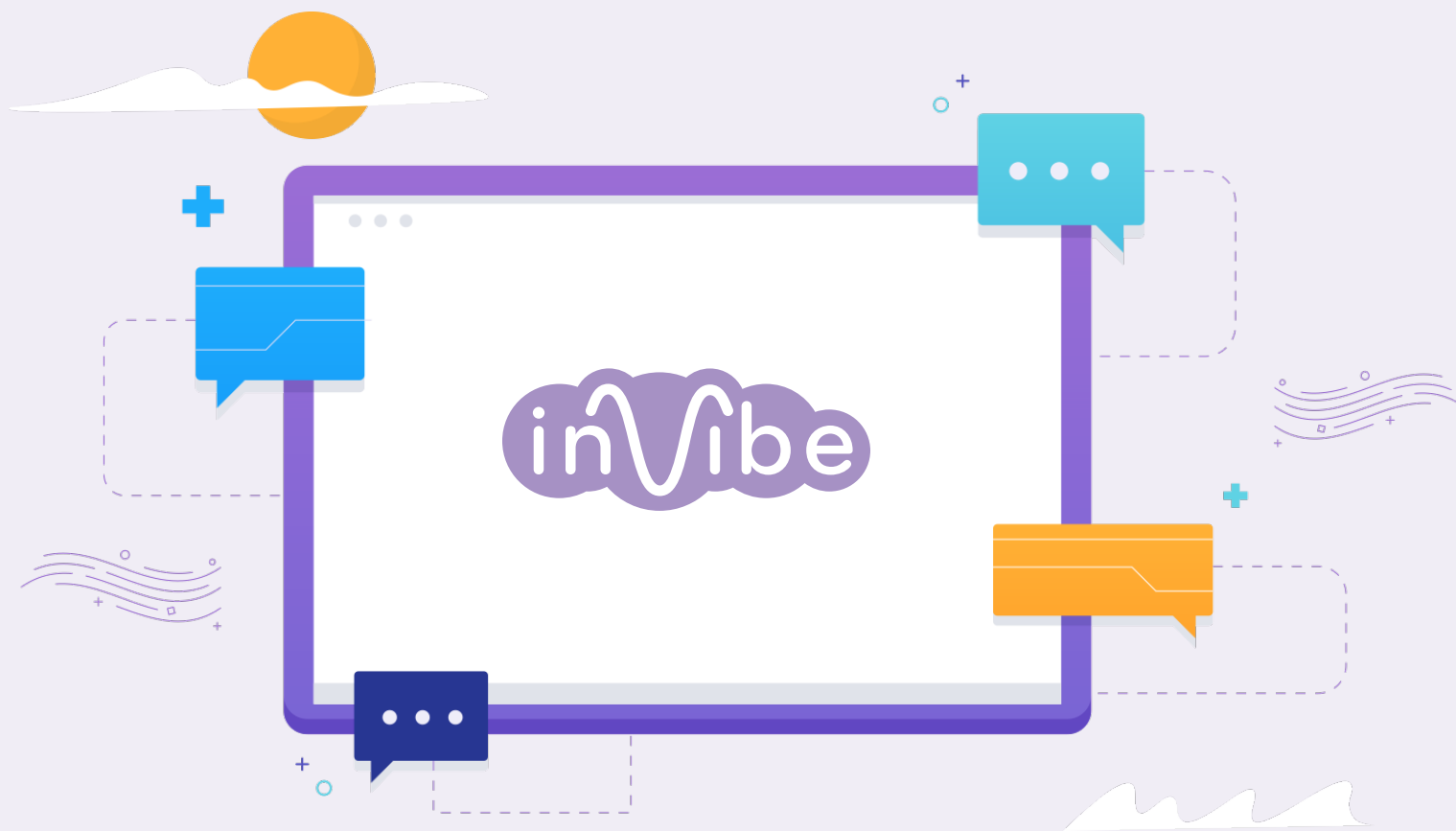


US Hospital Pharmacists' Current Perceptions and Utilization of Biosimilar Products and their Corresponding Innovator Brands

A Qualitative Case Study Utilizing an Automated Voice-Response Research Platform in a Topical Subject Area



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Research Background

The Biologics Price Competition and Innovation Act (BPCIA) was formally signed into law in March 2010 as part of President Obama's Patient Protection and Affordable Care Act. It created a clear, abbreviated approval pathway for US biosimilar products. A biosimilar's approval under this pathway signifies that it is highly similar to the originator's brand and with no meaningful clinical differences, including in indications outside of the biosimilar product's confirmatory clinical trial.

