Innovation – From Mining to Pharmaceutical Manufacturing – The Inspiring Role of the Theory of Sampling (TOS)

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ABSTRACT

TOS has guided the author in addressing multiple challenges in the sampling and analysis of the powder blends that are compressed into the tablets that many patients ingest.
Real time measurements of pharmaceutical manufacturing processes are possible through near infrared and Raman spectroscopy. These real-time measurements form part of a systematic effort called Process Analytical Technology (PAT) designed to guarantee the quality of pharmaceutical products. In PAT sampling is performed through spectroscopic methods. Sampling errors have been identified in real time PAT measurements. This report also presents a two-fold composite sampling approach developed to improve the accuracy of the real-time spectroscopic methods. Pharmaceutical processes include 1-D lot transformations just like processes in mining and other industries. Variograms can be used to evaluate the sources of sampling and analytical errors in near infrared and Raman spectroscopic methods, even though the true mass of the sample analyzed is not known. Variographic analysis is practically custom made for continuous manufacturing of pharmaceutical formulations, providing valuable information.
As part of innovation initiatives, the author has been involved in intensive customer discovery efforts for the development of new sampling technology. The Stream Sampler Kit, inspired by the Theory of Sampling, is now commercially available for pharmaceutical processes.

1. Introduction – Sampling Always Present (overt, covert)

The author thanks the Editor for the kind invitation to share with the sampling community the story of how the Theory of Sampling (TOS) has inspired research at the University of Puerto Rico – Mayagüez campus. Research at academic institutions constantly requires writing proposals and competing for funds through calls 'Request for Proposals'. In the United States, these competitions are organized by organizations such as the National Science Foundation (NSF). TOS has become a competitive advantage in these calls for proposals.

TOS has made it possible to gain a greater understanding of how heterogeneity affects the results obtained in many PAT approaches in pharmaceutical manufacturing. The author has always studied the random and systematic errors associated with analytical methods. TOS has made it possible to obtain a greater command of the sampling errors influencing analytical results (Romañach et al., 2021).
Analytical chemists seek to extract information from data produced by a specific analytical instrument or method, to optimize current methods and to design and construct more powerful instrumentation (Booksh & Kowalski, 1994). However, most importantly, this information is critically dependent on how samples and aliquots are obtained; sampling to the fore!

The Theory of Sampling (TOS) originated in the mining industry (1950-1975) and is today progressing into many other industries (Esbensen, 2016, 2018, 2020). The present author has been asked at several World Conferences on Sampling and Blending: "What mining company do you work for?" or told: "I did not know about mining in Puerto Rico".

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I have then explained that I have never been in a mine (Romanach & Mendez, 2019), but that I am chemistry professor focused on improving pharmaceutical manufacturing processes! Puerto Rico is only 156 km long by 55 wide but has exports exceeding $20 billion in pharmaceutical products on a yearly basis (U.S. Bureau of Labor Statistics, 2025) to over 130 countries (Invest Puerto Rico, 2019). The attendees at world sampling conferences are always pleasantly surprised to learn that my reason for participation was to learn about the Theory of Sampling (TOS), specifically for application in pharmaceutical manufacturing.

TOS has been a great inspiration for the R&D activity in our research group at the University of Puerto Rico-Mayagüez campus. The first interaction with TOS was through Pierre Gy's book 'Sampling for Analytical Purposes' (Gy, 1998). Since then, a lot of progress has been made, recently culminating in the development of a new Stream Sampler Kit designed to sample and analyze powder blends (Romanach & Mendez, 2019). This achievement has been a significant challenge, but with very rewarding results. The Stream Sampler Kit is now commercially available, and it has also served to train graduate students who contributed to its development (Nasrala-Alvarez et al., 2025) and application for new pharmaceutical products (Alvarado-Hernández et al., 2020; Rangel-Gil et al., 2023; Sierra-Vega, Martínez-Cartagena, et al., 2020; Sierra-Vega, Romañach, et al., 2020). The Stream Sampler projects have contributed to training four Ph.D. students, two M.S. in Chemical Eng., one M.S. in Chemistry, and one M.S. in Industrial Engineering student.

2. Sampling – a personal journey

Sampling has always been a part of the author's career. The author's first job involved obtaining water samples from a lake close to an oil rig in South Louisiana. The objective was to determine whether soil from the lake was moving towards an area rich in oysters. Another project with the same independent testing laboratory was to sample frozen meat imported into the United States. This job required working in very cold freezers, opening heavy boxes of meat and using a drill to obtain an entire tubular crosscut of the slab of meat. The meat removed by the drill was then analyzed for fat and protein. At that time, I wondered why someone would pay us to damage all that meat. I later learned that if our results showed that the meat had higher fat, the importer received a discount. If the results showed higher protein; thus, less fat, the meat could then be sold at a higher price (backed by the certificate of analysis from the testing laboratory).

Regardless of the results, the meat importer always made more money with the results obtained from the independent testing lab. This was my first meeting with the economic conditions surrounding and sometimes guiding analysis.

In the author's first job in pharmaceutical manufacturing, a Quality Control laboratory supervisor complained about the high volume of solvent needed for analysis of pharmaceutical powder mixtures(Romañach, 2015). These excessive solvent volumes forced the quality control laboratory to exceed the year's budget for solvents. Each sample required about 500 mL of solvent for analysis of what was the weight of 10-20 dose units. At some point, I realized that a sample preparation error could occur when a sampling thief (spear) was used to bring the powder into a small 20 ml bottle, where some of the powder could easily be lost during material transfer. The method was 'improved' with larger wide mouth bottles which facilitated the transfer of the powder mixture from the thief, and by increasing the percentage of water in the sample preparation steps. The QC laboratory budget was also favored when a legal decision required that the same size of analytical blends be reduced to the mass of 1 – 3 the dose units (Berman, 2001). However, reduction of the analytical mass resulted in many other problems associated with the use of sample thieves (Muzzio et al., 1997), a theme that has been front and central for many activities developing since.

In 1999 the present author moved from Puerto Rico's pharmaceutical manufacturing industry to Mayagüez Campus of the University of Puerto Rico. The University has a total of 11 campuses, with Mayagüez being the campus dedicated to agriculture and engineering. Mayagüez is a land grant institution that includes farms as well the actual main campus. It was founded in 1911 and now has about 11,000 students. The Department of Chemistry recently celebrated its 75th anniversary, started its MS in Chemistry program in 1959 and its Ph.D. in Applied Chemistry in 2004. The present author came to Department with the idea of using near infrared spectroscopy for the analysis of drug content in tablets. He did not know that some of the first papers on near infrared spectroscopy were published by Professor Owen H. Wheeler at this same Chemistry Department (Wheeler, 1959, 1960) before he moved to projects on natural products, organic, and nuclear chemistry. The author worked with Wheeler in the pharmaceutical industry for several years before his retirement. He was a true gentleman and scientist who knew about many different topics.

Wheeler called near infrared spectroscopy: a neglected field study, due to lack of analytical instruments suitable for observing this spectral region. Luckily in 1999, a good near infrared spectrometer was available for the author to start his research project in the analysis of tablets (Ramirez et al., 2001). However, a pivot towards the sampling and analysis of pharmaceutical powder mixtures was required to continue the progress of the research efforts.

