Theory of Sampling meets the National Science Foundation I-Corps™ program

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ABSTRACT

The authors have presented their ideas for developing a powder sampling device in the I-Corps™ program sponsored by the National Science Foundation (NSF). This is an intensive customer discovery program developed to increase the economic impact of the research sponsored by NSF.

The I-Corps™ program requires performing at least 100 interviews with potential customers in various industries. These interviews are essential to establish the need for a particular product or solution, and identify potential commercialisation partners and competition. The interviews have revealed the absence of Theory of Sampling (TOS) principles in many companies. The interviews are designed to identify the difficulties associated with current sampling practices that do not meet TOS principles.

The I-Corps™ program is a significant challenge for scientists who often avoid discussing a concept in fear of losing their research idea. The program teaches how to obtain information without releasing the important intellectual property related to a product development idea. The I-Corps™ methods have been used to discover the prevailing ideas on sampling in various industries.

I-Corps™ also teaches how to present ideas to investors; another significant challenge for a scientist. We are currently learning to present sampling and TOS to investors and business development experts, and will share some of these experiences.

INTRODUCTION

The authors have received funding for the development of a new sampler based on Theory of Sampling (TOS) principles for pharmaceutical manufacturing. This sampler would be used with the powder mixtures that are compressed to become the tablets that billions of patients take. The powder mixtures usually include at least five components which differ in particle size distribution and particle morphology. The sampling of these powder mixtures is required as described in 21CFR211.110: Section 211.110 of the Code of Federal Regulations (CFR, 2016) (legal requirements for the manufacture of drug products in the United States). These legal requirements also known as the current good manufacturing practices require written procedures for sampling and in-process tests (211.110, point a), in-process specifications (211.110, point b), and the acceptance or rejection of the material by the quality control unit (211.110, points c, d) (Romañach, 2015; CFR, 2016). The sampling of these powder mixtures was the subject of two draft guidances evaluated by The United States Food and Drug Agency, but never approved (Esbensen *et al*, 2016). Thus, currently every pharmaceutical company must develop and justify a system for the sampling and evaluation of the powder mixtures needed to manufacture tablets. A powder sampler based on the principles of TOS was proposed, and the research proposals were funded by the National Science Foundation (NSF), through their Small Business Innovation Research (SBIR) program, and the Puerto Rico Science Technology and Research Trust.

The two research grants have required the considerable commitment to meeting research goals just like all research proposals. However, they also require efforts to transition the advances to a successful commercial product that will contribute to economic growth. The goal is to turn scientific advances into products or services that will provide a benefit for society and create jobs. The grants have required that we undertake the I-Corps™ Teams training. NSF has created the Innovation Corps™ Teams (NSF I-Corps™ Teams) training to advance the research to a point where it will attract investors. I-Corps™ facilitators are entrepreneurs who have started their own businesses. Thus, TOS and this research team have met the I-Corps™ Teams program. The team has had to adapt to performing customer discovery while it performs the research needed to develop the sampler. The team has received questions from the facilitators such as: 'What is the cost of non-representative sampling, in terms of dollars how much should I care about non-representative sampling, what is the pain, in dollars, that occurs from not using your sampler, is this a new customer archetype, is this sufficient

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evidence to justify the development of the product?'. These questions cannot be answered with laboratory experiments, and force the researcher to move to customer discovery. TOS has met the start-up world.

Customer discovery requires that 'founders get out of the building' (Blank and Dorf, 2012). In customer discovery, the team is expected to perform more than 100 customer interviews. This requirement often meets a certain resistance to change from scientists who know that their ideas are correct and are the best, and who are focused on protecting their research ideas to keep them from being stolen. Unfortunately, this means not learning enough about the resistance to change that innovative ideas will face. A professor or scientist could spend months developing a careful research proposal following one of the complex formats that are typical of funding agencies, and then face resistance to change for the first time when the proposal is evaluated. The I-Corps™ training includes the book 'Talking to Humans', where the authors recommend starting questions with the words *what*, *who*, *why* and *how*, and avoiding questions that start with *is, are, would* and *do you* (Constable and Rimalovsky, 2014). The interviewing requires building a conversation to identify opportunities to help an industry or field.

The interview process is based on the scientific method. A set of hypothesis are developed, and then a set of experiments (interviews) are needed to validate or invalidate the hypotheses. Thus, the researcher could be convinced that all industries want to have representative sampling. In customer discovery, the researcher needs to transform this belief into hypotheses that must be tested. The researcher must become a listener, to gain the information necessary to validate or invalidate a hypothesis. The researcher must separate from his belief and be open to a feedback that he might not like, and realise that his ideas are not necessarily shared or needed by everyone. Thus, the requirement of 100 or more interviews. The course strongly recommends face to face questions to provide the opportunity of seeing the facial expressions of potential customers. The customers could be thousands of miles away and NSF provides a travel budget to make these face to face interviews possible. The researcher and his team could ask questions such as:

- How is powder sampling performed in your operations?
- What is considered representative sampling in your operations?
- What would be the cost of wrongly rejecting a lot because of a sampling error?
- What would be required to accept a new sampling method?
- Why are samples obtained from a static powder bed?
- What would be the value of discerning between sampling and process variation?
- How should I as a researcher help your industry in improving powder sampling?
- Who else should I speak with?
- Anything else that I should have asked?