Prior to the BPCIA, follow-on biologics were subject to the traditional Biologics License Application (BLA) approval process. Granix® (Teva's tbo-filgrastim), for example, was studied for reducing neutropenia in non-myeloid malignancy patients receiving myelosuppressive chemotherapy and was granted BLA approval for this one limited indication. As a result, Granix and BLA-approved biologicals, including several somatropins and insulin glargines, are not considered true biosimilars.

The promise of biosimilars in the US has been slow to develop. Prior to last year, the FDA had approved only four biosimilars; however, in 2017 an additional five biosimilars gained approval status. Still, largely due to patent litigation, only three biosimilars, listed in the Table below, have reached the US marketplace.

Biosimilars Currently Marketed in the US

Originator Product	Biosimilar	Biosimilar Launch	Therapeutic Areas
Neupogen® [Amgen's filgrastim]	Zarxio® [Sandoz' filgrastim-sndz]	March 2015	Neutropenia associated with chemotherapy, bone marrow transplant, and chronic conditions; cell mobilization for autologous stem cell transplant
Remicade® [Johnson & Johnson's infliximab]	Inflectra® [Celltrion/ Hospira's (Pfizer) infliximab-dyyb]	April 2016	Rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis, psoriasis
	Renflexis™ [Samsung Bioepis/ Merck's infliximab-abda]	April 2017	

Additional biosimilar launches are expected soon, and at least five more biosimilars currently are undergoing FDA review prior to possible marketing approval. After initial excitement followed by almost a decade of delayed promise, the topic of biosimilars is hot again.

Research Approach

More so than physicians, nurses, or payers, hospital pharmacists are closest to issues related to biosimilars and can provide a broad perspective on this subject. In February 2018, inVibe fielded an open-ended, eight-question survey to 12 Hospital Pharmacy Directors and Associate Directors responsible for making formulary recommendations, including purchasing, acquiring, and dispensing biosimilars. The screener and survey were written in one day, and were fielded immediately with full results subsequently returned within 48 hours. The specific study objective was:

To understand how hospital pharmacists currently perceive and utilize biosimilars in comparison to the originators' corresponding biological products.

inVibe Research Methodology

Qualified pharmacists were sent a text message to their mobile phone, which provided a link to the background of the research and a preview of the eight open-ended questions. Upon reviewing the information, a simple 'tap' on their phone enabled them to call in to inVibe's secure, automated interview phone line, where they listened to a recording and answered each question simply by speaking. Upon completing the survey, the audio files were validated,* transcribed, and analyzed.

The following whitepaper sections provide Hospital Pharmacy Directors' and Associate Directors' understanding and perceptions of US biosimilars.

*The validation process included monitoring for adverse events and personally identifiable information.



SURVEY RESULTS: Hospital Evaluation of Biosimilars

The normal hospital evaluation of a new biosimilar is as follows: After a pharmacist member of a hospital's Pharmaceuticals and Therapeutics (P&T) committee learns of a new biosimilar, either themselves or via a hospital prescriber, they search the medical literature to evaluate the biosimilar's clinical data. Their review focuses on the biosimilar's efficacy and safety as well as any differences from the originator brand. Other considerations may include product formulations and administration, whether the drug is generally for in-patient or out-patient care, the manufacturer's experience in producing biologicals, reliability of supply, patient education and support, and state regulations. If they judge that the biosimilar and the originator brand are essentially equivalent, then they analyze the biosimilar's comparative price and possible cost savings to the institution.

"We have three basic criteria for any drug considered for formulary approval or rejection. The first is efficacy ... We try to evaluate the data supplied by the manufacturer whenever possible. The second is a comparison between what we currently have on the formulary ... If we find they're similar, we'll go ahead and go to the next step, which is cost."

Price evaluation is done in the context of payer/insurance preferences, and possible existing contracts for the originator brand and/or similar biologicals. The evaluation also weighs transition costs, including changing electronic health records and establishing new inventory.