The multiple problems related to sampling of powder mixtures in the pharmaceutical industry coincided with the author's decision to start an academic career at the University of Puerto Rico Mayagüez campus in 1999 (Berman, 2001; Boehm et al., 2003; Romañach, 2015). Experience with many sampling issues lead to a call for proposals from Puerto Rico's INDUNIV (Industry University and Research Consortium) for novel approaches to the sampling of pharmaceutical powder mixtures. The response to this call became the author's first research grant, and the research group's first publication on the sampling and analysis of pharmaceutical powder blends (Popo et al., 2002). This paper indicated that "Stream sampling takes advantage of a process that has to occur, as tablet compression requires the flow of the blend from a hopper or bin located over the compressing machine". Stream sampling was presented as an alternative to insertion of a spear or sample thief into preselected locations of the traditional pharmaceutical blender. The group's research continued to progress and in 2019 an automated stream sampling approach was patented (Romanach & Mendez, 2019). In 2020 the first research papers with the sampler were published (Alvarado-Hernández et al., 2020; Sierra-Vega, Martínez-Cartagena, et al., 2020; Sierra- Vega, Romañach, et al., 2020). In 2024, the stream sampler was licensed by the University of Puerto Rico, and since then we call it the Stream Sampling Kit (SSK). This article presents the story of the progress made by bringing TOS into pharmaceutical manufacturing.

3. Innovation – the key focus

Innovation is encouraged by funding agencies, universities, and governments. Funding agencies guide and encourage research in academia through various calls for proposals. The National Science Foundation has a Small Business Innovation Research (SBIR) program for "supporting startups and small businesses to transform scientific discovery into products and services with commercial and societal impact" (National Science Foundation, 2025a). The SBIR program provides funds for the research that startups need to develop the intellectual property required for success. Similar programs are available in other agencies of the United States government. The many current efforts to encourage innovation have contributed greatly to focusing on the development of our group's research projects.

Proposals to the SBIR programs are strengthened if the applying researchers have performed customer discovery through the U.S. National Science Foundation Innovation Corps (I-Corps™). This immersive, intensive customer discovery program facilitates the transformation of invention to impact (National Science Foundation, 2025b). The I-Corps program seeks to help discoverers and researchers transform knowledge from the laboratory into a commercial product. The achievement of this objective requires conversations with over 100 potential customers (Constable, 2014). The interviews require that researchers face unwelcome realities. The acceptance and implementation of a good idea or product is often a slow and painful process. Many companies and people are simply used to living with a problem and have no desire to overcome it. Three I-Corps™ trainings helped our group in discussing the idea of an automated stream sampler/analyzer for flowing powder blends – focused on facilitating PAT applications. In 2017, we presented a summary the experiences of the I-Corps™ program to the sampling community at the WCSB9 in Perth (Pinzon de la Rosa et al., 2017). This presentation emphasized the importance of bringing TOS to the commercial sector, an idea that was later emphasized through a wide-spanning special issue of Spectroscopy Europe in 2021 "Economic Arguments for Representative Sampling" (Esbensen (ed), 2021) with no less than 27 key academic, technology and industry leaders contributing a massive assemblage of different scopes, objectives, hard-core results, economic and societal achievements – all because of involvement of TOS. Our group chose to focus on "Sampling in Pharmaceutical Manufacturing a Critical Business Case Element"(Romañach, 2021).

With multiple calls for innovation, it is difficult for a researcher who is confident of leading an "innovative" research program to capture what is meant by innovation. A popular book on 'Design Thinking' states that innovation requires inspiration and an open mind to new ways of thinking and moving beyond current established practices (Brown, 2009). IDEO, a highly recognized global design and innovation company, sees innovation as the effort to design something better and "Build products, services, & experiences that break through" (IDEO, 2025). The Penn Center for Innovation (The University of Pennsylvania) indicates that it "helps to translate discoveries and ideas created into new products and businesses for societal benefit"(Penn Center for Innovation, 2025).

At the University of Puerto Rico – Mayagüez Campus, innovation is developed through courses that bring together engineering students from a Design Thinking course with marketing students enrolled in a Consumer Behavior course, to develop technology-based products that address current problems faced by society (Lugo et al., 2016). Therefore, innovation is not just a new idea or research project, it requires the entire path from invention to the commercial world where it must be accepted and implemented.

4. Innovation in practice – the NIR spectroscopy example

The development and advancement of near infrared spectroscopy (NIR) could be considered an example of innovation. Chemists weigh and dissolve materials to determine their chemical composition. However, manufacturing processes are often dominated by the physical properties of materials. When a sample is dissolved, valuable information on the physical properties of samples is thrown away. Near infrared spectroscopy has emerged as a powerful technique for obtaining information on the physical properties of materials as well as their chemical composition (Ciurczak et al., 2021). Many types and brands of NIR spectrometers are now commercially available from multiple vendors. The United States Pharmacopeia (USP) which sets rigorous science and the public quality standards has a general chapter on near infrared spectroscopy (United States Pharmacopeia, 2020).

There are now guidance documents on how to submit documents involving near infrared spectroscopy to regulatory agencies (European Medicines Agency, 2014; Food and Drug Administration, 2021). Near infrared spectroscopy is clearly an example of innovation that has progressed from an idea to the commercial world where it is now used in multiple industries.

Figure 1 shows a photograph of a rock brought to our lab by a local Geology professor a few years ago. This rock was part of a beloved collection that started when the geologist was four years old. It took a few minutes to convince the professor that near infrared spectroscopy was non-destructive and would not affect the rock. As we started obtaining NIR spectra, the professor mentioned that the white area in the rock was talc. The fiber optic probe of the NIR spectrometer was focused on the white area as shown in the figure. Talc has a very distinctive O-H first overtone band in its near infrared spectrum. NIR bands are usually broad, while talc provides a sharp O-H band. The right side of figure shows the spectrum of the white area from the rock and a spectrum of a commercial talc sample purchased at a local drug store. The difference between the two is likely due to the heterogeneity of the materials. However, the most important message from this figure is that the intact rock was returned to the happy professor. Most analytical chemistry methods would require removal of the white area of the rock and dissolving it for analysis.

