
- patent production and product line extensions
- competitive differentiation using convenience targeted/controlled drug-delivery

### North America

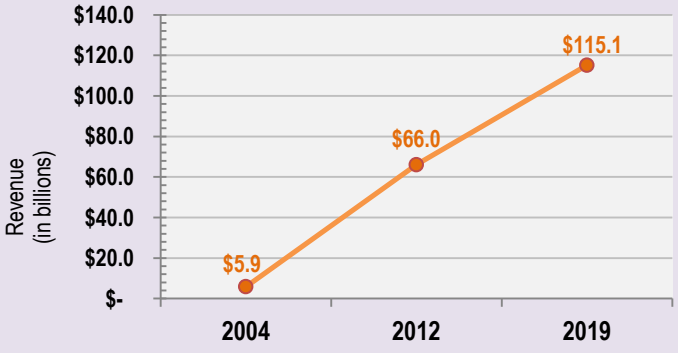
Currently dominates the global drug-device combination products market because of:

- growing baby boomer population
- corresponding rise in prevalence of various chronic diseases such as cardiovascular disorders, obesity and diabetes

### Asia

Expected to experience the fastest growth over the next several years because of:

- economic development of emerging nations such as India and China with high unmet medical needs
- increasing population
- rising disposable income and increasing healthcare awareness
- increase in healthcare expenditure, and development of healthcare infrastructure
- increase in support by local governments and international organizations




The global combination products market was estimated at $5.9B in 2004, and at $66.0B by 2012. The market is expected to reach $115.1 billion by 2019.

A **20X** increase within 15 years.

Sources: Transparency Market Research, Drug Device Combination Products Market (Drug Eluting Stents, Infusion Pumps, Photosensitizers, Orthopedic Combination Products, Wound Care Combination Products, Inhalers, Transdermal Patches, Intraocular Implants and Drug Eluting Beads) - Global Industry Analysis, Size, Share, Growth, Trends and Forecast, 2013 - 2019 , 24Dec2013. "Industry Statistics." PharmaMedDevce2009. Reed Exhibitions, Mar 2009. Web. 25Nov2015.

## SURVEY RESPONDENT DEMOGRPAHICS:

### 33 INDIVIDUALS FROM 18 COMBINATION PRODUCT MANUFACTURERS ANSWERED QUESTIONS ABOUT THEIR *PERCEPTIONS* OF THEIR COMPANIES' CAPABILITIES TO COMPLY WITH 21 CFR PART 4

- A diverse cross-section of individuals from the combination product industry participated in our survey, which was conducted between during 2015 and released in early 2016.
- Majority of survey respondents identified a combination product with either the drug or biologic constituent as the Principal Mode of Action (PMOA). Therefore, the findings presented in this report *may not* be representative for combination products where the device constituent is the PMOA.
- Results are also presented where differences were noted between respondents within a functional role, the respondents' titles or years of experience.

**Exhibit 1: Company Representation**

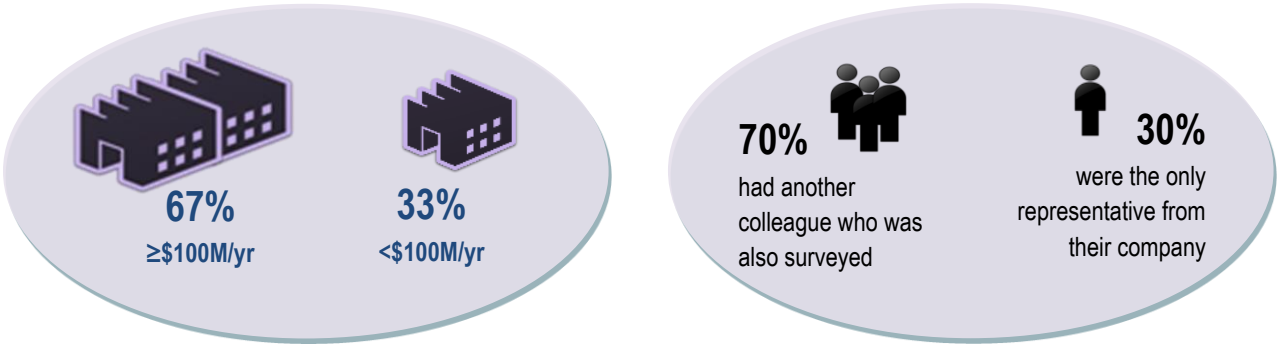
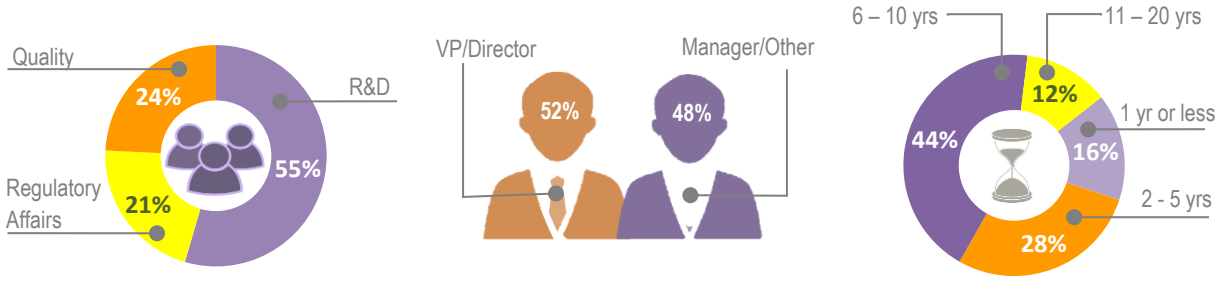



**Exhibit 2: Respondent Demographics**

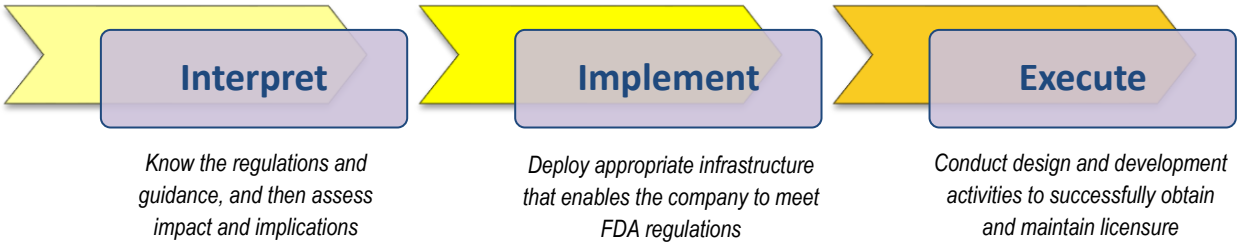



Participation by Function | Participation by Job Level | Participation by Experience with Combination Products

*Note: Individuals participated in our survey with the understanding that their identity and company affiliation would be kept confidential. In addition, the opinions expressed and presented in this article are those of the individuals participating in the survey and do not reflect the opinions of their employer. Responses were solicited using multiple-choice, rating, ranking, and open-ended questions. Although all respondents answered most questions, there were instances where one or more individuals declined to provide a response to a specific inquiry. Consequently, quantified results presented in this report are based on the number of individuals who provided a response for each specific survey question.*

# COMPANIES' CAPABILITIES TO INTERPRET, IMPLEMENT, AND EXECUTE AGAINST FDA REQUIREMENTS FOR COMBINATION PRODUCTS

Fundamentally, the key to complying with the FDA regulations for combination products is to demonstrate integration of the components as a system. This means that a manufacturer must effectively interpret, implement, and execute against the regulations. Several questions in the survey focused on various aspects of interpretation, implementation and execution of the regulations, and the following summarizes these results.