The interviewing process also requires seeking permission from a company or individual for the interview. The interview process is designed to learn about the problems and pains of the customers, not to sell the researcher idea. The interview should not be a pitch to convince the customer that they're doing things wrong, but an opportunity to understand whether the idea has the potential to alleviate their pains. The best approach has been to indicate that the research group wants to identify opportunities for improving powder sampling in the pharmaceutical industry, to eventually develop a new powder sampler. Companies often do not want to speak about their current problems. However, a good conversation on opportunities for improvement will usually identify the problems that they are having. The interviews are essential to identify current sampling practices and the customers need to solve the problems associated with these sampling practices. The interviews evaluate whether the new product will be used by a sufficient number of customers. The interviews must eventually progress to a second stage where the features of a minimum viable product are presented to customers. If a sufficiently high number of customers enthusiastically accept the solution (product), customer discovery has achieved its goal.

I-Corps™ Teams is built on the belief that nobody should invest money in a new business without doing customer discovery first, and obtaining evidence that the product or service is needed. Many new companies fail because they provide services or products that are not needed. Other businesses provide good products, but fail because they are located in places that are difficult to reach or where it is nearly impossible to park a car. The information obtained from the interviews are the basis for start-ups. Start-ups should not be miniature versions of large companies, but temporary organisations that operate in a 'search mode' with the purpose of developing a repeatable and profitable business model. Start-ups need to do significant research to understand the needs of potential customers, a process that has been termed customer discovery (Blank and Dorf, 2012).

This contribution discusses some of the knowledge gained through more than 100 interviews and provides a 'snapshot' of the current level of knowledge in sampling. The second goal of this contribution is to share the experience of bringing TOS to the business community dedicated to the development of 'start-ups'. Finally, the 'customer discovery' process is shared as a tool that may be used to increase the impact of TOS.

RESULTS

Through more than 100 interviews, the research team interviewed representatives from 23 pharmaceutical companies. The team also interviewed eight representatives from companies with expertise in powder characterisation equipment, blenders and other equipment used by the pharmaceutical industry. The interviews also included scientists from the United States Department of Agriculture, the Bureau of Engraving in the United States Department of the Treasury, and the National Institutes of Standards and Technology to learn about sampling practices in other fields. The interviews revealed the following findings which should be of interest to the TOS community:

- Pharmaceutical companies interviewed rely on thief or spear grab sampling to obtain powder samples from different locations within a blender (Romañach and Esbensen, 2015). A total of 20 of the 23 pharmaceutical companies interviewed used thief sampling. The three exceptions are now employing real-time near infrared spectroscopy ('optical sampling') in continuous manufacturing systems. Five companies are making investments to improve powder sampling in their operations (including the three companies working with near infrared spectroscopy). One of the five companies is using both thief sampling and near infrared spectroscopy.
- At least ten persons indicated that thief sampling is the only way to do sampling for pharmaceutical blends. When asked what could be improved several of the respondents indicated that an automated thief sampler would be an option. Many of the interviewed assumed that the team

was developing a new thief, the only option that they are aware of.

- Representative sampling is often considered as taking samples from different levels of a blender (top, middle and bottom). The industry relies on preselected locations for obtaining powder samples.
- Some scientists believe that the powder samples currently obtained are not representative because the drug concentration in these samples often differs with that found in tablets compressed with the same blends.
- Two scientists indicated that powder sampling is not representative, it is designed to check drug concentration in areas of the blender where adequate mixing might not be occurring. They believe that sampling is performed to identify worst-case scenarios.
- About 90 per cent of the pharmaceutical formulations that are evaluated with a thief meet the specifications established for those blends. The current industry view is that the sample thief is adequate for formulations with components that have similar particle size.

DISCUSSION

The interviews revealed that 89 per cent of the companies interviewed were using sample thieves to sample powder mixtures after blending. This result is surprisingly similar to a survey conducted more than 15 years ago (Boehm, 2001), where 25 of the 28 companies that responded the survey revealed that they used a side-compartment thief.

The interviews reveal many opportunities for improving the sampling of powder blends through TOS. The current regulations provide ample opportunity for bringing TOS into the pharmaceutical realm. The current good manufacturing practices for pharmaceutical manufacturing indicate:

> *Representative sample means a sample that consists of a number of units that are drawn based on rational criteria such as random sampling and intended to assure that the sample accurately portrays the material being sampled.* (CFR, 2016)

However, these rational criteria must be determined and justified by the pharmaceutical industry. Thus, the pharmaceutical regulation provides ample opportunity for minimising sampling error and developing scientific justifications through TOS.

The TOS community thoroughly understands that sampling is the basis of quality control. Quality control analyses will not provide reliable products if non-representative materials (specimens) are analysed. Yet, many analytical chemistry textbooks hardly discuss sampling, and simply indicate that representative sampling should be performed. Unfortunately, Pierre Gy's legacy: the TOS is not included in most analytical chemistry textbooks. The organisers and participants of the Eighth World Conference on Sampling and Blending are not solely organising a conference; they are also in a quest to increase the impact of the TOS. This goal has some surprising similarities with modern theories on how to increase economic development through start-ups. Start-ups cannot assume that everyone will want their product, and need to operate in search mode to obtain a repeatable and profitable business model. The TOS community also needs to operate in 'search mode' to understand the current level of understanding of TOS and use this information to guide future efforts.

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