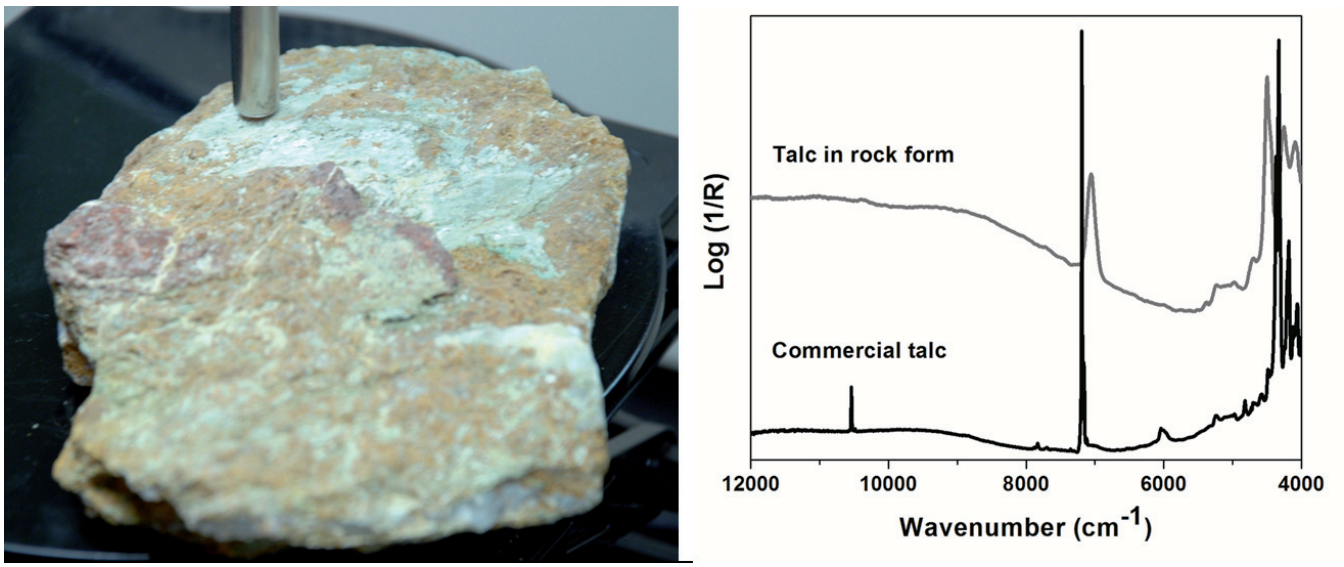

Figure 1: Left: Spectroscopic sampling of a rock from a geologist's collection through the fiber optic probe of a near infrared spectrometer. Right: spectrum of the rock (top); spectrum of a commercial talc sample (bottom).

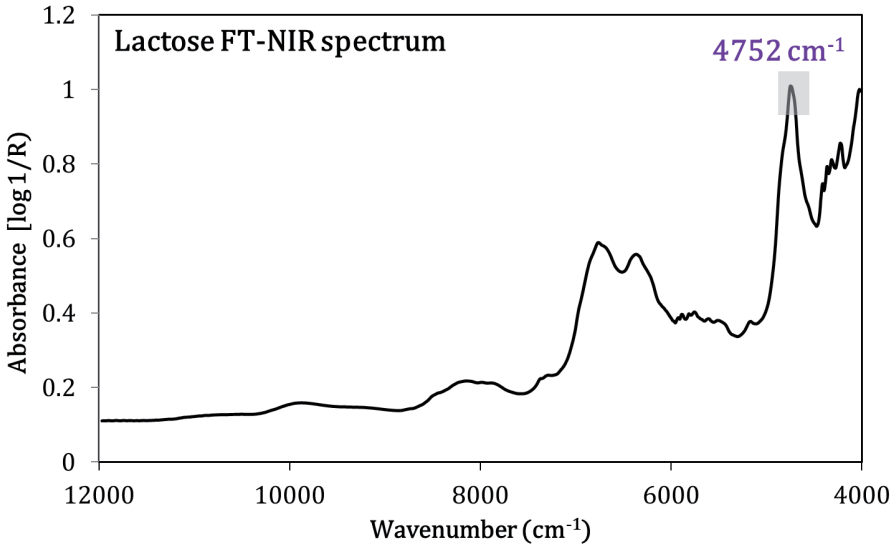

Figure 2: A NIR lactose spectrum with broad, overlapping bands.

Chemists usually wait in a laboratory and expect to receive samples when a manufacturing process is completed. However, chemists could also work with instruments installed at the manufacturing site and monitor the process as it occurs (real time). This concept was originally called Process Analytical Chemistry (Callis et al., 1987).

New ideas require time for acceptance. It was not until 2004 that Process Analytical Chemistry was adopted as a Process Analytical Technology (PAT) approach in the pharmaceutical industry (FDA, 2004). Many pharmaceutical processes involving PAT have since been approved by regulatory agencies (Vargas et al., 2018). There are now analytical instruments designed to work at/within manufacturing sites, even though in most manufacturing processes, samples are brought to the chemist who waits at the (hopefully nearby) Quality Control laboratory. Today there are many commercially available systems working with the signals from NIR PAT sensors to monitor and control pharmaceutical processes (Celikovic et al., 2025; Singh et al., 2014). The United States Pharmacopeia has recently published a general chapter on PAT for public comments to establish a comprehensive guide in alignment with scientific and regulatory standards and guidance for the implementation of PAT within pharmaceutical companies (United States Pharmacopeia, 2025). This chapter is additional evidence that PAT has walked the full path from its beginnings in the early 1980s as process analytical chemistry to its commercial adoption in pharmaceutical manufacturing.

5. Process Analytical Technologies (PAT) – the pharmaceutical case

PAT could also be considered a Human Resources initiative. Scientists have been trained to work with data and turn it into useful information. However, most pharmaceutical processes do not have information showing how the materials are transformed during the manufacturing process. A scientist may be asked to help improve the process, but most of the time the only information that is available is from when the process started, e.g., the weights of materials used, who weighed them, and when the process was completed. Because of this lack of relevant process information, it is impossible to know how the manufacturing process evolved. Scientists may provide multiple possible mechanisms for process evolution, but objective data is needed. The productivity of scientists would be increased through PAT methods which track the progress of a process.

NIR spectroscopy is now one of the most used analytical methods in PAT systems, for example offering the potential process information present in NIR spectra, which can be obtained continuously every 1 – 5 seconds without dissolving any sample material. This advantage has facilitated NIR PAT sensors to be implemented in very many pharmaceutical processes (see other contributions in this issue).

However, this same advantage also brings forth challenges. NIR spectroscopy may penetrate only up to 5 mm into the materials that are being analyzed (Iyer et al., 2002; Ortega-Zuñiga et al., 2017).

When a NIR spectrum is obtained through diffuse reflection, the radiation that returns to the detector, is only from the top 3 mm of a sensor's field-of-view (FOV) under ideal conditions (Ortega-Zuñiga et al., 2017). The radiation penetrating below 3 mm is transmitted or absorbed by the material and never returns to the detector. The depth of penetration of near infrared radiation also varies according to the properties of the material and to the frequency of the radiation. Figure 2 shows the spectrum of lactose, one of the most used excipients in pharmaceutical tablets. Lactose shows a weak broad absorbance band near 8000 cm-1. The depth of penetration of the NIR radiation is much greater at 8000 cm-1, than at the strong absorbance band around 4752 cm-1. At 4752 cm-1 the radiation is strongly absorbed by the top layers of the lactose particles. The depth of penetration is much smaller in spectral regions where the material strongly absorbs the radiation. N.B. The mass of the sample that is interacting with the NIR radiation can be estimated but is not known! NIR spectroscopists have famously been accused of being the only analysts that do not know the precise volume/mass for which an analytical result is reported(Esbensen et al., 2018; Esbensen & Romañach, 2021)! Furthermore, the material that resides closer to the surface receives more radiation than the material below (Dahm et al., 2000). Thus, NIR radiation could be interacting with only the top 1 – 2 mm of a 100 mm thick flowing blend (Romañach, 2017). In this case at least 98 mm of the flowing blend would not be sampled for analysis. In the TOS parlance, this is clearly a gross increment delimitation error (IDE), highlighting the need to improve spectral sampling for NIR methods. Clearly the geometric aspect of the process sampling interface plays a crucial role here; see another contribution to this SST issue.

Therefore, sampling is an essential element of PAT (probe sampling), even though a sample does not physically need to be removed from the process stream (Esbensen & Paasch-Mortensen, 2010). The Fundamental Sampling Principle (FSP) applies to sampling of dynamic, moving lots (process sampling) just as much as to stationary lots: all parts of the lot (or of a segment of the streaming lot) must have the same opportunity of being selected as a sample. Once this sample interacts with the analytical instrument, a spectrum or signal can often be acquired within seconds. This past year, the US Pharmacopeia published a stimuli article on 'TOS within PAT' (Romañach, 2025). The goal of stimuli articles is to seek input from the scientific community that could be used to develop future chapters in the Pharmacopeia.