Given a favorable evaluation, pharmacists discuss the biosimilar with hospital nurses and physicians to educate them on biosimilar data, seek opinions, and gauge any objections. Members of the P&T committee then review all input, usually in conjunction with quarterly meetings, and vote to determine whether or not to provide access to the biosimilar by placing it on their hospital's formulary. At some hospitals, formulary evaluation is a relatively quick process taking six months or so. Other hospitals may wait a year or longer before considering a marketed biosimilar to see how it performs in terms of safety and efficacy in actual patients.

About half of the survey respondents said their hospital would add a new biosimilar alongside of an originator brand, and the other half said they would replace the originator product with the biosimilar. If adding alongside, hospitals commonly grant preferred status to the biosimilar, so that it must be used unless the prescriber shows reasons otherwise. If replacing, hospitals commonly institute a six to 12 month phase-out period where patients already receiving the originator brand can finish its use. For these hospitals, all new starts are required to be with the biosimilar.

"When we place (biosimilars) into formulary, they become step one and the originator becomes step two. So all new patients will be required to use the biosimilar unless the physician can show a reason otherwise. However, any current patients on originator brands are never required to be moved over to the biosimilar."



Differences between Biosimilars and Originator Brands

All marketed biosimilars have advanced through FDA approval and its stringent regulatory standards. P&T committees therefore, normally accept that biosimilars are equivalent to the originator brand. Although equivalent, biosimilars are not identical to their corresponding originator brands. They are biologicals produced in complex, living systems and under differing conditions.

As mentioned previously, biosimilars go through an abbreviated regulatory pathway. They only must show clinical similarity in one indication, which is extrapolated to similarity with the originator brand's other indications. The originator brand is almost always backed by numerous clinical trials, which investigate various aspects of the brand. Originator brands also benefit from safety and effectiveness demonstrated by post-marketing data and years on the market. Nonetheless, FDA-required evidence from non-clinical and clinical studies convinces most Pharmacy Directors that biosimilars are essentially equivalent with their corresponding originator brands and provide the same clinical outcomes. Most, but not all, Pharmacy Directors are readily willing to substitute biosimilars for originator brands.

Price:

The one overriding driver governing choice of a biosimilar product is price. This factor is an ever-growing concern, given the high cost of biologicals and the fact that many hospitals are facing

financial difficulties. Once biosimilars are placed on a hospital's formulary, pharmacists often view them and their corresponding originator brands as commodity items differentiated by purchase price and individual payer reimbursement.

Pharmacy Directors reported that their bottom-line price of biosimilars is between 10% and 50% lower than originator brands with 20% to 25% roughly the average. Even a 10% to 15% price difference is enough to cause many to switch to biosimilars, although a number of Pharmacy Directors indicated that a 20% to 25% benefit is required and/or that the annual volume must be sufficient to provide substantial savings.

As an example, one respondent said she pays \$100 (approximately one-third) less for the biosimilar Zarxio[®] than for the originator brand Neupogen[®]. Despite the fact that Neupogen[®] is sold in both pre-filled syringe and vial formulations, whereas Zarxio[®] comes only in pre-filled syringes, price is her choice determinant. Her hospital has replaced Neupogen[®] with Zarxio[®] on its formulary.

In some cases, the originator brand has countered biosimilar pricing and prevented switching with price decreases, discounts, rebates, and/or product bundling. Also, government-required discounted pricing for outpatients treated through designated 340B institutions – those recognized as serving vulnerable patient populations – often may be more favorable for an originator brand than for a biosimilar.



“Once they have indications, we treat them as commodities, and the deciding factor is purchasing price and reimbursement.”

Preference between Biosimilars and Originator Brands

Biosimilars usually are significantly cheaper than originator brands, and hospital pharmacists generally dispense biosimilars in preference to the originator brand. However, there are several exceptions:

- If a patient is already on an originator brand and it is working, pharmacists generally do not switch them to the biosimilar product
- In indications where the biosimilar has not been through Phase III confirmatory trials, pharmacists will more easily defer to a physician’s selection of the originator brand
- Pharmacists in hospitals that add as opposed to switch to biosimilars are more likely to defer to a physician’s choice. Older physicians are more likely to reject biosimilars than their younger colleagues
- Outpatient usage is often dictated by insurance coverage, and pharmacists do not stand in the way of patient access to biosimilars costing them less

“The majority of the older doctors prefer to stay with the regular name-brand drugs. Newer doctors coming out of medical school, they don’t seem to have as much problem with these particular newer medications.”

