



# COMBINATION PRODUCTS

## Inspection Readiness and Outcomes

Many companies think that because they have a good relationship with the FDA Center they interacted with during their submission reviews that this rapport will translate to a successful inspection. However, there is limited communication between the FDA Centers and the Field Offices who handle inspections. When preparing for an inspection – whether pre- or post-market – it is best to assume that the field investigator has no previous knowledge of what has transpired between your company and the FDA reviewers.

Currently, there is no combination product inspection model that would allow for consistency during an inspection, like the QSIT model for medical devices. However with FDA's Program Alignment Initiative (2017), the Office of Regulatory Affairs (ORA) hopes to establish a product-based versus management-based regulatory program across the various offices to enable staff and programs to work in a complementary fashion. The FDA's goals are to optimize the coordination and efficiency of the work performed between all FDA centers, directorates and the ORA, to strengthen accountability and to reduce duplication. Additionally, this new structure will align staff to work more closely with FDA scientific and technical experts on complex, scientific, manufacturing and other regulatory challenges.<sup>1</sup>

Although this paper focuses on combination products and FDA inspections and outcomes, the philosophy of preparing and managing a successful inspection is the same whether the manufacturer is focused on pharmaceuticals, medical devices or combination products.



### PREPARATION

In preparing for an inspection, there are several areas that an organization should focus on. One is the product portfolio and where various manufacturing activities occur. This data is presented to FDA during the opening meeting. However, with combination products, not all sites may be manufacturing or conducting R&D activities associated with a combination product. It is therefore important to outline where combination product activities are occurring. This would include design control, manufacturing and the subsequent packaging and distribution activities. The various GMP-related processes need to be documented within the Quality Manual. Additionally, those GMP functions that are excluded, such as installation and/or special testing requirements, should also be documented within the Quality Manual so it is clear who is responsible for what GMP activity.

<sup>1</sup> [www.fda.gov/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ucm549087.htm](http://www.fda.gov/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ucm549087.htm)





Another key consideration is the contract manufacturers. Many manufacturing companies use these facilities to “combine” the drug with the device. If the contract manufacturers comply with 21 CFR Parts 210 and 211, it is essential that their Quality Manual and SOPs also include the applicable 21 CFR Part 820 requirements. The same would apply to a medical device manufacturer that is compliant with 21 CFR Part 820; it would need to include those additional 21 CFR Part 210 and 211 requirements applicable to its manufacturing activities.

Finally, personnel who are critical to establishing and sustaining a compliant quality program are many times overlooked when preparing for an inspection. It is imperative that individuals involved in critical GMP activities associated with combination products have the background and training to support the 21 CFR Part 4 combination product requirements. When preparing for the inspection, the organizational chart needs to be reviewed and those key GMP functions highlighted. As part of that preparation, job descriptions and training records need to be assessed to ensure that those personnel meet the job qualifications. This would include any subject matter experts (SMEs). The job descriptions should have the applicable 21 CFR Part 210 and 211 as well as 21 CFR Part 820 requirements included, as well as the associated combination product GMP training highlighted in the training matrix.

The personnel who conduct the company's internal or external audits are an example to highlight why qualifications and training are important. These

individuals would be expected to be qualified to adequately conduct combination product audits. Although FDA cannot review the audit reports themselves, it can review the qualifications of the people conducting those audits. For example, an auditor who has only taken a class on 21 CFR Part 4 may not understand the various GMP intricacies and therefore when auditing may not be looking at the documentation with the right optics. To address this gap, a number of companies are using consultants to supplement the lack of Part 4 expertise. Their internal auditors then shadow the consultants as part of their training to gain this working knowledge.

## FDA INSPECTION RESULTS

In 2017, as a follow-up to a 2015 survey, NSF International conducted a client survey to determine if industry saw any changes in FDA's approach to combination product inspections versus medical or pharmaceutical device-only inspection. The first survey received 20 responses, while the 2017 survey had 55 responses. Individuals who provided input to the 2017 survey represented a cross-section of not only quality and regulatory professionals, but also original equipment manufacturers (OEMs), contract manufacturers (CMs) and component suppliers (questions 1 and 2).