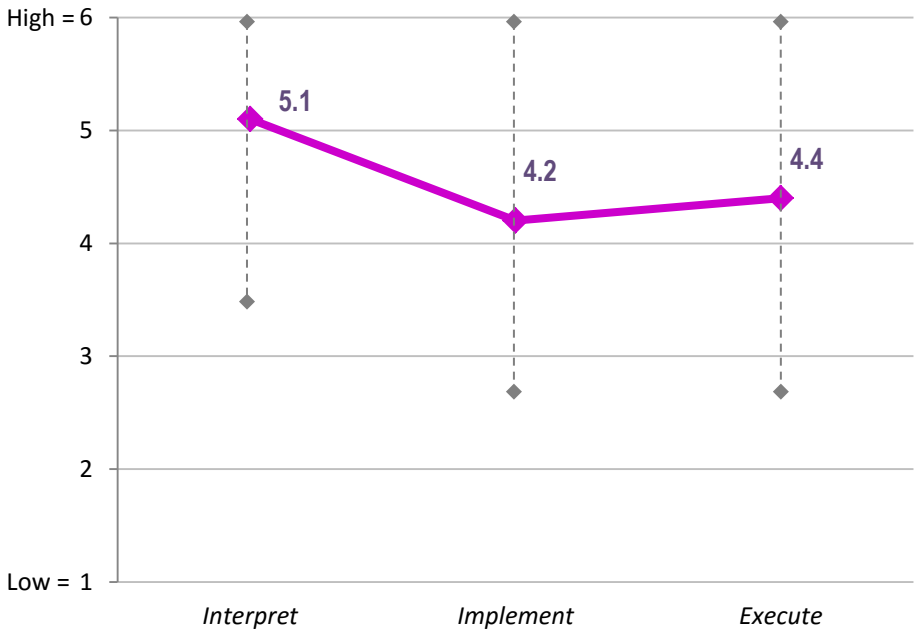

## 1 Ability to Implement & Execute Regulations Ranked LOWER THAN Interpretation

The majority of respondents rated their company on the higher end of the scale (i.e., 4 or above) for interpretation (97%), implementation (67%), and execution (77%). However, there was a notable range of scores for each capability.

Exhibit 3: Overall Average Compliance Capabilities Scores

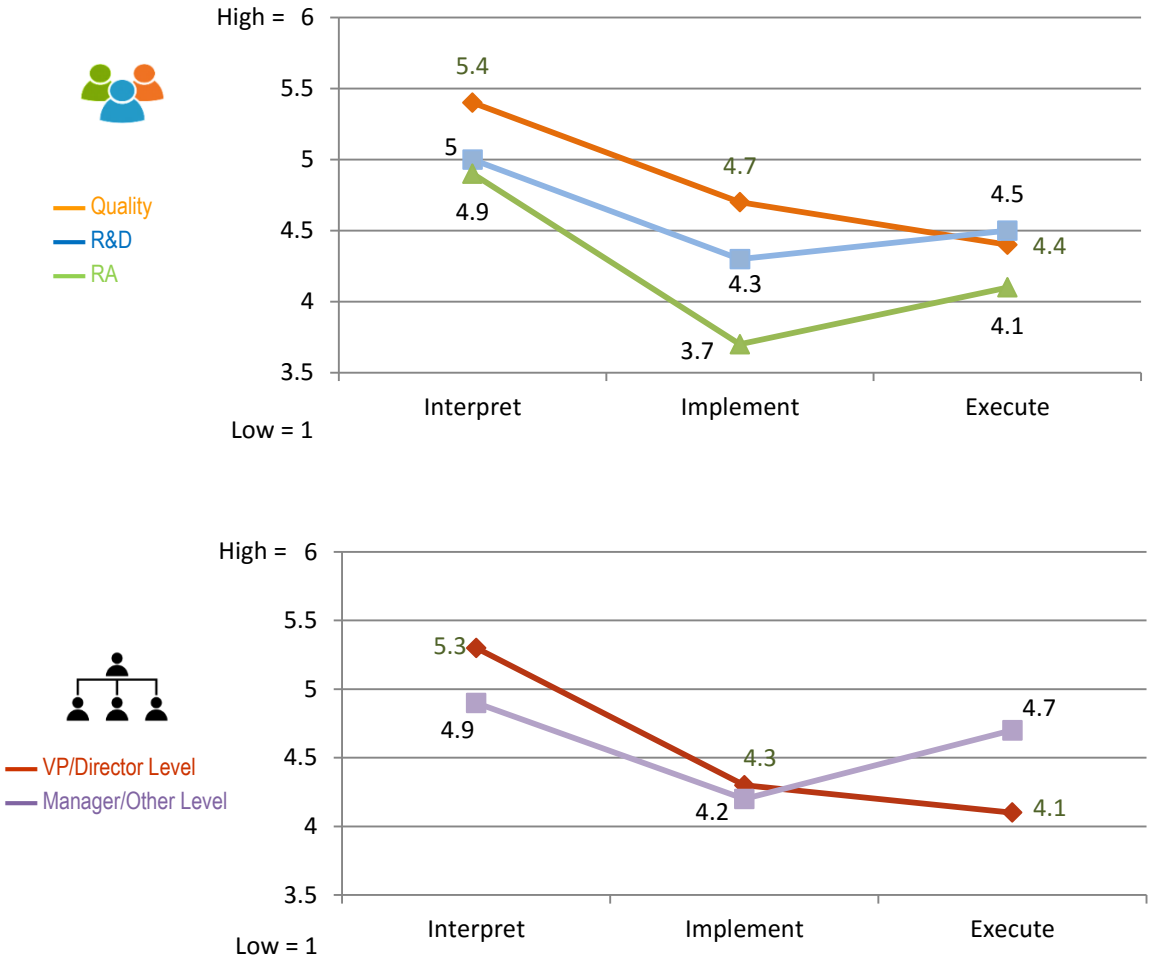
Respondents rated their companies' capabilities using a 6-point scale.

(1 = low and 6 = high).



- Similar trends were observed across functional roles of quality, R&D and regulatory, and job-levels, however, regulatory individuals consistently gave lowest ratings than their colleagues. In addition, while VP/Director level individuals on average had one of the highest ratings for interpretation, for execution they provided lowest ratings along with regulatory respondents.

**Exhibit 4: Average Capabilities Ratings by Respondent Sub-Sets**




INSIGHT

*It comes as no surprise that the ratings for implementation and execution drop given that the majority of survey respondents are from drug and/or biologic companies,. The magnitude and impact of change to these types of companies is significant, more specifically they need to acquire some level of device development expertise in order to comply with the regulations, and the scientists developing the drug and/or biologic will need to be more aware and considerate of the device requirements earlier in the process. While it may seem trivial, the mental shift required for an organization that has traditionally been science focused will yield growing pains. This may be why the VP's and Directors provided the lowest average rating for the organizations ability to execute per the regulations.*