As a group, specialist physicians are less accepting of biosimilars than Pharmacy Directors. Physicians often are comfortable and familiar with originator brands, and they know that clinical testing of biosimilars is less extensive. Although the volume of biosimilar literature is smaller, physicians who review it gain an understanding and are more likely to accept biosimilars. Oncologists are used to trying new and special medications for life-saving conditions. As a result, they are less likely to object to biosimilars than other specialists, such as Rheumatologists, Gastroenterologists, and Infectious Disease practitioners. Younger physicians are more accepting of biosimilars than their older colleagues. Speakers for originator companies may be less likely to adapt biosimilars, sometimes due to conflicting interests.

Adoption of Biosimilars

It is common for some physicians to resist when a new biosimilar is added to a hospital formulary. Since few biosimilars have reached the US market, physician experience with them is relatively limited, and comfort level is still developing. Specialists often prefer the originator brand due to habit and familiarity.

Favorable clinical experience will facilitate biosimilar acceptance as will education from biosimilar manufacturers, either via proper interactions with knowledgeable sales representatives or through discussions and studies presented at medical conferences. Several Pharmacy Directors said that it is their responsibility to educate physicians on the role of biosimilars. They provide

clinical data to physicians who are hesitant to dispense, show studies demonstrating that biosimilars are safe and efficacious in comparison to originator drugs, and explain cost savings.

Overall, most hospital specialists willingly accept biosimilars and care only that the patient receives their needed medication. They understand the need to use biosimilars over originator brands to contain hospital costs.

Physicians who Refuse to Adopt:

inVibe’s survey included the following scenario to test how Pharmacy Directors would react to a specialist physician refusing to use a biosimilar on formulary:

We Asked:

Q: *Assume that your institution’s formulary has recently added a new lower-priced biosimilar for treating rheumatoid arthritis. Imagine you are having a conversation with Dr. Keller, one of your hospital’s rheumatologists. He tells you that he will not switch to the new biosimilar. He says he has prescribed the originator’s product for a long time and is comfortable with it. The indication of use is one for which the biosimilar was studied and approved. What is your position? What would you say to Dr. Keller?*

The scenario is set-up so that there is no strong justification to stick with the originator brand. Specifically, the indication of use is for a non-life-threatening condition. Also, the biosimilar is lower priced on the hospital’s formulary, and was studied and approved in the indication of use.

Pharmacy Directors understood the scenario and had significant experience in dealing with similar situations. Several emphasized that first they would listen to the rheumatologist’s position. To varying degrees, all would attempt to convince the rheumatologist to use the biosimilar. All would lead with a discussion of the biosimilar’s clinical efficacy and safety, and most would emphasize cost savings to the institution and the patient.

If the rheumatologist still objects after the initial discussion, only a few Pharmacy Directors would stop and accept the situation. Several would require the specialist to document or explain the reasons for refusal to the P&T committee, which would likely decide in favor of biosimilar usage. A few others would strictly refuse to allow future usage of the originator product.



“I would also tell Dr. Keller ... to provide clear, sound reasoning for the need to use the originator product, and if the information is not sufficient that we would receive for the pharmacy to review, and if necessary, other members of the medical team. Then we would simply have to have a request that the doctor order the biosimilar product as originally requested.”

Biosimilar Status in the US Market

The last survey question revealed Pharmacy Directors' true feelings on biosimilars. They provided their opinions on the fact that Europe is far ahead of the US with biosimilars marketed for 14 different originator brands, while biosimilars for only 2 originator brands have reached the US marketplace.

Pharmacy Directors were aware of this discrepancy and showed little surprise. Almost all expressed hope that more biosimilars will be approved in the US to contain costs and for the benefit of patients:

“

“We wait anxiously for those drugs to be approved here in the States, so we can go ahead with our process and hopefully switch to the biosimilars and ease some of the burden on the pharmacoeconomic system.”

“My hope is that some of these will soon come into the US market so that cost containment within budgets will occur ... The biologics, in particular, are just ruining healthcare budgets at an exponential rate.”