6. When TOS is not the guiding principle

There is unfortunately a widespread mindset that views grab sampling as a convenient approach to quickly obtain a 'sample' and then move to what is of much more immediate interest: analysis. The challenge is to overcome this type of thinking and convince all players and stakeholders that sampling should rather always be a multi-stage sampling/sub-sampling process (Danish Standard 3077, 2024; Esbensen, 2025). Sampling is not easy and true representative sampling is challenging (Paoletti et al., 2006; Tittlemier et al., 2024), but there is no other way.

7. Continuous manufacturing

The development of continuous manufacturing processes for the manufacture of tablets is another example of innovation. Most pharmaceutical manufacturing is traditionally taking place through batch processes, where the entire batch is processed in isolated units. The materials from one unit are then moved to subsequent unit operations. In 2006, the National Science Foundation approved a proposal from Rutgers University, in partnership with Purdue University, the New Jersey Institute of Technology, and the University of Puerto Rico – Mayagüez campus to establish an Engineering Research Center on Structured Organic Particulate Systems (C-SOPS) focused on the systematic application of engineering methods to design continuous processes (Oka & Muzzio, 2022). There are now companies that provide equipment for continuous manufacturing processes and software for modeling those processes. In summary, an entire set of service providers is available for the support of continuous manufacturing. Continuous direct tablet compression has progressed from idea to the commercial world. In October 2021, continuous direct compression became the first technology to graduate from the FDA Emerging Technology program (FDA, 2025). Graduation means that submissions with continuous direct compression can be handled through the established quality assessment programs at FDA, because the reviewers now understand the technology and have the required expertise and procedures to evaluate it. Therefore, continuous manufacturing has already walked the entire path from idea to the commercial world.

Figure 3 shows the continuous manufacturing rig at the Analytical & Pharmaceutical Lab at UPR-Mayagüez where students from chemistry and chemical engineering are introduced to R&D in pharmaceutical manufacturing.

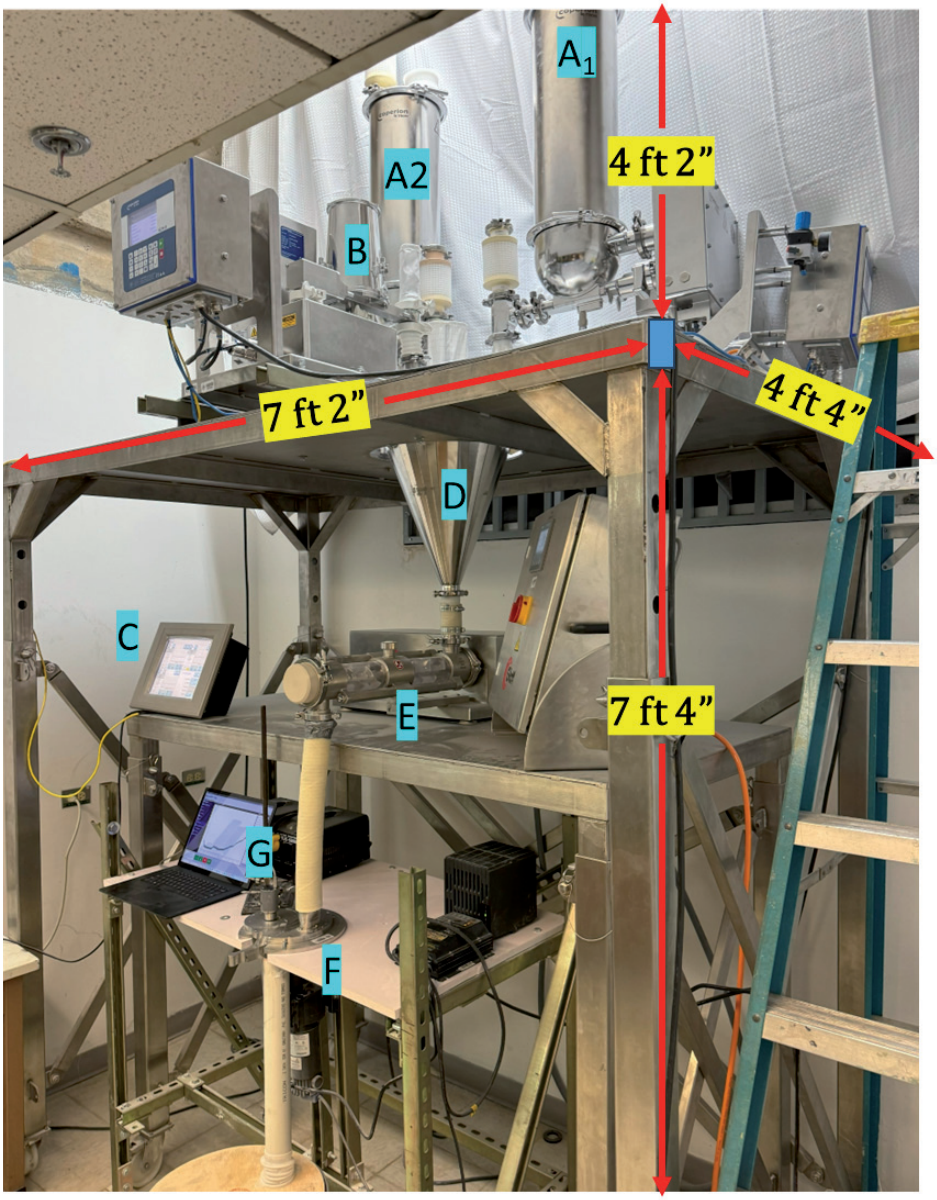

Figure 3: Experimental and pilot scale continuous manufacturing system at the University of Puerto Rico – Mayagüez dedicated to training of students and local industrial workforce. Compare this to traditional pharmaceutical manufacturing plants

The figure shows one of the advantages of continuous manufacturing - the very significant reduction in the size of the manufacturing space required. The maintenance and operation of pharmaceutical manufacturing operations is expensive so such reduction potential is highly beneficial. The design of these systems also makes it possible to use the same equipment both in research and manufacturing. In research work, the system could be run to manufacture tablets for 5 – 10 minutes (Rangel-Gil et al., 2024), while in manufacturing it could be run for 120 hours, or more, to manufacture millions of tablets (Holman et al., 2021).

With such a setup, tablets can now be made within minutes of starting an integrated continuous manufacturing system. Novel design of continuous processes is now possible through a thorough understanding of the physical properties of active pharmaceutical ingredients and excipients (Razavi et al., 2022). Therefore, transfer of continuous processes from research and development to manufacturing is now facilitated and effectuated with extreme ease. Continuous processes can be used to respond to drug shortages and make needed products easily available to patients worldwide (Lee et al., 2015; Romañach et al., 2023). Continuous manufacturing is a valuable asset to address future pandemics.

8. PAT opens up new vistas through interaction with TOS

It should be obvious why PAT is nowadays often used to monitor and control such continuous processes. Variographic analysis, as will be described below, provides valuable information of continuous processes. The potential benefit from the marriage PAT-TOS is almost unlimited.

9. Encountering TOS

The author's first encounters with TOS occurred in 2010 thanks to an invitation to write a chapter on sampling and validation of powder blends (Cullen et al., 2015). The invitation was for writing about "the general sampling approaches, sampling probes, errors and indeed sampling with NIR". The initiating literature search for this chapter revealed that many published papers and book chapters on sampling were mostly repetitive and without a progressive outlook – indeed discussing spoon sampling, coning-and-quartering and several other methods that were not practical in an industrial setting. There had to be a better approach!