Two survey questions provided some insight into the current state of combination product inspections. Question 6 determined that 71 percent of the 34 respondents had undergone a 21 CFR Part 4 inspection within the past several years. This data was different from the original survey in 2015, where 90 percent of the participants had been through a 21 CFR Part 4 inspection (sample size 10). The difference could possibly be attributed to the number of companies which realized that they had combination products and not a change in the frequency of FDA inspections.

Question 8 addressed the duration of the audit. Unfortunately, there were only 11 responses out of 55 participants. Of those responses, most inspections were a week long, with only one site having a two-day inspection. Thus it is important to note that

combination products do not incur longer inspection times than medical device or pharmaceutical products.

Overall, there have been few regulatory actions since the ruling became effective in 2013. The survey showed that over the past four years, there were no actual trends specific to combination product inspections. These results may have been due to the fact that the ruling did not necessitate new GMP requirements but clarified the existing applicable ones. In addition, companies understood FDA's expectations and what was required to be 21 CFR Part 4 compliant. Finally, it reinforces the thinking that proper planning for any type of FDA inspection and having a solid understanding of your products tends to yield a successful FDA inspection outcome.

The next section details the specific questions and answers in the survey.

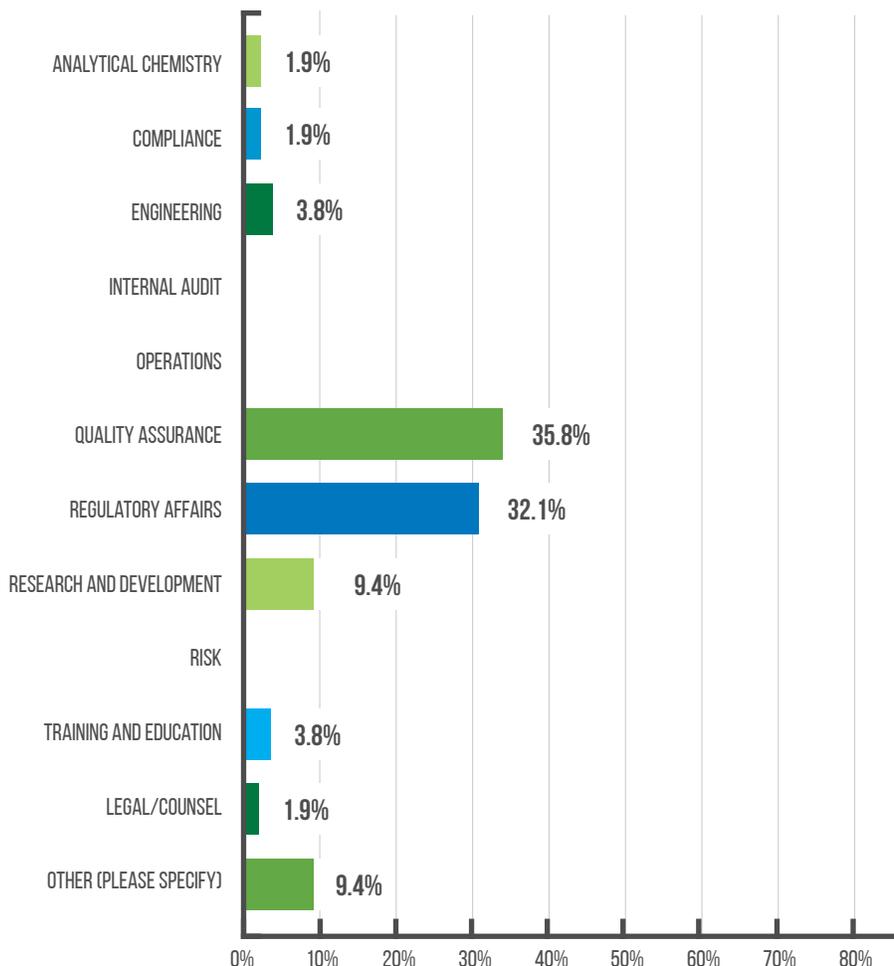
## 2017 NSF INTERNATIONAL COMBINATION PRODUCTS WORKSHOP SURVEY RESULTS

### QUESTION 1: RESPONDENT FUNCTION

Which of the following best describes your function at your company or organization?