Interpret

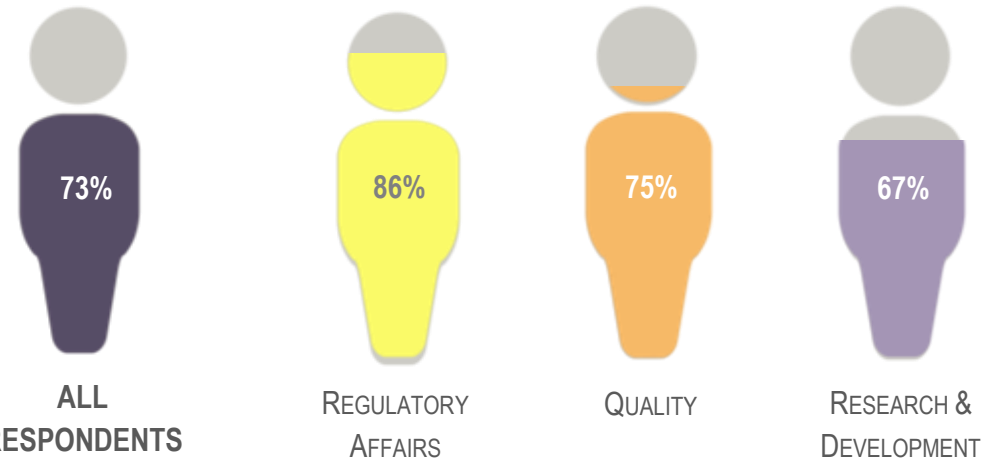
# KNOWING THE REGULATIONS AND GUIDANCE, AND ASSESSING IMPACT AND IMPLICATIONS

## 2 Majority of Respondents are Familiar with 21 CFR Part 4

The FDA's final rule entitled Regulation of Combination Products (21 CFR Part 4) became effective in 2013. The focus of the regulation is on good manufacturing practices, with draft guidance on the same topic issued by FDA in January 2015. At the time the survey was conducted, 21 CFR Part 4 had been in effect for at least 1.5 years.

- The most predictive factor of respondents' familiarity with the regulations was functional area.

Exhibit 5: Level of Awareness of 21 CFR Part 4




INSIGHT

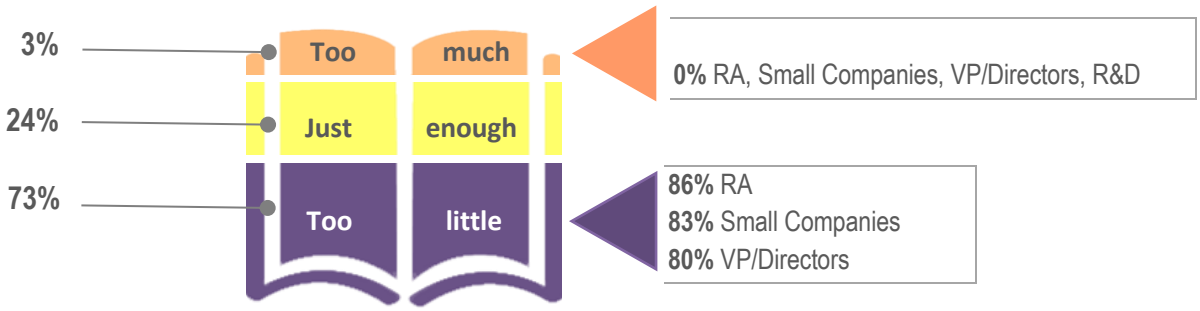
*The R&D respondents had the lowest level of familiarity with the new regulations. This is not surprising given that R&D team members typically don't read the specific FDA regulations. Rather, they receive their direction/guidance on how to comply with FDA regulations via the Regulatory Affairs and company product development procedures and training sessions which are commonly owned by Quality. In this instance however, the changes to the regulations are significant (rather than an update) and by not having R&D personnel familiarize themselves with the new combination product regulations, they will not be additive to the implementation and execution stages.*

## 3 Industry Requesting more Detailed Guidance from FDA

The FDA's Office of Combination Products (OCP) was established on December 24, 2002 via the Medical Device User Fee and Modernization Act of 2002 (MDUFMA). Among other things, the OCP is responsible for being the focal point for combination product issues for agency reviewers and industry and also to develop guidance and regulations to clarity the regulation of combination products. Since its inception, the FDA has updated portions of 21 CFR Part 3, issued 21 CFR Part 4, and released a little over a dozen guidance documents on combination products.

**Exhibit 6: Adequacy of FDA Guidance**

*Of the three perspectives (functional, company size and title), those in RA, at small companies, and VPs/Directors were more likely than their counterparts to indicate that more detailed guidance from FDA is needed.*




- **Human Factor (Usability) Testing** for combination products was mentioned most frequently as a subject area needing more detail from FDA. The FDA clearly was the recipient of many questions on this topic as they recently issued the following Draft Guidance: Human Factor Studies and Related Clinical Study Considerations in Combination Product Design and Development, Feb. 3, 2016.

- The other topics requested by respondents for further guidance from FDA were divided into the following three (3) categories:

| Product Development | Regulation / Submission | Life Cycle Mgmt Support |
|---|---|---|
| ○ Design Control<br>○ Design History Files (DHF)<br>○ Requirements: Product Shelf Life, Clinical Study, Product Testing.<br>○ Off-the-shelf (OTS) devices and pre-filled syringes | ○ CP Classification<br>○ Regulatory submission requirements<br>○ FDA review process | ○ Facility Inspections<br>○ Product complaint management<br>○ Medical Device Reporting (MDRs)<br>○ Clinical requirements for Life Cycle Management |

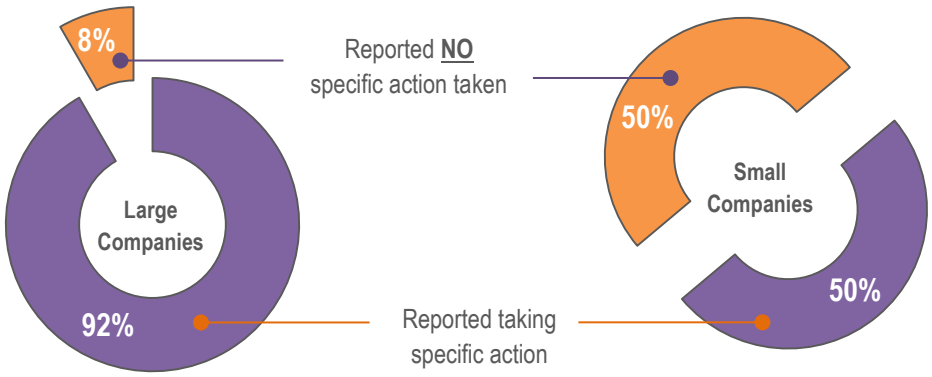
INSIGHT

*Prior to the issuance of the combination product regulations, the majority of combination products were device as PMOA. When considering that the majority of survey respondents are drug or biologic companies, it reasonable to expect the Regulatory Affairs (RA) function would indicate that the FDA provides too little guidance. Drug and Biologic RA are in a sense the new players in the combination product ballgame, and with the requirements being applicable to on market products as well as those in development, the learning curve for the drug/biologic RA function is steep.*

## 4 Majority of Organizations Reacted upon Issuance of 21 CFR Part 4

Company size seemed to be the most predictive factor whether organization took some type of action to assess impact of new US FDA regulations on their combination product development efforts.

**Exhibit 7: Actions Responsive to Rule Issuance**




INSIGHT

*It seems obvious that large companies would take an immediate and pro-active response to issuance of the new guidance. Due to the size of their organization, number of products on market and in development, and number of site locations, implementing a change of this magnitude requires adequate planning, development and resources. The risk of not responding jeopardizes, amongst other things, their future submissions and audit results, both of which could have significant negative impact of company financials. On the contrary, smaller companies are typically more nimble in their organizational infrastructure, have fewer sites in their organization, and their product portfolio is significantly smaller. As such, they can plan and implement their response with a shorter reaction time.*

Most frequently reported initiatives taken by companies in response to regulations were:

1. Convening internal task force teams to assess impact and address gaps
2. Contracting external consultants to educate internal teams and/or conduct impact assessments
3. Membership / Participation in industry and trade associations
4. Hiring staff and leadership who are experienced in combination products.