The literature search revealed an application of TOS by Merck scientists (Green et al., 2005) to understand the sampling errors observed during fluid bed drying. This study was the first to introduce the concept of sampling errors to pharmaceutical applications and stated that "even the most "homogeneous", well-controlled processes are prone to sampling errors". The study included a first order approximation of sampling errors for a 300-L scale fluid bed dryer, indicating that the effect of sampling errors were reduced as moisture content became more uniform when the final moisture level was approached. The study also described efforts to reduce the sample mismatch error between spectra measured in-situ by near infrared spectroscopy and the Karl Fischer reference method which is based on extracted 'samples' and is done in the laboratory.

The second clue was from a seminal book that presented the golden rules of sampling (Allen, 2003):

- "A powder should always be sampled when in motion".
- "The whole of the stream of powder should be taken for many short increments of time in preference to part of the stream only being taken for the whole of the time".

These early Golden Rules of Sampling also indicated: "Observance of these rules, coupled with an understanding of the manner in which segregation takes place, leads to the best sampling procedure. Any method that does not follow these rules should be regarded as the second-best method, liable to lead to errors. Finally, the need for care and skill in abstracting samples cannot be over-emphasized." For connoisseurs of TOS, these are remarkable insights regarding process sampling, but here promulgated within an industry sector unknown to the TOS community.

The Allen book cited the second edition of Pierre Gy's book Sampling of Particulate Matter, Theory and Practice, published in 1982, and a 1953 article by Pierre Gy. The present author was able to obtain another book by Pierre Gy (1998), his famous "Sampling for Analytical Purposes" which marked his official start in studying the Theory of Sampling (TOS) in full earnest.

The first golden rule is addressed through "Lot Dimensionality Transformation, one of the governing principles of TOS. This golden rule is for example followed when near infrared spectra of flowing powders are obtained using the stream sampler designed in our laboratory, see further below.

The second golden rule presents another way of expressing the Fundamental Sampling Principle (FSP), which is met when a sampling process ensures that all extracted increments have an identical, non-zero extraction probability while covering the entire width and depth of the streaming material that is sampled (Danish Standard 3077, 2024). The second golden rule also seeks to avoid increment delimitation errors, when demanding that the whole of the stream (width and depth) should be sampled instead of only a part of the stream being taken for the whole of the time. Complying with this rule/principle effectively transforms a 3-D lot (e.g., on a conveyor belt, or in a pipeline) into a 1-D lot. Sampling will then only be a feature along the direction of movement (the process direction); this has a tremendous simplification potential, see the TOS literature (Esbensen, 2020).

In 2014, the author had the honor (and pleasure) of organizing the International Diffuse Reflectance conference in Chambersburg, PA. The author had a great scientific advisory group which suggested inviting the editor of SST, professor Esbensen, to the conference. The conference was organized without scheduled presentations in the afternoons providing a safe space for amenable conversations away from the stressful environments of offices and research laboratories. These fruitful conversations helped the author start to understand the intricacies of the deeper layers of Theory of Sampling. The present author is now a student and fan of 'Strategic Doing', a method for developing collaborations (Morrison, 2021).

Step 1 in Strategic Doing is to create and maintain a safe space for conversations of ideas. This safe space is essential for scientists and investors to think and develop new ideas. The different meetings and discussions with Prof. Esbensen at the World Conferences on Sampling and Blending have been very helpful in bringing together the governing principles and sampling unit operations of TOS for specific use and application within pharma.

10. The stumbling block to TOS Acceptance

The author's own stumbling block to accept TOS was that composite sampling would hide the heterogeneity of pharmaceutical blends. A quiet meeting in a brewery (before happy hour) in New Brunswick, NJ provided the safe space needed to overcome this stumbling block in a very relaxed conversation with Prof. Esbensen.

The author's concern was based on previous experience and research with pharmaceutical powder blends and reading of reports that indicated that "blending equipment is poorly characterized", and "questions and issues that are often ignored include dead spots; scale-up", and "products' tendency to segregate, agglomerate or break" (Timmermans, 2001). Therefore, there is a need to determine whether pharmaceutical blends contain poorly mixed areas which could lead to an over or underdose for a patient. How could composite sampling be implemented without the risk of hiding heterogeneity that could affect patients? This was a serious concern for the author.

The pharmaceutical blends which become tablets will always have some degree of heterogeneity at various scales between lot size and final tablet volume (Esbensen et al., 2016); therefore, it will not be homogeneous as is otherwise a much-declared goal within the traditional pharmaceutical realm. Heterogeneity will always exist as indicated by TOS (Gy, 2004), it is only a matter of to which degree, at which scale (Esbensen 2020). The issue is to evaluate the heterogeneity that is acceptable for drug products or other commercial materials.

The author finally understood that different composite sampling approaches could be evaluated through the concept of Lot Heterogeneity Characterization (one of the six Governing Principles of TOS). A composite sampling scheme can be designed to assure that a product is manufactured within its expected specifications, and composite sampling schemes could then be applied to evaluate the material produced. Composite sampling is critically needed to overcome the effect of heterogeneity (not to hide it), as otherwise the use of grab sampling (process of extracting a singular specimen), will always lead to a different, unreliable analytical result (Danish Standard 3077, 2024). Of course, composite sampling shall always comply with the Fundamental Sampling Principle. Once this stumbling block was overcome, the author continued on a much happier trajectory internalizing more and more of TOS.
Heterogeneity and Sampling Errors

Heterogeneity is in fact an unavoidable characteristic of all pharmaceutical manufacturing (at the process scale) (Romañach & Esbensen, 2015). Heterogeneity is also a feature of drug particles. The drug, often called the active pharmaceutical ingredient (API), is usually synthesized and purified at an industrial site apart from the plant that manufactures the final dose a patient receives (e.g., tablet, ointment, injectable). The API will need to be stored to be transported to the manufacturing site. Drug particles may vary in terms of particle size for which reason transport will often induce at least some form of segregation heterogeneity. Heterogeneity will occur as the API on the top of the storing container will be more exposed to moisture from the environment, while particles on the bottom of the container will be more protected from moisture. Drug particles may also exhibit polymorphism, with more than one crystal form of the drug (Reid et al., 2025). Therefore, heterogeneity is a ubiquitous feature at all scale levels including compositional variability within the final particles themselves.

Heterogeneous drug particles are usually mixed with various excipients. The tablet that a patient takes is not composed solely of drug particles. Some of the tablets have very small amounts of a potent drug and a diluent is needed to create a mass that can be compressed and then handled by the patient. Lactose and microcrystalline cellulose and two of the most common diluents, also called fillers. The blend may also include excipients to improve the flow of the particles or facilitate their disintegration. Excipients are essential in pharmaceutical manufacturing and will also show significant heterogeneity. Pharmaceutical processes further include mixing unit operations (Figure 3). Pharmaceutical unit operations such as milling and mixing are also viewed as part of the complement of five Sampling Unit Operations (SUO) in TOS (Esbensen, 2020; Danish Standard 3077, 2024). Correct representative sampling - and analysis - of pharmaceutical blends destined to become tablets have constituted the major objective for a dominating part of the research effort of our lab during the past 25 years.

