The Regulatory Watchcat

REVIEW

FDA Impact on U.S. Medical Technology Innovation:

A Survey of Over 100 Medical Technology Companies (November 2010)

Work in Progress, May 31, 2021

Foreword

This is another project I've had enough of for awhile, so once gain I'll share what I've done so far as a work in progress.

The report's reference to "FDA dependent/related" costs associated with 510(k)s and PMAs is what originally caught my eye. Apart from the cited average costs being way too high, this is the closest I've ever seen anyone come to admitting out loud that they would happily inflict their medical device on patients without spending a dime to assure its clinical safety or effectiveness, if only FDA would be more "reasonable."

I haven't really spent that much time on this one. But as Einstein so charmingly observed, our perception of time is relative. Reading this thing is like kissing a hot stove. At this point, I have mostly begun to determine which basic elements of a study and a study report it did and did not include. Didn't even get as far as the main results, with one "interesting" exception.

The best thing I can say about the report is that it seemed to have no impact on Congress, FDA, or the Institute of Medicine. (Or, given how that little saga played out, maybe it did, just not of the kind that the authors were hoping for.) Otherwise, it struck me as a textbook example of what happens when people pursue something they are not at all qualified to do, making it sadly analogous to many "innovative" medical device startups.

What I can say bad about it, I hardly know where to start. This was not a "study." No study design. No explicitly defined research question. A laundry list of objectives, none clearly tied to a potential research question. No "sample," just a group of people who decided to answer some questions. Skimpy description of the methodology. Data that can't be generalized beyond the respondents. Failure to describe the survey instrument allowed for selective reporting. So badly organized, I started a list of all the information that was reported in the wrong section of the report, just to help me sort out the confusion. So many unsubstantiated claims, I started a list of those, too.

Then I got to the part where the authors argued that, if we would just "consider" the companies profiled in an Ernst & Young market research report to be their target population, then somehow they had "sampled" 20% of…the entire US medtech industry or maybe just "U.S. medtech industry innovators," hard to say.

At that point, I knew it was time to take a long break..

If you have any idea how to write a study report or any basic understanding of survey methodology, read it and weep. Or laugh. Or maybe just run screaming off a cliff. Your call.

The report can still be found here:

https://www.advamed.org/sites/default/files/resource/30_10_11_10_2010_Study_CAgenda_makowerreportfinal.pdf

The Research Question

Good research has the characteristic that its purpose is to address a single clear and explicit research question. The end product of a study that aims to answer a number of diverse questions is often weak. Weakest of all, however, are those studies that have no research question at all…

When reporting survey research, it is essential that a number of key points are covered:
1) Explain the purpose or aim of the research, with an explicit identification of the research question.

Kelley K, Clark B, Brown V, Sitzia J. Good practice in the conduct and reporting of survey research. Int J Qual Health Care. 2003 Jun;15(3):261-6.

The report does not identify a research question. The closest it comes to addressing a research question is in the first paragraph of the Background section, which alludes to not one, but four potential research questions:

1. *Is FDA becoming less predictable, transparent, and reasonable?*
2. *Do FDA's requirements for demonstrating the safety and effectiveness of new devices continue to increase?*
3. *Does CDRH's current approach toward device regulation effectively balance protecting and promoting the public health?*
4. *Has CDRH become so cautious that its policies are denying patients timely access to the latest technologies and negatively affecting innovation in the industry?*

Study Objectives

…the study objective is an active statement about how the study is going to answer the specific research question. Objectives can (and often do) state exactly which outcome measures are going to be used within their statements. They are important because they not only help guide the development of the protocol and design of study but also play a role in sample size calculations and determining the power of the study.

Farrugia P, Petrisor BA, Farrokhyar F, Bhandari M. Practical tips for surgical research: Research questions, hypotheses and objectives. Can J Surg. 2010;53(4):278-281.

The report has no section dedicated to study objectives. This seems to have left the authors free to establish objectives as they went along, and they seem to have taken full advantage of the opportunity. I am now up to nine and potentially still counting, including two that were not identified until the authors wrote the Executive Summary,:

1. *To gather quantitative and qualitative data from a representative subset of medtech companies to elucidate the impact of the FDA's current regulatory practices on medical technology innovation and the advancement of public health so that Congress, the FDA, and the IOM would have more information to consider in their evaluations. (Background, p. 15)*
2. *To obtain a more systematic understanding of the perceptions and experiences of medtech companies in dealing with the FDA. (Methodology, p. 16)*
3. *To collect information from medtech industry executives about the how U.S. and European premarket regulatory processes compare. (Methodology, p. 16)*