> "Our organization has made piece meal efforts to date. They have not been holistically coordinated, and I feel it's a little late to the game." **~Device Manager**

> "Initially did 6 month limited duration, cross-functional team and worked out impact and necessary schedule of activities by prioritization of products based on design changes, value to company, volume and complaints. Then formed steering committee @ VP level and small working group w/ PM - this way as issues on projects were identified, remediated and elevated to steering committee." **R&D Sr. Manager**

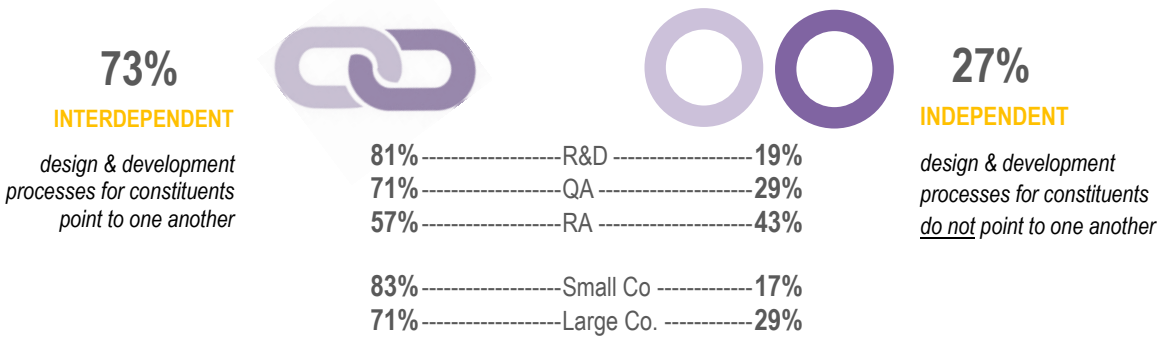
Implement

## DEPLOYING APPROPRIATE INFRASTRUCTURE TO ENABLE COMPLIANCE WITH FDA REGULATIONS

### 5 MAJORITY of Companies have Integrated Design and Development Processes

The new combination product regulations indicate that the FDA is expecting organizations to establish design and development processes that point to one another, thus demonstrating an integrated (interdependent) design and development process. Results support that organizations are moving toward an integrated approach, but 30% of large company respondents indicate processes are still not integrated, and regulatory team members are the harshest critics in belief that integrated process exist.

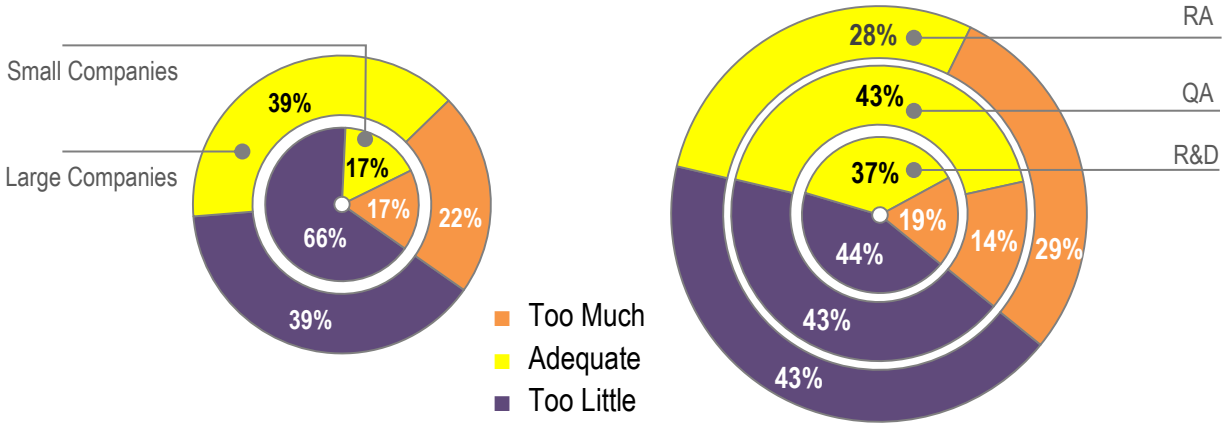
Exhibit 8: Basic Characterization of Design & Development Processes




### 6 Design and Development Processes Contain TOO LITTLE Detail

Varying trends across organizational sizes and functional roles provide insights as to the perceived level of detail contained within respondents Design and Development Processes.

Exhibit 9: Level of Detail in Design & Development Processes



## 7 Device Constituent introduced TOO LATE into Drug/Biologic Program

Company size was the most notable correlation with how respondents perceived the timing of when their companies' processes accommodated for the integration of the constituents of a combination product.

Exhibit 10: Perceptions of timing of constituent integration

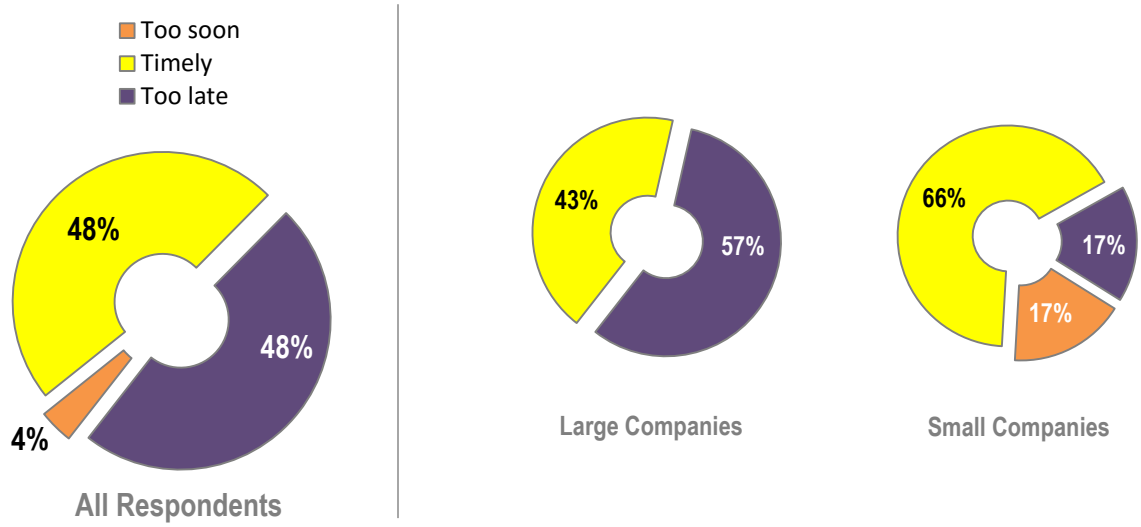



Exhibit 11: Causes and Implications of Late Constituent Integration

| Root causes | Consequences |
|---|---|
| • Lack of device experience within biopharmaceutical companies<br>• Failure to anticipate potential impact of device integration on the drug/biologic<br>• Late-stage decision to integrate a device constituent with drug/biologic | • Costs and time delays associated with unplanned studies and product re-designs<br>• Post-marketing product complaints stemming from sub-optimal commercial configuration of the device constituent |

"By the time the drug team realizes the device is needed, they are on the verge of a phase III clinical. This is too late to begin development of a device constituent part." **~Associate Director, R&D**

"Device development is a mystery to the pharma world." **~Sr R&D Project Manager**

"We developed the biologic first and then brought in the device. We didn't appreciate the complexity of the overall CP (combination product) when compared to individual components. The impact to the project was discovered too late - delays were inevitable." **VP R&D**

## 8 65% of Organizations are Remediating Design History/Drug Master Files (DHF/DMF)

While company size was correlated with whether respondents indicated their companies' DHF/DMF files for combination products were being remediated, it was not predictive of whether respondents indicated those files were maintained together or separately.