“Go Europe! The US is behind the times and slow in our approval process ... I hope that we here in the US continue to support the approval process for biosimilar agents, as it is what is going to allow us opportunity to improve the cost of healthcare as well as the access to medications for our patients.”

“It's absolutely acceptable to have biosimilars for all the medications named ... This (discrepancy compared to Europe) is one of the reasons why the United States spends the most per capita on healthcare.”

“Hopefully things are changing here and we will have more biosimilars just so that we can take advantage of the cost-savings. The costs right now, especially in the oncology field are just astronomical ... Things have to change. We do need some sort of major change here.”

“I feel very comfortable dispensing biosimilars because studies we've seen so far, proves that biosimilars are very safe and as efficacious as originator drugs. The future of the pharmacy industry should really add more biosimilars, because they're much cheaper than originator drugs but yet clinically as efficacious.”

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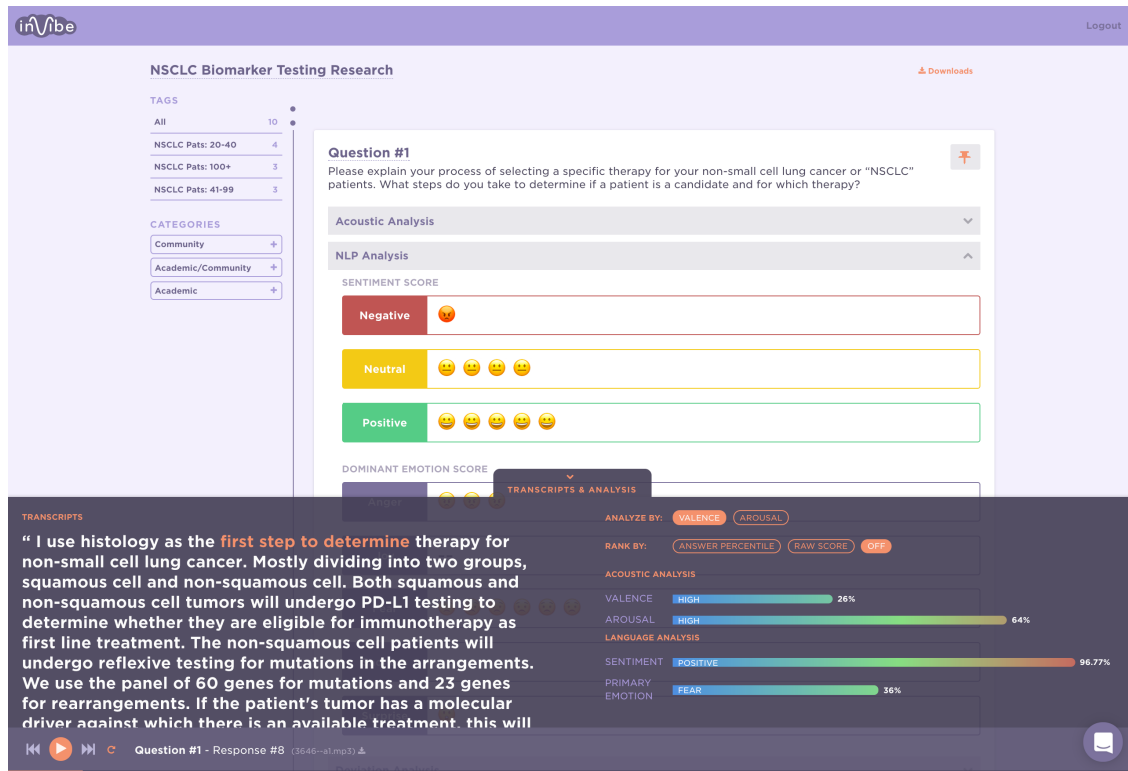


Future Research

On occasion, a second round of qualitative research may help to answer questions that become apparent from the first iteration or questions that are extensions of the subject area. A second round of inVibe qualitative research could address the following topics, among others that you might suggest:

- Factors impacting the uptake of specific biosimilars
- Evaluation of follow-on biosimilars or biosimilars in new areas
- Assessment of additional formulations of current or soon-to-be-marketed biosimilars
- Optimal interactions between the biosimilar marketer and important hospital stakeholders
- Perspective of other stakeholders, including relevant specialists, nurses, and payers

Such research could be accomplished easily and effectively by similar methodology with either selected first-round participants or with a new group of respondents.