4. *To collect information from medtech industry executives about the cost and time to navigate the U.S. premarket regulatory processes. (Methodology, p. 16)*
5. *To collect information from medtech industry executives about what aspects of the U.S. premarket regulatory processes are most challenging to innovators. (Methodology, p. 16)*
6. *To quantify the time it takes for a new product to navigate the entire regulatory process (Results, p. 21)*
7. *To shed light on where the greatest problems exist. (Discussion, p. 33).*
8. *To address the need for data that could be used to evaluate the impact of U.S. medical device regulation on innovation and patients. (Executive Summary, p. 5)*
9. *To identify where the greatest deterrents to innovation exist within U.S. premarket regulatory processes and the costs (in time and dollars) these issues place on U.S. medtech companies. (Executive Summary, p. 5)*

The authors reported that they used the results "to help determine if concerns about the efficiency of current U.S. regulatory processes were isolated or widespread across the medical technology ("medtech") industry." (Discussion, p. 33) They may have tried to use the results for this purpose, but they could not, because the results were not suited for that purpose. All protestations to the contrary, the authors failed to sample the medical technology ("medtech") industry or any other population to which their results could be generalized.

The survey measured only the concerns of 203 individuals who, for whatever reasons, choose to respond to the survey. They were not "sampled."

In addition, although the authors described these individuals as "medtech industry executives," they did not define "medtech," nor did they describe any methodology by which they confirmed that respondents were in the medtech industry, even though all three of the organizations from which respondents were drawn may well include members who are not in the "medtech" industry:

1. The trade association keeps its Active members confidential, but it lists Associate and Allied members that might or might not be considered part of the "medtech" industry.
2. The members of the investor association invest in a wide range of industries, not just "medtech."
3. The membership of many state trade associations includes companies in the pharmaceutical, biotechnology, and other life science industries in addition to "medtech."

The report also did not describe any methodology by which the corporate positions of the respondents were verified.

Methodology

Survey Design

Although the authors reported that they "designed a survey" (p. 16), no survey design is described in the Methodology section or elsewhere in the report. It seems that they equated developing a survey instrument with designing a survey, as the report describes the "survey" that they designed in terms of the topics addressed in the survey instrument (see below).

Survey Instrument

> *The survey instrument or questionnaire used in the research should be described fully…*
> *Authors should provide sufficient detail for reviewers to be able to discern that the items and response options are congruent and appropriate for the variables being measured.*
> Draugalis JR, Coons SJ, Plaza CM. Best practices for survey research reports: a synopsis for authors and reviewers. Am J Pharm Educ. 2008 Feb 15;72(1):11.
>
> *… survey methods [should] be fully disclosed and reported in sufficient detail to permit replication by another researcher*.
> Best practices for survey research. American Association of Public Opinion Research.

The report provides virtually no information about the survey instrument. It describes its scope very briefly and only in broad terms:

1) how U.S. and European premarket regulatory processes compare,

2) the cost and time to navigate the U.S. premarket regulatory processes, and

3) what aspects of the U.S. premarket regulatory processes are most challenging to innovators.

Because the report fails to identify the details of the survey instrument, it is impossible to evaluate the questions for clarity or bias, or to replicate the results. This omission also makes it possible to selectively report the resuls. Somewhat ironic, given that the survey attempts to assess transparency.

Target Population

> *The target population is the entire population, or group, that a researcher is interested in researching and analysing. A sampling frame is then drawn from this target population.*
> Market research glossary, DJS Research Ltd. https://www.djsresearch.co.uk/glossary/

The authors identify their target population as "U.S. medtech innovators," (Methodology, p 16), which they describe as "product-driven medical device manufacturers actively working on bringing innovative new medical technologies to market (i.e., those smaller companies that represent the medtech innovation engine)."

They further describe 1,023 companies that were profiled in an Ernst & Young market research survey as "the types of companies" that their survey "was designed to reach." They did not describe this design in their report, nor did they describe any methods that were followed in an effort to sample that population. Instead, their methodology was "designed" to recruit respondents from companies that were members of specific organizations the authors invited to participate in the survey.

The only data the authors provide that related the participants in their survey to the companies profiled in the Ernst & Young survey were that over 50% of both groups were located in California, Minnesota, and Massachusetts and that two of the three largest specialties in the two groups were cardiovascular and orthopedics. The third largest specialties were general and plastic surgery for their survey and "non-disease specific" for the Ernst & Young survey.

Sampling

A survey's intent is not to describe the particular individuals who, by chance, are part of the sample, but rather to obtain a composite profile of the population. In surveys using a probability-based sample, the sample is not selected haphazardly or only from persons who volunteer to participate.
Draugalis JR, Coons SJ, Plaza CM. Best practices for survey research reports: a synopsis for authors and reviewers. Am J Pharm Educ. 2008 Feb 15;72(1):11.