Top three functional responsibility areas:

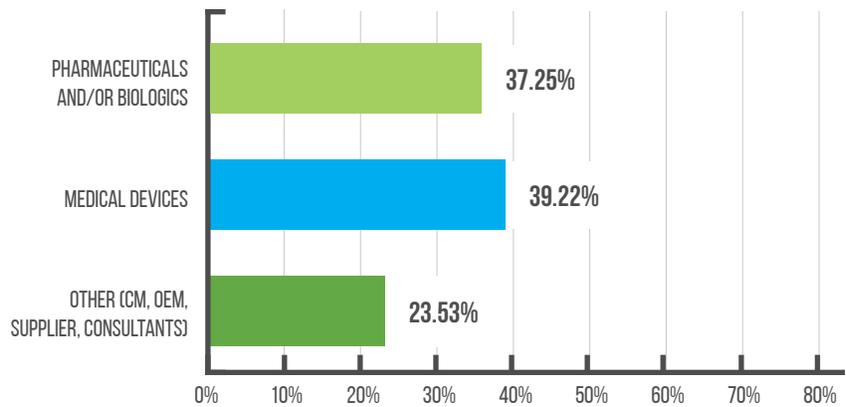
- > Quality assurance: 36%
- > Regulatory affairs: 32%
- > R&D: 9%



## QUESTION 2: PRODUCT TYPE

Select the product that your company primarily manufactures.

Survey responders: 55

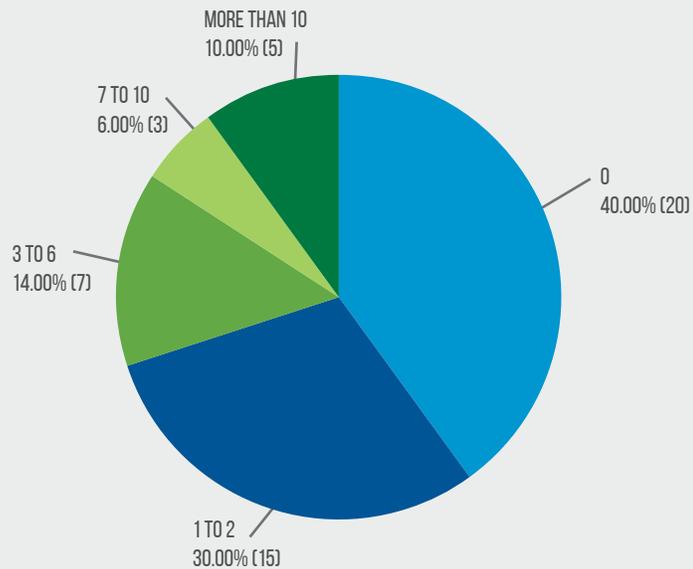


## QUESTION 3: NUMBER OF COMBINATION PRODUCTS

How many types of combination products does your company manufacture?

Out of 50 responses:

- > 15 companies (30%) produced one or two types.
- > 7 companies (14%) produced three to six types.
- > 5 companies (10%) produced more than 10 types.