Final Thoughts

We have shared a whitepaper summary of our findings, but what inVibe delivers to its clients is even more informative, interactive, and actionable. Along with an easy-to-interpret Excel matrix of findings (transcripts of the respondents' voice recordings), clients have access to a dashboard, which allows them to follow along with the audio responses from each participant along with emotion analytics. Although our real-time emotion analytics overlay is still in early beta, the initial findings from thousands of minutes of analysis have yielded promising results.

If you are interested in seeing how our quick-turn research methodologies can support your business research goals, **please call or email info@inVibe.co** for an in-person or web demonstration of inVibe's qualitative and quantitative research methodology with built-in emotion analytics.

See next page for a sneak peek.

Sneak Peek into inVibe's Emotion Analytics



ONE OF THE UNIQUE ATTRIBUTES OF INVIBE'S PROPRIETARY VOICE-RESPONSE PLATFORM IS ITS ABILITY TO ANALYZE THE ACOUSTIC SIGNAL CARRIED IN A PERSON'S VOICE UTILIZING INNOVATIVE SPEECH EMOTION RECOGNITION (SER) TECHNOLOGY.

Emotion is a psycho-physiological process triggered by conscious and/or unconscious perception of a stimuli or environment. The changes that occur in a person, ranging from increased heart rate and breathing to dryness of mouth, ultimately impact a person's speech. The resulting changes, such as shift in pitch, increased speed and acoustic frequency, can be precisely measured by capturing and analyzing a person's voice.

Because emotions can play a vital role in decision-making, the ability to quantitatively measure signals correlated to specific emotions while concurrently analyzing *what* is being said can lead to a deeper understanding of a person's affected state, which may either reinforce or contradict their stated responses.

inVibe Speech Emotion Recognition in Action

Once inVibe captures a person's response to a question, the acoustic signal is processed through an algorithm which assigns scores based on well-studied dimensions of emotion such as Valence (negative/positive), Arousal (calm/active), and Dominance (powerless/controlling).

From a physiological perspective, emotion is defined as a disruption in the homeostatic baseline. To establish a baseline inVibe asks the respondent to answer a "non-emotional" question, and then measures deviation from this value.

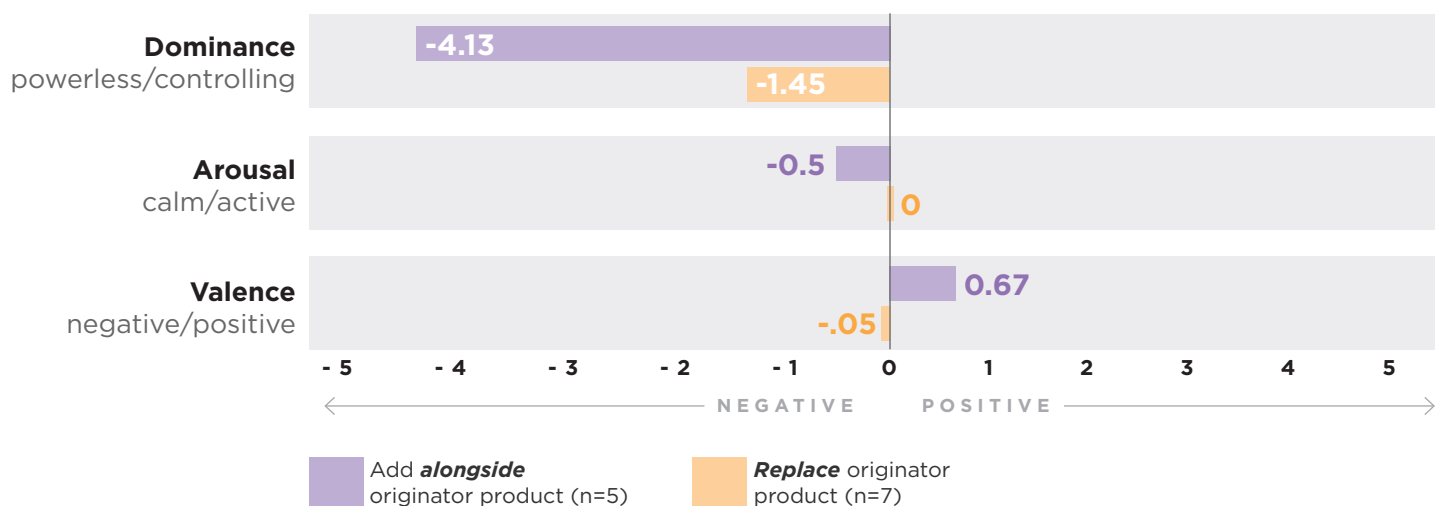
Are Pharmacy Directors Confident in Their Decision-Making?