No sampling plan is described in the report. Instead of a plan to select a sample from one or more sampling frames that are part of the target population, the Methodology described the authors' efforts to recruit respondents.

Sampling Frames

A sampling frame is a database of potential respondents that can be invited to take part in a given research project.. Sampling error reflects the difference between results derived from a sampling frame and the value that would be obtained if the entire target population were surveyed.

Market research glossary, DJS Research Ltd. https://www.djsresearch.co.uk/glossary/

The 260 members of a large trade association, the 750 companies in the portfolios of the members of an investors association, and an unreported number of companies that were members of an unreported number of state trade associations might have been used as sampling frames, but that would have been problemmatic. As noted previously, it seems likely that these sampling frames included some number of companies that were not in the "medtech" industry. Had the authors used these frames for sampling without some method to assure that all the respondents were at companies in the medtech industry, the survey results could not have been generalized to their target population, anyway. However, since they didn't sample respondents from these frames, but left them to self-select, the point is moot.

Participant Recruitment

The authors attempted to recruit participants by inviting the members of a large medical device trade association, an association for investors, and an unidentified group of state trade associations to participate in the survey.

Data Collection

The report indicates that participants could respond in-person, by telephone; or via a web-based form.

- It describes the interaction by telephone as an "interview."
- It describes the web-based form as having a "slightly smaller" subset of the "most relevant" survey questions.
- It did not identify the most relevant survey questions, nor did it report the number of "most relevant" questions or the number of questions in the "slightly smaller" subset of those questions.

Pooling

The authors pooled the data from all respondents without providing a pooling justification. It is therefore impossible to know the extent to which the pooled results might be representative of any of the three groups that were given an opportunity to participate, much less their target population. The average results obtained from each the three groups might different substantially from the pooled averages presented in the report.

Results

Response Rates

Although the literature does not reflect agreement on a minimum acceptable response rate, there is general consensus that at least half of the sample should have completed the survey instrument.
Kelley K, Clark B, Brown V, Sitzia J. Good practice in the conduct and reporting of survey research. Int J Qual Health Care. 2003 Jun;15(3):261-6.

A response rate was reported separately for each of two associations that were invited to participate in the survey:

- A 31% response rate for the members of the large trade association was calculated as 80 respondents out of it 260 members.
- A 17% response rate for members of the investor association was calculated as 131 respondents out of the 750 companies in the investment portfolios of its members.
- No response rate was calculated based on the 20 responses received by companies that were members of state trade associations.

The authors suggested that, if the 1,023 companies that were profiled in the Ernst & Young survey were "considered to be" the target population for their own survey, it could be concluded that approximately 20 percent of "U.S. medtech industry innovators" had responded to their survey. This interpretation seems inconsistent with other information in the report:

- FDA cleared "approximately 3,000" 510(k)s in 2009 alone,
- The "U.S. medtech industry innovators" that responded to their survey reported that it took them an average of 20 months just for prototype production and proof of concept for a 510(k) device.
- The vast majority of the companies in the survey were focused on a single product family
- The 1,023 companies profiled by Ernst & Young represent the medtech innovation engine, while only "a minority" of the remaining 3,750 companies that registered with FDA as manufacturers file premarket applications in a given year.

The survey results indicate that the average 510(k) device is in development for over 2½ years. In that case, it seems that no more than a third of the smaller companies that represent the medtech innovation engine are likely to have a 510(k) cleared in any given year. If at least half of the cleared 510(k)s were submitted by the "smaller companies that represent the medtech innovation engine," it would seem more reasonable to assume that the total population of "U.S. medtech industry innovators" is closer to 5,000 companies than 1,000 companies. This would have resulted in a lower response rate, but given that the accepted standard for a viable response rate is at least 50%, it's not clear that this matters.

Selection Bias

Because the authors left it to the members of the two populations to determine who among them responded and who did not, the results of this study are subject to self-selection bias. Unless data are provided to confirm that the respondents were representative of the groups from which they were sampled, the results cannot be generalized to other members of the same group. However, as described above, the groups from which they were recruited are unlikely to be representative of "medtech" industry, so that point is probably moot. The respondents are just that…respondents. They were not sampled from a population, only recruited to respond to a survey. Consequently, the results of the study are applicable only to them.

Respondents

Since the authors didn't provide any details about their survey instrument, how much data they collected on the survey respondents is unknown. Given the authors' apparently strong interest in affirming the notion that the respondents of their survey were somehow reprentative of "U.S. medtech industry innovators," it is suprising that they reported so little data about the respondents.