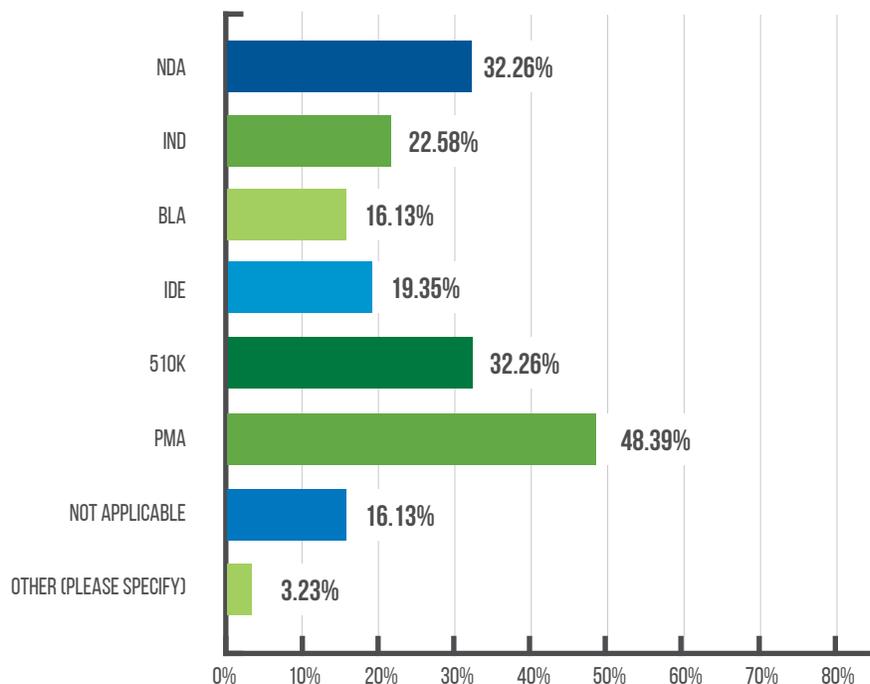


## QUESTION 4: PREMARKET REGULATORY PATHWAY

Which premarket regulatory pathway is associated with your combination product?

Top three pathways:

- > PMA: 48%
- > 510K: 32%
- > NDA: 32%

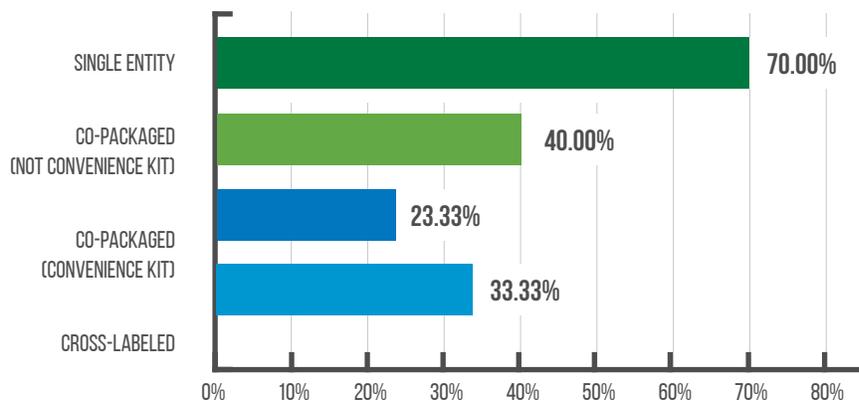


## QUESTION 5: TYPE OF COMBINATION PRODUCT

Are the combination products your manufacture considered (select all that apply)?

30 respondents (with multiple products) reported:

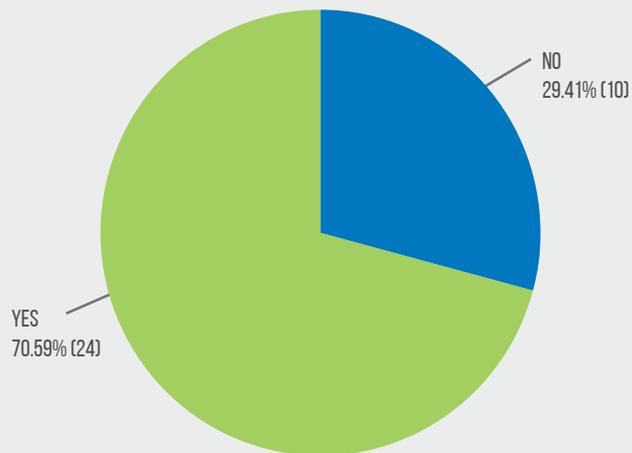
- > 21 single entity
- > 12 co-packaged (not convenience kit)
- > 10 cross-labeled
- > 7 co-packaged (convenience kit)



## QUESTION 6: FDA INSPECTIONS

Has the facility/facilities where your combination products are manufactured been inspected by FDA?