Exhibit 12: Organization of DHF/DMFs for Constituents

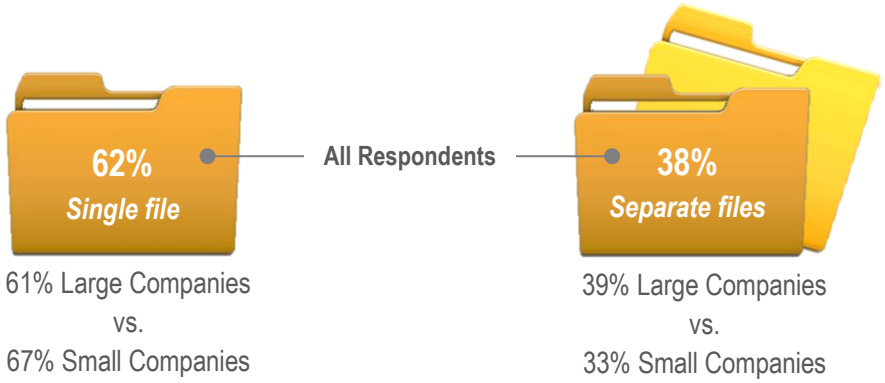
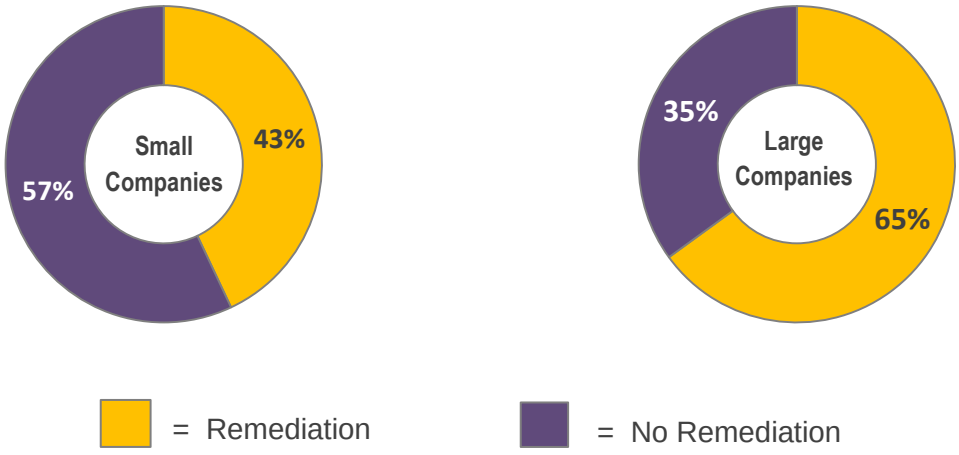



Exhibit 13: Remediation of DHFs



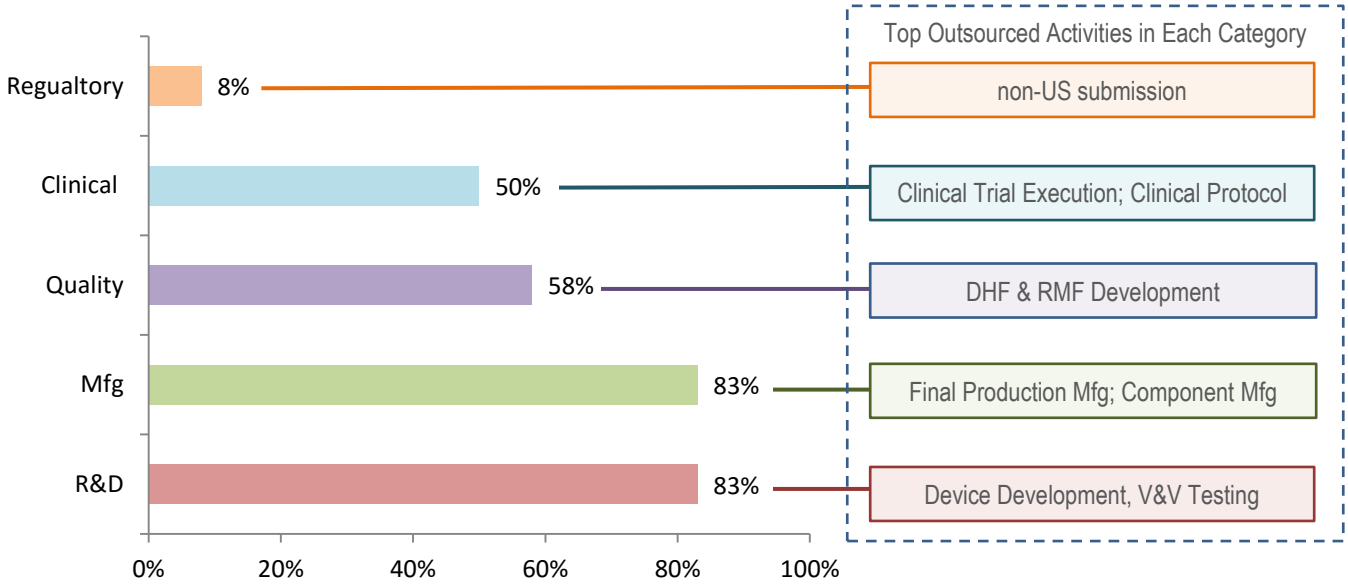

*Several of those who reported that no remediation was currently underway did expect that such efforts would likely take place at a later point in time at their company. Others indicated that there was no perceived need for remediation of DHF' s at their company.*

## 9 Trend of Outsourcing Design and Development Activities Continues

Company size was correlated with how likely respondents indicated that their company outsourced design and development activities for combination products.

**Exhibit 14: Outsourcing Status of Design and Development Activities**


**Exhibit 15: Outsourced Support at Large Bio/Pharma Co by Functional Area (n=12)**




INSIGHT

*Only one large company indicated no outsourced activities; they maintain full control of all aspects of development and manufacturing. In contrast 50% of small companies don't outsource. This is to be expected given that smaller companies either adopt a lean organizational model that relies on outsourcing, or they have a very small product portfolio that allows them to retain full control of all aspects of product development and manufacturing.*

Execute

## UNLESS UNDERGOING INSPECTION BY FDA, COMPANIES RELY ON OTHER MECHANISMS TO ASCERTAIN COMPLIANCE OF THEIR SYSTEMS AND DOCUMENTATION WITH 21 CFR PART 4