Number The report describes the results of the authors' sampling efforts in the Methodology section, instead of the Results section. They eliminated duplicate entries and did not "permit" some companies to submit more than one response. They provided no justification for limiting responses to one per company. They identified the criteria that they used in allowing a small number of companies to submit more than one response, but provided no justification for these criteria.

The report indicated that the authors' recruitment efforts resulted in 204 participants, and that these participants provided their experiences with 213 "unique" products. The Methodology section did not describe the criteria that were applied to determine if a device was "unique," nor any procedure that was followed to confirm that the 213 devices met these criteria.

Characteristics

- 90% of the respondents were private companies and 10% were publicly held.
- Over 50% of the respondents were located in California, Massachusetts, or Minnesota.

  This seems like an odd statistic to report. The authors did not report the percentage that were located in each of these three states, or the percentage located in other states or outside the US. They did not identify any other states or countries in which respondents were located. If the survey collected data on geographic location, why were the rest of the data not reported? If the survey didn't collect data on geographic location, the report should have identified the source of this one statistic.

  Based on this limited information, it seems that at least one company (0.5%) must have been located in each of the three identified states, while 50-99% could have been located in only one of these states. It is also possible 100% of the respondents were located in just these three states.
- "The majority" were "considered" small companies. The authors reported the median size of…either all respondents or only those that were venture-backed, hard to say. They did not report the number or percentage of the companies that were small, mid-sized or large. As with the data on geographic data, if these data were available, they should have been reported in full or the source identifed.
- "The majority" were venture-backed. The authors did not report the number or percentage of companies that were venture backed or the number or percentage that were funded by other sources. Again, why not?
- "The vast majority" were early-stage entities. Again, if they had solid data on investment stages, why didn't they report them? If they did not, how did they know that "the vast majority" were early-stage entities?

"Average Cost of a 510(k)"

I skipped forward to this one, because the amount that the authors cite struck me as wildly off the mark. Nonetheless, I was open to the possibility that the 204 companies that responded actually spent an average of $31 million per 510(k) and that the investors who picked up the tab actually invested $31 million in "U.S. medtech industry innovators" that were developing the "average" 510(k) device. Had that been all the authors had claimed, I might have thought smugly, "just desserts," and not even bothered to review this report.

But *n-o-o-o-o*. That wasn't all the authors claimed.

In spite of their failure to design a survey so that the results could be generalized beyond the participants, they just had to claim their survey showed that "the average cost of taking a product through 510(k) clearance is $31 million (p. 37)." Big mistake.

This figure is predicated on the nonsensical assumption that the "average" 510(k) device goes through all six of the product development stages identified in the report. But virtually no 510(k) devices go through these six stages. On the contrary, virtually all 510(k) devices go through only three of the stages. Oops.

But no worries. As it turns out, it is pretty easy to calculate a much more realistic average cost of a 510(k) based on the data provided by their participants and a little bit of information from FDA's 510(k) database.

The authors estimated that FDA cleared approximately 3,000 510(k)s in 2009. CDRH's database identifies 35 as having been supported by a clinical trial. These 35 companies would have completed all six development stages, while the (still) "approximately 3,000" would have completed only three.

The authors reported the average cost of completing each stage: Well, sort of. They didn't report any actual numbers, just presented the results in a pretty bar graph. But, as a guy I used to know would say, close enough for government work. And for U.S. medtech industry innovator work, too, I gather.

The approximately 3,000 510(k)s not supported by a clinical trial would have borne the costs associated with three product development stages, for a total of $11,900,000. But what the heck, let's go with $12 million and call it even.

Product Development Stages	**Total $**
Concept Development and Proof of Concept	3,500,000
Clinical Unit Development	3,000,000
510(k)	5,400,000
Total Cost for a Non-Clinical 510(k)	**$11,900,000**

The costs of the other three stages (IDE, safety/feasibility study, pivotal trial) would have been borne only by the developers of the 35 510(k)s that were supported by a clinical trial. On the 35 supported by a trial would have borne the cost of all six development stages, which the authors estimate at a total of $31 million:

3,000 x $12,000,000 =	36.000,000,000
35 x $31,000,000 =	1,085,000,000
	$37, 085,000,000
	÷ 3,000
Average cost through 510(k) clearance =	**$12,361,667**

Since I will be posting this on LinkedIn, I expect someone will tell me if I'm wrong. Basic arithmetic has never been my strong suit, so that is entirely possible. But I'm pretty sure I'm not wrong when I say that this figure is far more realistic than the average cost of $31 million that the authors claimed in their report.