- > 24 of the 34 responders (71%) had been audited by FDA.

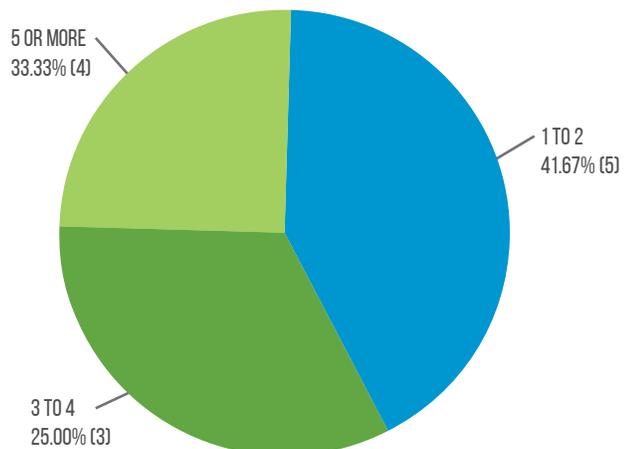


## QUESTION 7: NUMBER OF INSPECTIONS/ TIME FRAME

Indicate the number of inspections your facilities have had and the time frame.

Of the 12 respondents:

- > Five FDA inspections were conducted in 2016 and three in 2015. The rest were prior to the 21 CFR Part 4 ruling being effective.
- > Most respondents (42%) had one or two inspections.



## QUESTION 8: FACILITY LOCATION / INSPECTION DURATION

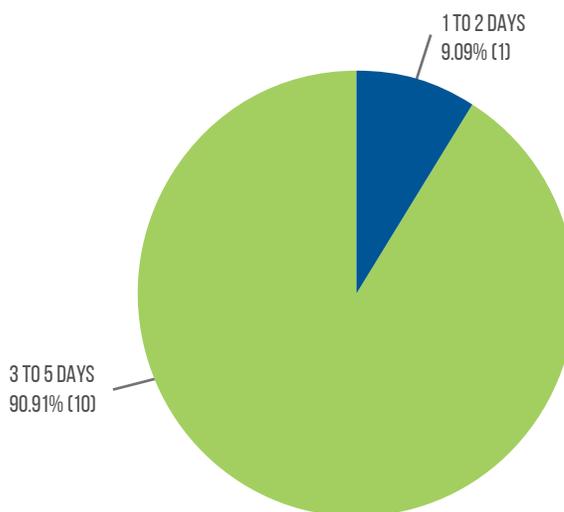
**Where were the facilities located and how long was the inspection?**

Location of sites audited:

- > U.S.: 8 sites (including Puerto Rico)
- > Germany: 3 sites
- > Costa Rica, UK, Mexico, Ireland, Denmark and Sweden: 1 site each

Duration:

- > 10 inspections lasted three to five days.
- > Only one site had a one-to-two-day inspection.