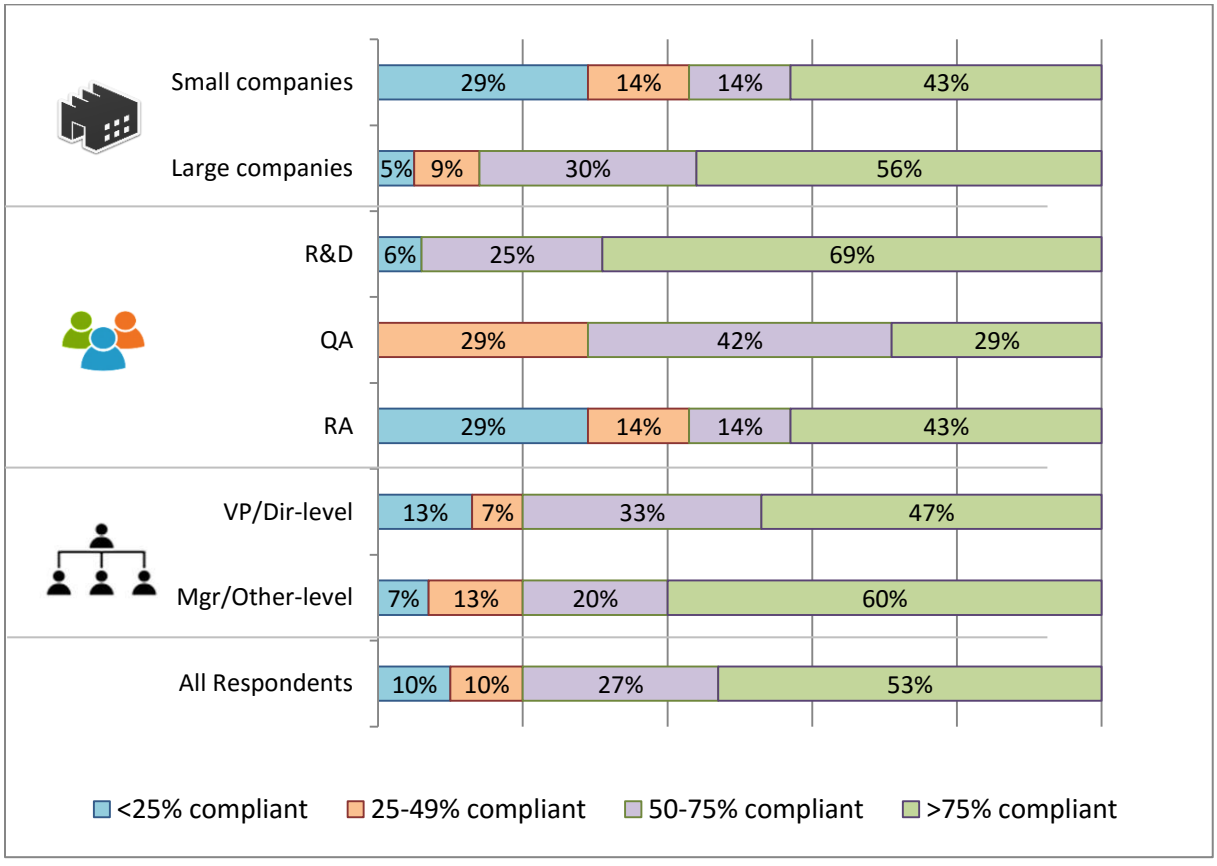
### 10 ONLY 53% rated their Quality Management System (QMS) as Compliant

53% of all respondents judged their companies' QMS as greater than 75% compliant according to 21 CFR Part 4, with another 27% rating it as between 50-75% compliant.

However, for 4 of the 8 companies who had multiple survey respondents, QMS compliance was rated very differently (i.e., more than one rating grade difference). Only 2 of these 8 companies had consistent QMS compliance ratings from respondents.

Exhibit 16: Perception of QMS Compliance

*Respondents in R&D, those at manager/other job level, and those at large companies were more likely than their counterparts to perceive their QMS as more than 75% compliant to the US regulations for combination products.*



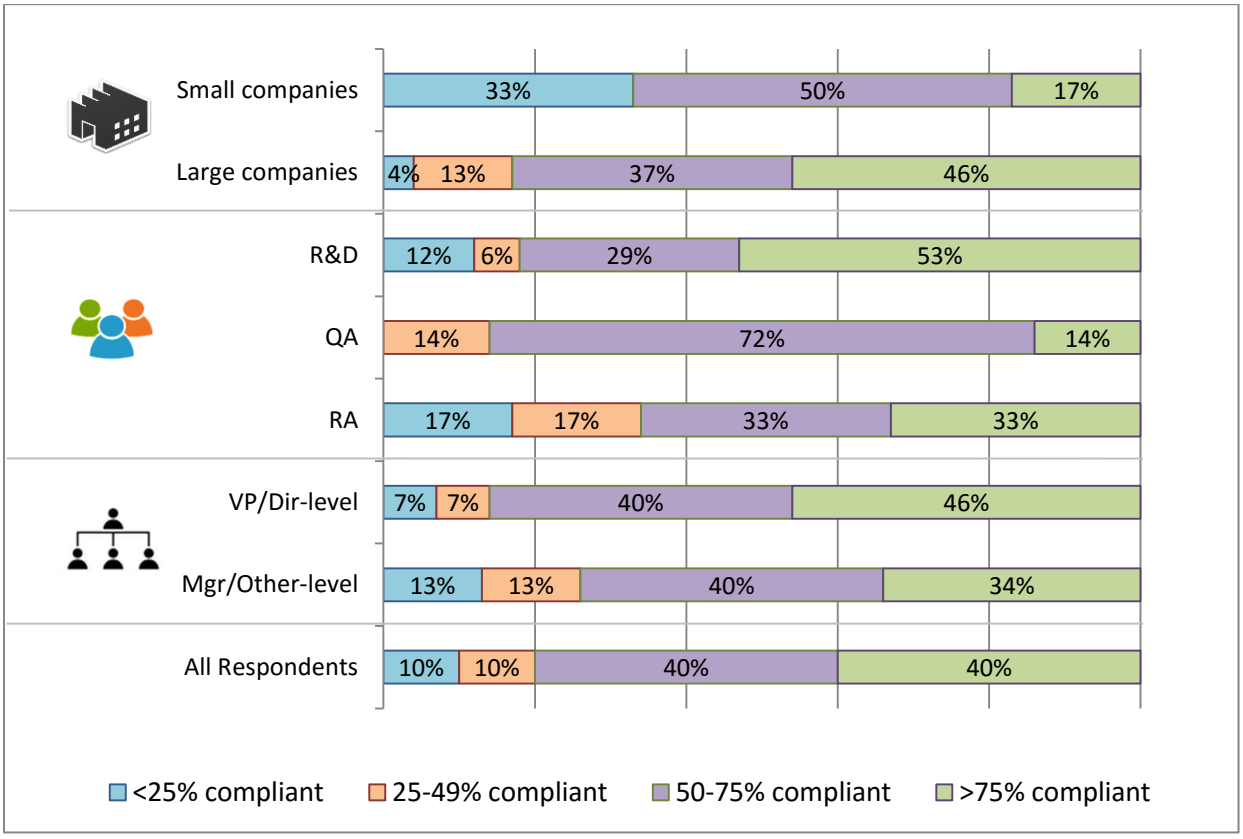
## 11 ONLY 40% rated their Design History Files (DHF) as Compliant

Although 80% of all respondents perceived their DHFs as at least 50% compliant per 21 CFR Part 4, only 40% rated their DHF as greater than 75% compliant.

Intra-company variances in DHF compliance scores were evident in 6 of the 8 companies with multiple survey respondents; representatives from 4 of those companies gave a rating more than one grade different from their colleagues in the same company.

**Exhibit 17: Perception of DHF Compliance**

*Respondents in R&D, those at VP/Director-level, and those at Large companies were more likely than their counterparts to perceive their DHF as more than 75% compliant to the US regulations for combination products.*



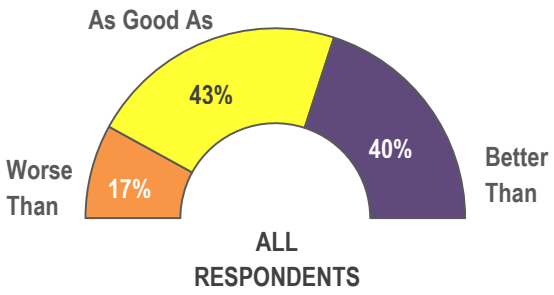

INSIGHT

53% and 40% of survey respondents indicated that their QMS and DHF's are greater than 75% compliant, respectively. One of the challenges facing organizations in adopting the new regulations is balancing and prioritizing remediation of legacy on-market products with new products under development. Due to limited organizational resources, funds and personnel, it is not uncommon for organizations to utilize a risk based approach in prioritization of developmental and remediation activities, thus accounting for a lower percentage of compliant DHF files. One could also argue that remediation of DHF's shouldn't begin until the QMS system is compliant, given that the DHF files should reflect compliance to QMS processes.