One of the interesting observations we made when looking at the output of the SER was related to the Pharmacist's confidence (as measured via the "Dominance" score). Prior to participating in the voice-response research, the respondents were asked a few background questions. In one of these questions a hypothetical scenario was constructed where they would be adding a new lower-priced biosimilar product to their institution's formulary, and they were asked whether they would (a) Add it alongside of the originator product's vial formulation, or (b) Replace the originator product's vial formulation with the lower-priced biosimilar.

After analyzing the scores from the SER, we found that there was a positive correlation between those that would add the new product along with the originator product and those who had a very negative dominance score when answering question 6 [Assume that a new biosimilar product is now available in the US marketplace. What are the steps you and your institution will take to consider and then grant access to your physicians?].

Respondents who said they would add a biosimilar (n=5) *alongside* the originator product expressed *lower confidence* when discussing the adoption process

***Question asked:** "Assume that a new biosimilar product is now available in the US marketplace. What are the steps you and your institution will take to consider and then grant access to your physicians?"



Dominance is defined as a sense of confidence or control.

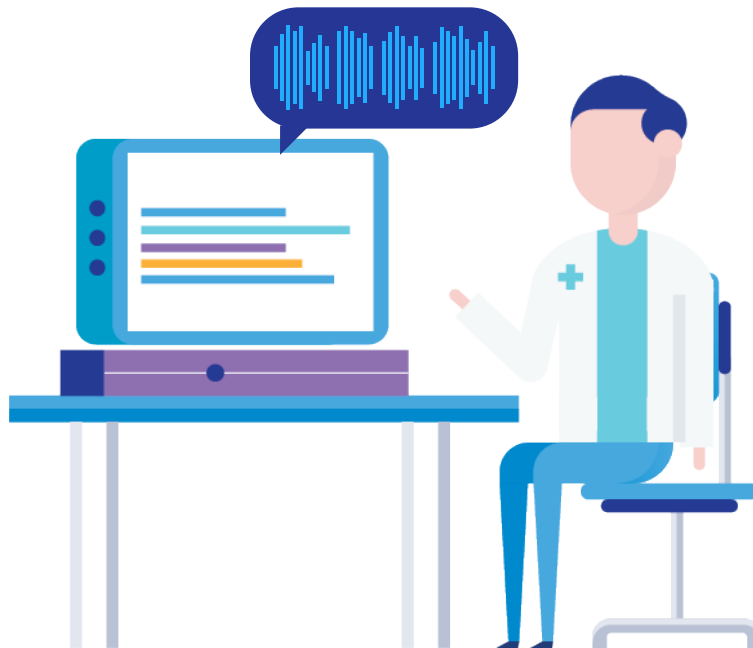


Interpreting Data

Negative dominance derived from the emotional speech signal suggests that a person feels powerless: they feel that they have little control over their situation or environment and, as a result, they believe that the actions they take are unlikely to have much of an impact on their situation. Negative dominance is frequently correlated with fear and anxiety.

UNDERSTANDING A PERSON'S EMOTIONAL STATE CAN SHED LIGHT ON THEIR MENTAL MINDSET, AND THIS UNDERSTANDING CAN IN TURN LEAD TO OPPORTUNITIES FOR COMPANIES TO SEGMENT THEIR AUDIENCES IN ENTIRELY NEW WAYS.

For example, if you are the manufacturer of a biosimilar and you want to ensure your product replaces the originator brand, you could leverage the dominance score from speech emotion analysis to help find formulary decision makers that tend to feel confident about biosimilars, and are both early adopters and fearless leaders — prone to making bolder decisions like completely replacing an originator brand with what they believe to be an equally efficacious, tolerable and low-priced alternative.



This is just a small glimpse into the possibilities of speech emotion analytics.

If you'd like to learn more,
please contact us at info@inVibe.co.



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