11. Composite Sampling through Spectroscopy – a novel TOS perspective?

Composite sampling does not necessarily require physical extraction of materials from a manufacturing process – PAT to the fore! Composite sampling may for example be achieved though repeated real time spectroscopic measurements of a process: Radiation from a near infrared or Raman spectrometer interacts with a small superficial mass of blend being transported or processed. These spectrometers average a number of scans into a spectrum, thereby improving analytical quality by increasing the spectral signal-to-noise ratio. If the powder flows or moves over a conveyor belt while repeated scans are acquired, this is spectral composite sampling, as illustrated in Fig. 4.

Figure 4 shows a blend with 20% (w/w) of the analyte. However, the results predicted through analysis of a single increment (grab sampling) are never 20% (w/w). The central illustration shows an example where the NIR radiation finds a 50% (w/w) concentration of the analyte. However, this is not an analytical error, as it rightly represents the true concentration of the analyte within the field-of-view (FOV) increment - this is a sampling error that can be reduced through the use of composite sampling. Figure 4 also shows an extraneous particle that will not be detected by the NIR radiation. This extraneous material will be present in the final product received by a patient, but it will not be detected in the PAT quality monitoring. This example is not a case where the NIR spectrometer is failing, it is again a spectral FOV sampling error. The concept of sampling errors is still relatively new to the analytical and pharmaceutical community, where focus overwhelmingly has been on validation of analytical methods. TOS is a welcome new scope in the pharmaceutical sector.

The mass of the material characterized by spectral sampling can be estimated through the equation shown in Figure 5. However, the most important aspect is to obtain a meaningful average spectrum in the form of a composite sample.

The understanding that composite sampling is possible with spectroscopy, which is highly desirable in pharmaceutical manufacturing, first came about in 2014 (Colón et al., 2014). A calibration model correlating features in NIR spectra with drug concentration was developed for powders moving over a conveyor belt and also for a static powder mixture deposited over a tray.

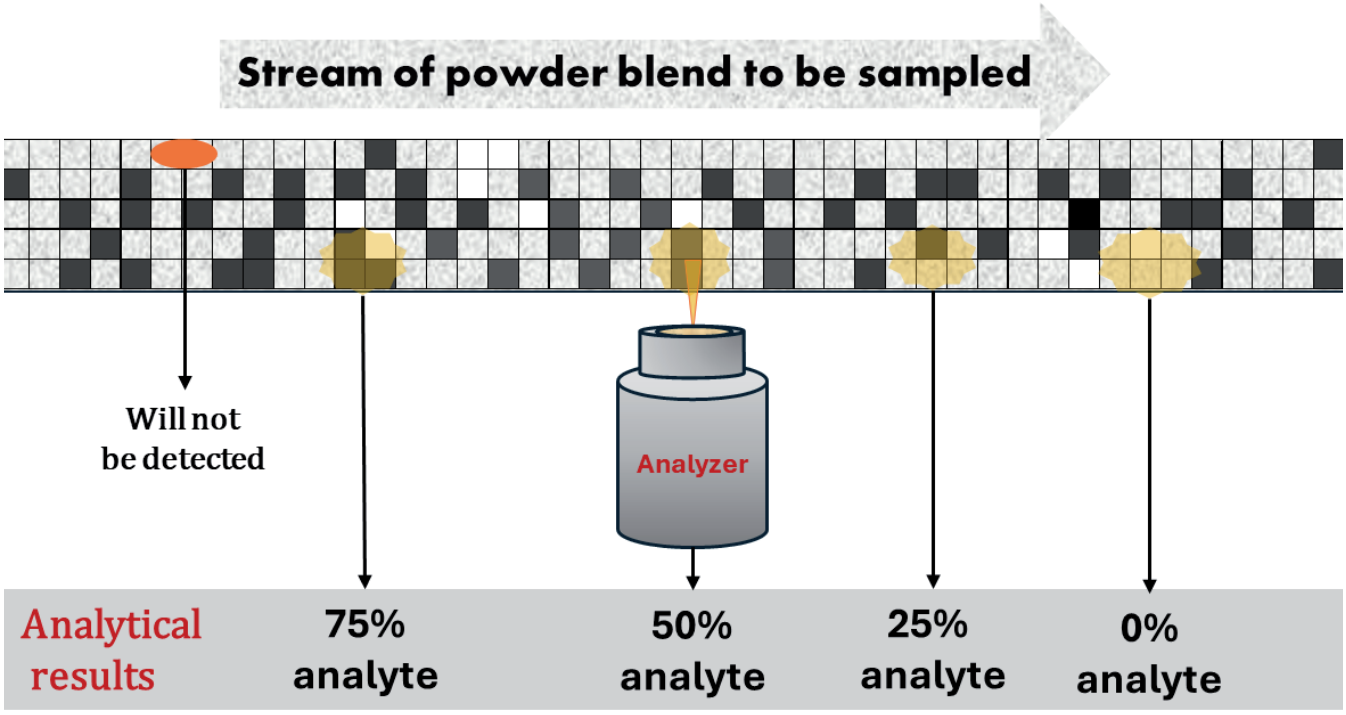

Figure 4: Principal sketch that has been helpful in describing sampling errors to chemical analysts.

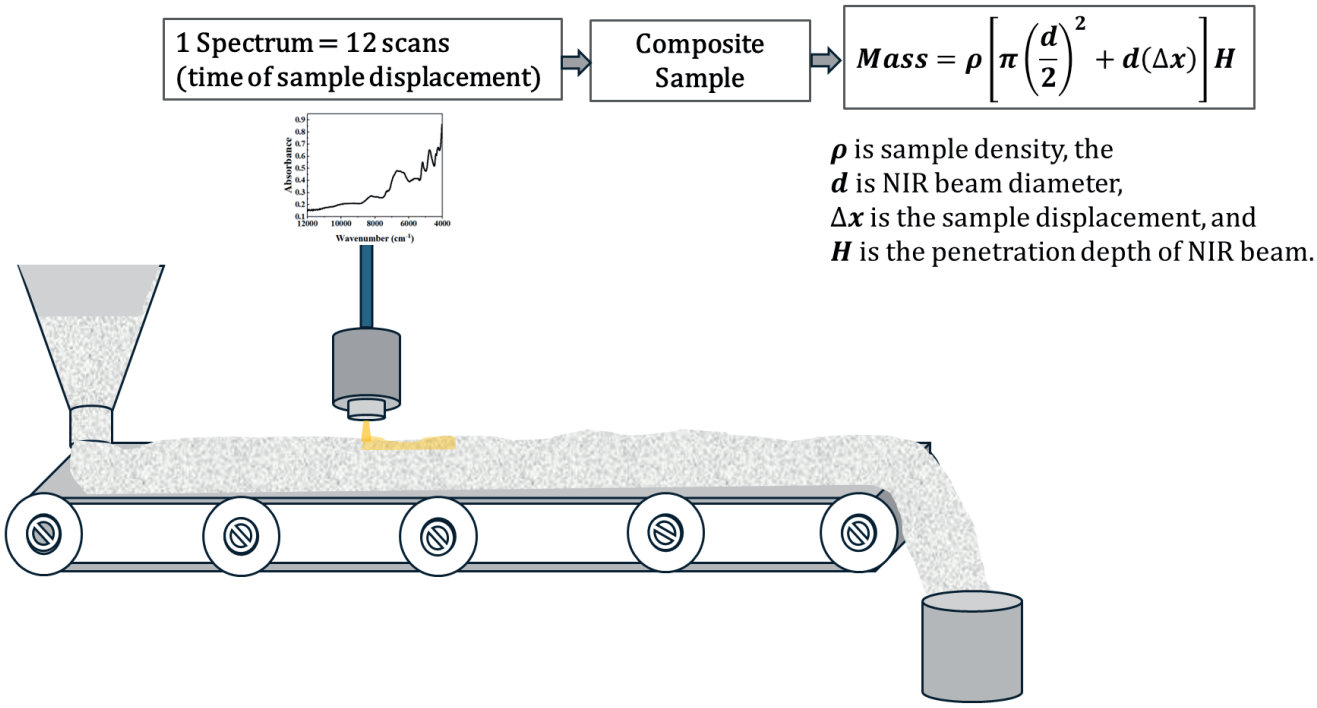

Figure 5: Sketch showing composite sampling through replicated spectroscopy of a moving target.