## QUESTION 9: FDA BRANCH, INSPECTION TYPE AND INSPECTOR EXPERIENCE

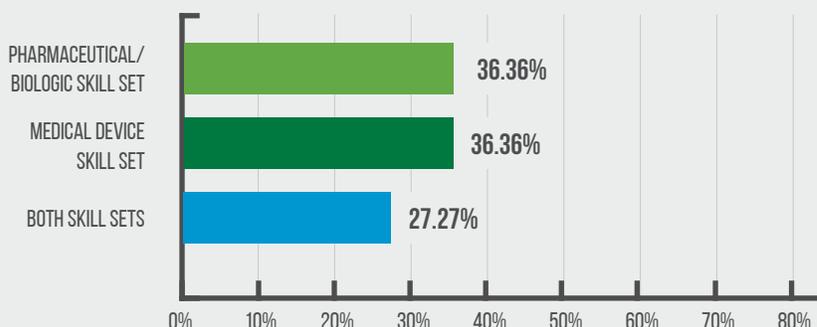
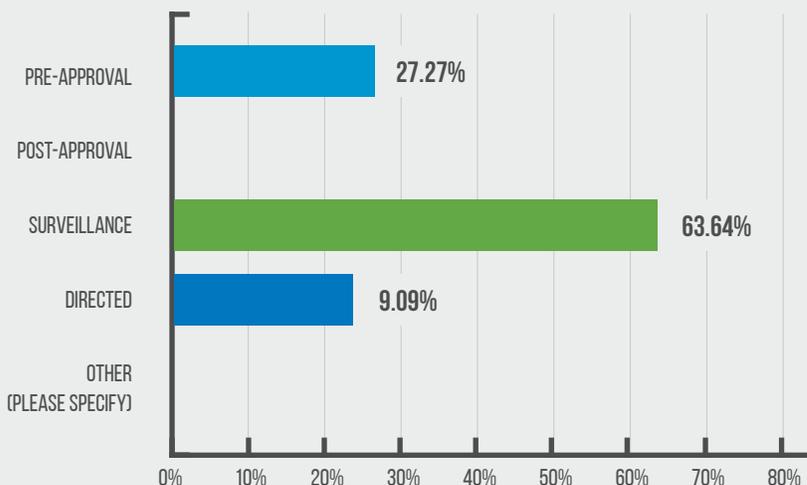
**Which FDA branch directed the inspection? What type of inspection was it and what was the expertise of the inspectors?**

FDA branch and type of inspection:

- > Half of the inspections were directed by CDER and half were CDRH.
- > 73% were post-market.
  - 64% were a surveillance inspection.
  - 9% had a directed inspection.
- > 27% were pre-approval.

Inspector technical experience:

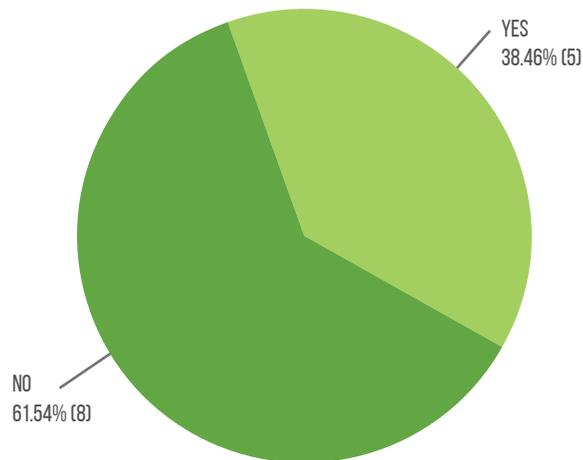
- > 75% had either pharma/biologic or medical device experience.
- > 25% had experience in both.



## QUESTION 10: FDA FORM 483

Did you receive an FDA Form 483 with observations associated with 21 CFR Part 4? If so, what subsystem was deficient? Did you receive any additional regulatory actions?

- > Most sites (62%) did not receive 483 observations related to Part 4 compliance.
- > One site that did receive a 483 had observations for reserve samples and release of components (medical device company).
- > **No warning letters were issued.**



### ABOUT THE AUTHOR

Mary C. Getz, Ph.D., is Vice President, Medical Device Quality Systems and Compliance at NSF International. She has over 25 years of industry experience, including extensive expertise in developing quality, compliance and regulatory affairs strategies and solutions. She also has hands-on experience with IVDs, 510(k) and PMA medical devices, as well as OTC and NDA pharmaceuticals. For more information, contact [medicaldevices@nsf.org](mailto:medicaldevices@nsf.org) or **+1 202.822.1850**.

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