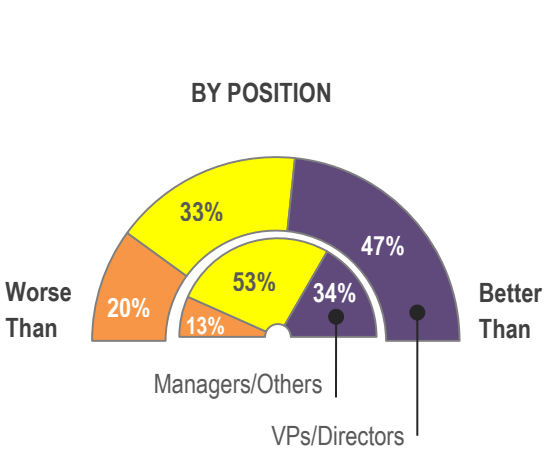
## 12 Majority believe their D&D Process is Equivalent or Better than Peers

Company size and functional area (specifically, RA) were correlating factors in how well respondents perceived their own company measured up with industry peers with regards to design and development of combination products.

Exhibit 18: Perceptions of Competitive Status




**83%** of all respondent rated their company as either "As Good As" or "Better Than" industry peers



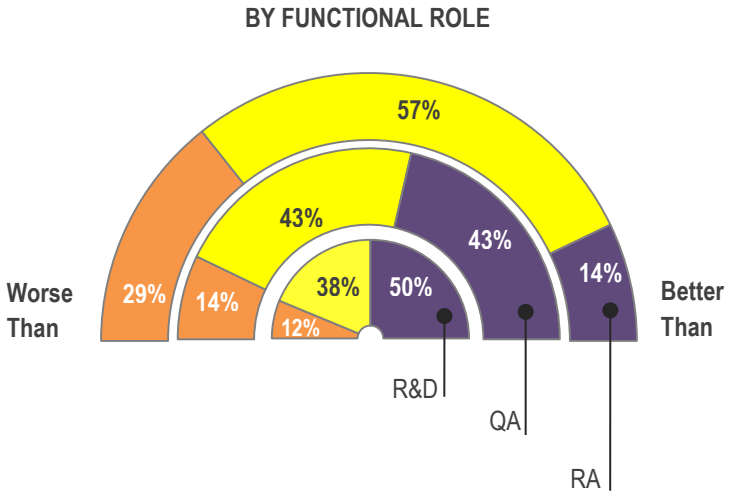




Exhibit 19: Rationales for Competitive Status Perceptions

**EXPLANATIONS FOR "BETTER THAN" RATINGS**

- My company has good quality management and documentation systems
- My company operates faster and at lower costs
- My company has internal device and/or combination product expertise

**EXPLANATIONS FOR "WORSE THAN" RATINGS**

- My company lacks organizational expertise with combination products
- My company has a conservative organizational culture
- My company has inadequate internal resources
- My company's product development program is commercialization-oriented, rather than regulatory or R&D focused

## 13 43% Anticipate a Negative Impact on Product Time to Market

Perceptions about the impact of the US regulations on product design and development timelines varied according to respondents' job-level, functional area, and company size. However, there was consensus among all respondents that the regulations were unlikely to accelerate time to market.

**Exhibit 20: Impact of Regulations on Design & Development Timelines**

*Respondents from large companies, in senior management, and/or in R&D or QA were more likely than their counterparts to predict that the regulations would negatively impact (increase) time-to-market.*


**57% ----------ALL---------- 43%**

| | | |
|---|---|---|
| 72% | Small Co | 28% |
| 53% | Large Co. | 47% |
| 54% | R&D | 46% |
| 50% | QA | 50% |
| 71% | RA | 29% |
| 50% | VP/Dir | 50% |
| 64% | Mgr/Other | 36% |

While many respondents provided explanations for their perceptions about timeline impacts, several pointed out that the new US combination product regulations were more likely to have impact on life-cycle management, rather than new product launches.

**Exhibit 21: Rationales for Timeline Impact Perceptions**

| | |
|---|---|
| **REASONS FOR EXPECTING INCREASED TIMELINES** | ▪ Learning curves (especially for biopharma-focused companies)<br>▪ More/different types of internal efforts<br>▪ Increased documentation requirements |
| **REASONS FOR EXPECTING NO TIMELINE CHANGES** | ▪ Amount of effort not changing, just types of required documentation<br>▪ Company already prepared for changes introduced by regulations<br>▪ Additional resources will be made available to keep timelines on track with company business and financial commitments |

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## 40% of Combo Product Applications had Deficiencies related to the Constituent

While no respondents from small companies reported having submitted a marketing application for a new combination product to FDA since the 2013 release of the latest regulations, respondents from 10 of the 12 large companies did report at least one filing.

**Exhibit 22: Deficiencies in Combination Product Marketing Applications**

*Of the companies that submitted a combination product marketing application to FDA since 2013, a notable percentage received notification about a deficiency in the submission related to the secondary constituent.*


## 3 THINGS TO KNOW ABOUT SUBMITTING MARKETING APPLICATIONS FOR COMBINATION PRODUCTS IN THE EU

**① Currently, there is no formal definition for "combination medical product" in the EU-level regulatory framework.**

Officially, a medical product has to be classified as either a medicinal product (drug/biologic) or a medical device, and receive marketing authorization or CE-marking, respectively – and never both.
In practice, depending on the degree of physical integration of the medicinal and device components, the principal mode of action (PMOA), and the manufacturer's claims about use will be reviewed under some combination of the Medicinal Products Directive (MDP 2001/83/EC as amended by 2004/27/EC), the Medical Device the Active Implantable Medical Device Directive (AIMDD 90/385/EEC).

**② At present, there is no central decision-making body or process that standardizes which regulatory pathway should be used for a product that has both device and medicinal product components.**

- The Innovation Task Force (ITF) was established in 2006 as a multidisciplinary group of experts to ensure coordination across the European Medicines Agency (EMA), and provide a forum for early dialogue with applicants. The ITF is formally charged with providing advice around "borderline" products, among other areas of applicant – Agency engagement.
- The ITF holds brief meetings with applicants covering regulatory, technical and scientific issues arising from the development of innovative medicines, new technologies, and borderline products. These meetings are free of charge and are intended to facilitate the informal exchange of information and the provision of guidance early in the development process.

**③ The European Commission (EC) issued an updated Manual to provide some demarcation guidelines around "borderline" products. While this Manual provides demarcation guidelines for specific borderline product types, MEDDEV 2.1/3 from 2009 remains the primary guideline for understanding demarcation between medical devices and medicinal products.**

- Manual on Borderline and Classification in the Community Regulatory Framework for Medical Devices; ver 1.17 released 09/2015.
- Medical Device Guideline 2.1/3 v3: Borderline products, drug-delivery products and medical devices incorporating, as an integral part, an ancillary medicinal substance or an ancillary human blood derivative; issued 12/2009.