The results for spectra acquired while the powder was moving were three times more accurate than for the static powders deposited on a standard laboratory tray. The present author could not believe the results and spent several days trying to improve the chemometric calibration models developed by the graduate students, but without any success. The original hypothesis was that a higher signal to noise ratio would be obtained for the spectra of the static powder mixture (deposited in the tray), resulting in more accurate results. However, the 12 scans of the static powder mixture were obtained for exactly the same material and could therefore not counteract the effect from the heterogeneity of the blend.

Later systematic studies have shown that a 2-level (2-step) sample composite is possible with spectroscopic measurements. Each 'individual' spectrum obtained for a calibration model is already a composite sample in the above sense in which a certain number of scans is averaged. However, the next level of composite sampling is also achieved when multiple such spectra are obtained for each calibration blend (Esbensen et al., 2018). As an example, 16 scans may be used to obtain a spectrum of a flowing powder blend, thereby obtaining a composite sample. This could be called the first level of composite sampling.

In total 200 spectra were obtained for each blend in the calibration set. These 200 spectra represent the second level (step) in composite sampling (Rangel-Gil et al., 2024).

12. Lot Dimensionality Transformation in Pharmaceutical Manufacturing

Lot Dimensionality Transformation (LDT) occurs 'naturally' in pharmaceutical manufacturing. Raw materials, blends and/or intermediate products will flow to the unit operation where the final product is made. Pharmaceutical blends should not be sampled from pre-selected sampling locations using a sample thief, which for decades has been the paradigm within the traditional pharmaceutical realm. One cardinal reason why not, is that this approach results in particles being dragged from one location of the blender to another (Muzzio et al., 1997). There are several other disadvantages, including the fact that pharmaceutical blends are not prepared with the intent to remain in blenders. They must unavoidably flow out to compressing machines to make the tablets that patients receive. This necessary flow provides the opportunity needed (LDT) to perform the optimal sampling known to TOS: process sampling (Alvarado-Hernández et al., 2020; Sierra-Vega et al., 2019; Sierra-Vega, Romañach, et al., 2020; Rangel-Gil et al., 2024).

Lot dimensionality transformation makes it possible for all parts of the blend in an otherwise 3-D mixer to have the same opportunity of being selected as part of a sample via the moving 1-D setup. There now exist multiple published studies showing how sampling may be performed with spectroscopic methods at the feed frame of a tablet press, immediately before tablets are produced (Harms et al., 2019; Li et al., 2018, 2019; Sierra-Vega et al., 2019).
However, changes take time and unfortunately thief (spear) sampling is still used in most pharmaceutical processes (Timmermans, 2001; Pinzon de la Rosa et al., 2017).

13. Most recent development – back to mining

The pharmaceutical industry now has continuous mixing facilities (e.g., Figure 3) which are thoroughly characterized as fit-for-purpose, and which has also addressed issues related to dead-spots or scale up difficulties (Osorio et al., 2015; Osorio & Muzzio, 2016; Roth et al., 2017).

Figure 6 shows a sketch of continuous mixing equipment in the laboratory compared to lot dimensionality transformations as typical in the mining industry. The top part shows loss-in-weight gravimetric feeders.

In most processes one of these feeders will hold the drug particles. The other feeders will deliver the excipients which are required to dilute the drug particles and facilitate tablet compression. The drug and excipient particles stored in the feeders may be considered 3D lot systems. Lot dimensionality transformations occur as soon as the powder flows to the feeder as shown in Figure 6. In fact, lot dimensionality transformation occurs more than once in the continuous pharmaceutical manufacturing system. When observing crushed rocks (mineralizations, ores) moving over a conveyor belt in a mining operation (Petersen et al., 2005) have been discussed at World Conferences of Sampling Blending, this author always thinks of a continuous manufacturing pharmaceutical system – The dualities and similarities are striking!

But the lot dimensionality transformation is not unique to the mining and pharmaceutical industry - indeed all of the Governing Principles (GP) and Sampling Unit Operations (SUO) in the framework of TOS are generic and find application across a wide swath of technological and industrial sectors (Danish Standard 3077, 2024).

Once the importance of understanding 1-D transportation from the viewpoint of TOS, the following 'discovery' was inevitable.

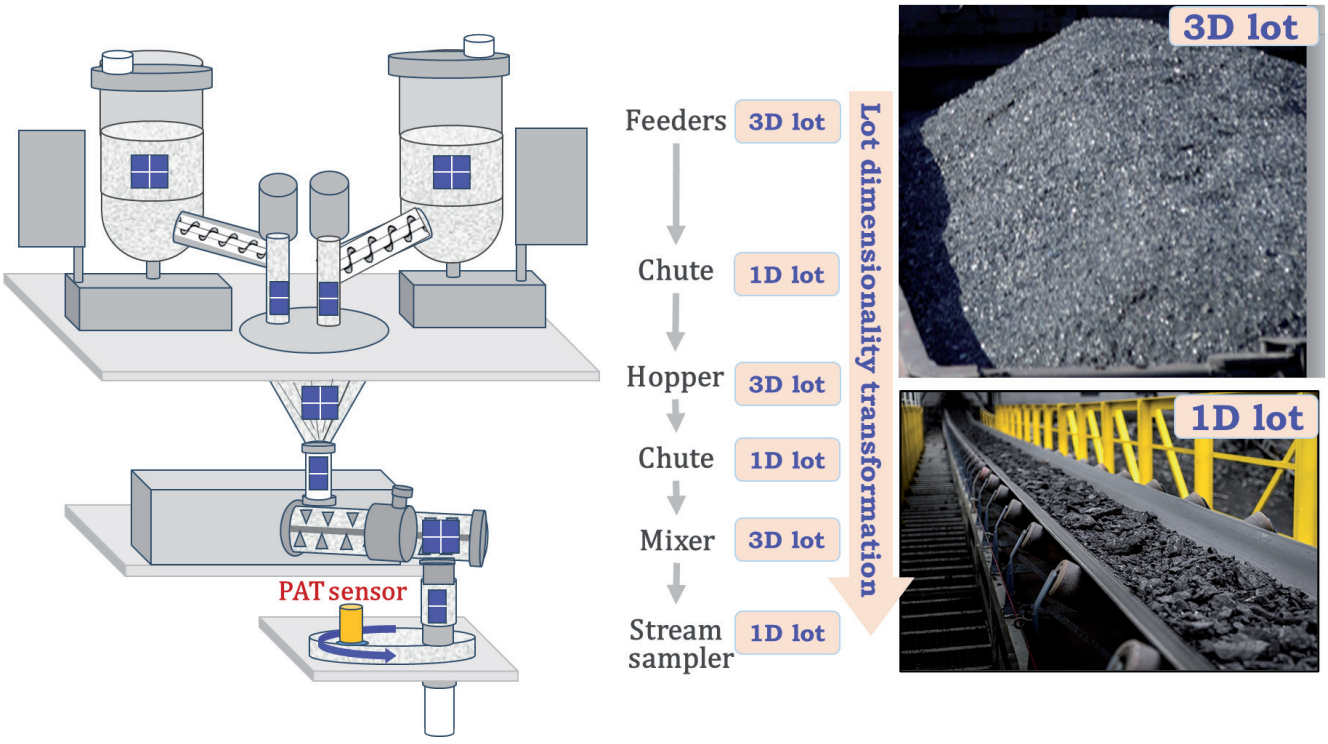

Figure 6: Parallel application of the lot dimensionality transformation principle in the pharmaceutical manufacturing system and in a mining/minerals processing operation (photos courtesy KHE Consulting Teaching Collection).