*Source: European Medicines Agency*

# ORGANIZATIONAL CHANGE: COMPANIES' ABILITY TO ADAPT TO A DIFFERENT WAY OF THINKING

**Reactive Organization**

*Focus is on the Primary Constituent; Secondary Constituent is an afterthought.*

**Proactive Organization**

*Primary and Secondary Constituents are co-developed with appropriate planning.*

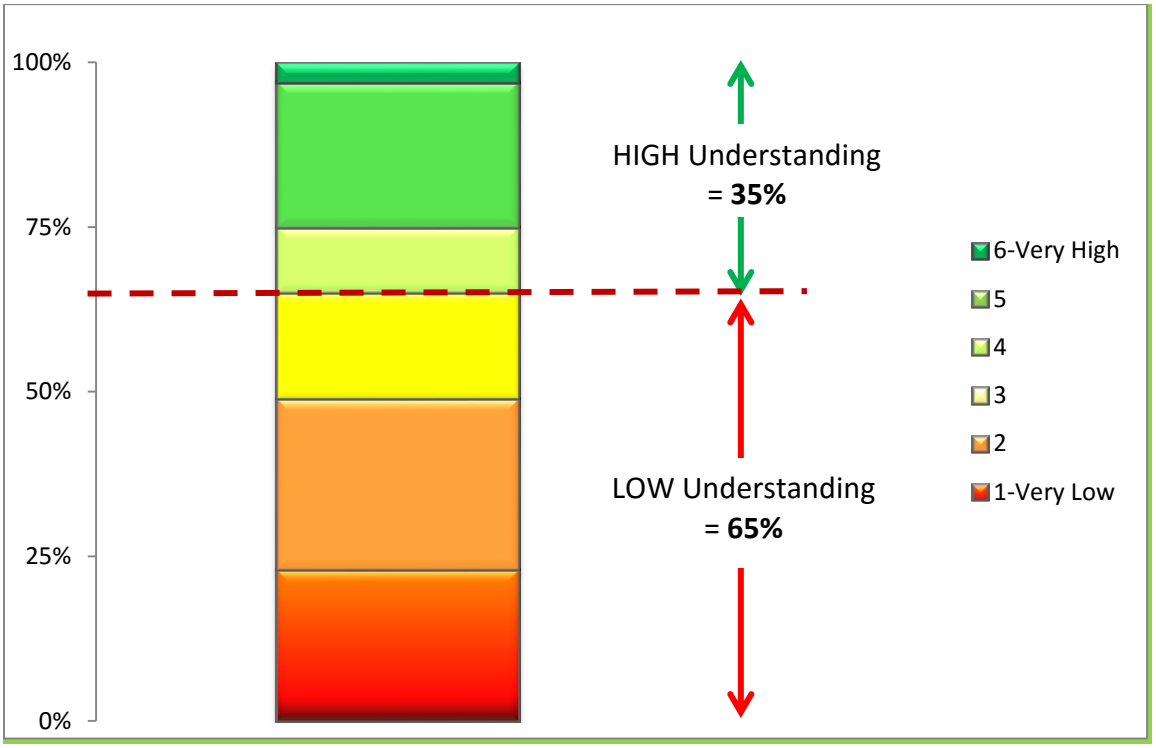
**SURVEY PARTICIPANTS WERE ASKED ABOUT THEIR PERCEPTIONS OF ORGANIZATIONAL CONDITIONS AT THEIR COMPANY TO DETERMINE IF THERE WERE ANY CHALLENGES OR FACTORS THAT MIGHT EMERGE AS CRITICALLY FUNDAMENTAL ACROSS THE INDUSTRY.**

15

## 65% Rated Senior Management Understanding of Combination Products as LOW

Neither job-level, company size, nor functional area emerged as a predictor of how respondents rated their leadership. However, despite the range of scores, a majority of the survey participants indicated that their senior leadership had a relatively poor understanding of the design and development process and requirements for combination products.

Exhibit 23: Perceptions of Senior Leadership Understanding of US Combination Product Regulations.



## 16 Top Challenges to Implementation of Combination Product Regulations

Participants' fell into three main categories: organizational (leadership, resources, talent, etc.), operational (procedures, systems, methodologies, etc.), and transactional (activities, documentation, etc.).

**Exhibit 24: Top Challenges Related to 21 CFR Part 4**


- Lack of awareness and understanding of combination products by Senior Management
- Lack of organizational education and experience on combination products (noted particularly for bio-pharm companies)
- Resource constraints


- Unproven compliance-assurance programs
- Inadequate QMS (especially for device constituent development and integration)


- Remediation of documentation for life-cycle (legacy) combination products
- Documentation and activities for off-the-shelf (OTS) constituents
- Human factor testing

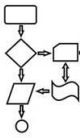
***WHEN ASKED IF THE TOP CHALLENGES ARE SHARED ACROSS ALL FUNCTIONAL AREAS*****…..**

- ***59%*** of respondents indicated their companies' top challenge *was shared* across functional areas,
- ***21%*** felt that the top challenge *was not* necessarily relevant to all functional areas, and
- ***20%*** weren't sure of the cross-functional implications.

## 17 Top 3 Best Practices for Success Identified

Only 64% of those surveyed were able to identify at least one best demonstrated practice. However, of those responses, three specific practices were most frequently cited:

**Exhibit 25: Best Demonstrated Practices for Combination Products**



**SIMPLE AND CLEAR STANDARD OPERATING PROCEDURES (SOP'S) AND WORKING PROCESSES**

**STAGE GATE REVIEWS AND OTHER FORMAL TOUCHPOINTS WITH MANAGEMENT DURING PRODUCT DEVELOPMENT**

**LEVERAGING MULTIPLE, EXPERIENCED VENDORS AND SERVICE PROVIDERS**

## CONCLUSIONS

We conducted this survey due to the growing applicability of these new combination product regulations in this rapidly emerging sector of the market. Several of our clients have requested information on how other companies are coping with these changes. This is our endeavor to provide insight into the challenges, practices and questions surrounding the combination product regulatory landscape, recognizing that the results reflect a specific point in time and reflect only the views of the survey participants.

There is no doubt that manufacturers are continually expanding their knowledge about combination product regulations, as evidence by the total number of requests for assistance submitted to the FDA OCP (650 in FY2014, an increase of 166% from FY2013)[6]. As industry gains more experience with the new and proposed FDA combination product regulations, some of the range of opinions provided within the context of this survey may decrease. However, due to the constantly evolving innovations that are developing in industry, e.g. nanotechnology, the regulations and guidance documents issued by the OCP will continue to be challenged. Despite these hurdles, technology will and must advance, and the FDA will continue to adjust to ensure proper processes and checkpoints are in place to protect the patients that will be the customer base for these products.

The Greek philosopher Heraclitus said "The only thing that is constant is change," and we fully expect those words to remain true for the combination product industry as it continues on the pathway of adopting and adapting to the regulations. EdgeOne Medical will continue to monitor the evolving regulations and practices closely and plan to update this survey in the future as more clarity is gained through experience and guidance policies.

***About EdgeOne Medical***

*EdgeOne Medical is a Combination Product device development consultancy and testing services firm that currently supports six of the 25 largest global Pharma and Biotech firms with the device constituent of their biologic-device or drug-device combination products. In addition, EdgeOne Medical supports many early-stage and emerging Pharma, Biotech and Medical Device firms with their device product development needs.*

*EdgeOne Medical is an ISO 13485 certified organization providing support to the medical device and combination product community via following core services:*

- *Verification & Validation Testing*
- *Quality System Support and Representation*
- *Regulatory Strategy and Submission (US/EU)*
- *Technical Project Management*

*Download this report, learn more and stay current @ [www.edgeonemedical.com/cp2016](www.edgeonemedical.com/cp2016)*

[6] FDA Office of Combination Products FY 2014 Performance Report

## ACKNOWLEDGEMENTS

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