14. Variographic Analysis for Pharmaceutical Manufacturing

Variographic analysis is practically custom made for the sampling and analysis of the powder blends that flow to a compressing machine and has recently become a highly valuable asset in the evaluation of continuous manufacturing(Nasrala-Alvarez et al., 2025; Rangel-Gil et al., 2024; Romañach et al., 2018; Sánchez-Paternina et al., 2019; Vargas et al., 2018).

A variogram is based on the sequential order of samples/analytical results. NIR or Raman spectra obtained while monitoring a continuous mixing process are digitally stored and the time ordering when they are acquired is known. The variogram concept requires that a monitored process is stable. In continuous manufacturing a steady state is achieved where the input and output flows are constant over time, and the mass flux realized is constant over time (Ganesh & Reklaitis, 2020). However, in the granular reality the system is always subject to input fluctuations. Engineering systems have been developed to dampen these so that the resulting output deviations are acceptable (Singh et al., 2014).

NIR spectroscopy is now used to sample-and-analyse drug concentrations in continuous 1-D mixing processes (Movilla-Meza et al., 2025). The use of NIR spectroscopy makes it possible to determine the drug concentration every 1 – 5 seconds (depending on the spectrometer used) during the continuous mixing process, which is a landmark speeding up of pharmaceutical process monitoring. Variographics to the fore!
However, use of standard variographic analysis in PAT applications in pharma has required adapting the variogram equation slightly as the mass analyzed through near infrared or Raman spectroscopic methods can be

$$V(j) = \frac{1}{2(Q_{Total} - j)} \sum_{q=1}^{Q_{Total}-j} \left(h_{q+j} - h_q\right)^2$$

estimated but it is not known (Sánchez-Paternina et al., 2019)
where h_{q+j} and h_q are the heterogeneity contributions in each sampling location evaluated to measure the analyte, j is the lag distance (the inverse of the sampling frequency). Q_{Total} is the total number of analytical increment results acquired. V(j) represents the variance between extracted increments. The V(j) values are calculated in this study with drug concentration values predicted by chemometric NIR calibration models. The lag distance (j) is the inter-distance between pairs of API concentrations predicted by the NIR calibration model.

V(j) for a lag of 1 is calculated for the sum of squares of the differences between the first and second NIR prediction, the second and third, the third and fourth, and continues until the last two predictions. V(j) for a lag of 2 refers to the differences between the first and third NIR prediction, the second and fourth, the third and fifth, and continues until the last two predictions. There are scores of explanations of variographic analysis in the TOS literature, to which further attention is directed(Esbensen & Paasch-Mortensen, 2010; Minnitt & Esbensen, 2017; Sánchez-Paternina et al., 2019).

Figure 7 shows a variogram from a recent continuous pharmaceutical manufacturing run. Variograms are always presented together with standard control charts of the results from real time predictions obtained through a NIR or Raman spectroscopic method. Thus, the left side of the Figure 7 shows the results for a blend prepared with 50% (w/w) of the drug. The left side provides a blending profile that is considered adequate for this formulation, as all drug concentration results within 5% (w/w) of the target concentration (50% w/w). However, the variogram provides a complementary profile characterizing the blending process in more comprehensive detail. The variogram obtained is an increasing variogram where the difference between the increments is increasing as the process progresses. The variogram indicates that the mixing process has a large range, the inter-sample distance at which the mixing product becomes stable; this information is of key importance in monitoring and optimizing the specific mixing process.

Variographic analysis has shown its value in detecting subtle variations that are not so easily perceptible in the blending profiles (Nasrala-Alvarez et al., 2025; Vargas et al., 2018).

15. The Stream Sampler

The drug content of the tablets that a patient takes depends on two factors. The first is the tablet weight, which must be controlled when the tablet is compressed. The second factor is the uniformity of the blend that is compressed as a tablet. If the drug is not distributed uniformly in the blend the patient could receive a higher or lower dose of the medication.

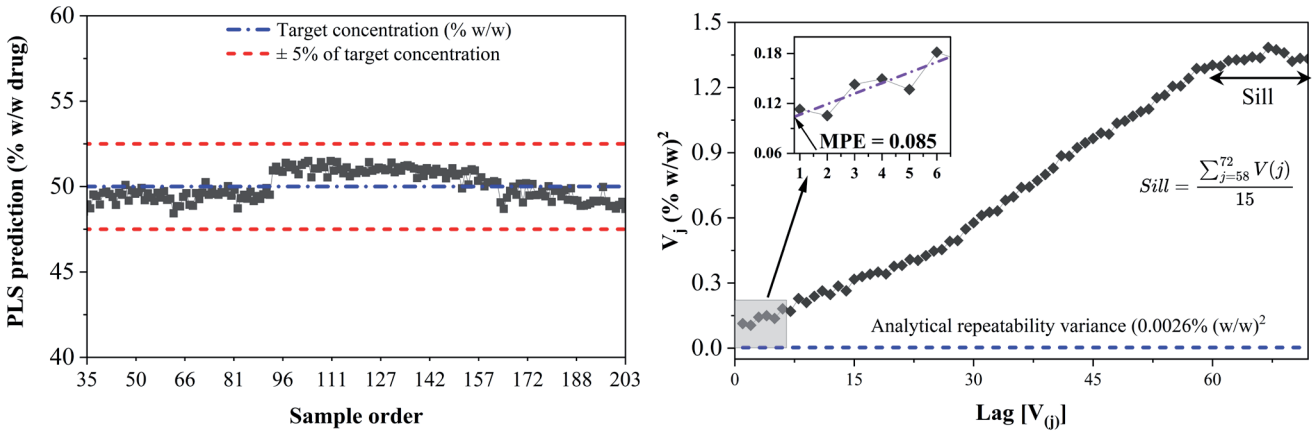

Figure 7: Left: Standard control chart of drug concentration results obtained during continuous mixing (steady state). Right: Increasing variogram characterizing the mixing process in more detail.

Sampling and analysis of the powder blends that will be compressed as tablets is required by the current Good Manufacturing Practices to assure uniformity of the drug (National Archives, 2025). The sampling and analysis of the powder blends that become tablets has been the major thrust of our research lab for the past 25 years.

This research has resulted in a patented sampler for powder blends (Nasrala Alvarez et al., 2024; Romanach & Mendez, 2019). The sampler is now commercialized as the Stream Sampler Kit (SSK) and has one paddle wheel that moves counterclockwise at 9 - 18 RPM to move the blend. The wheel has 20 paddles or blades forming twenty sectorial gaps that are filled with the powder blend. The flowing powder is confined within the paddles. The studies performed so far have shown that the physical properties of the blend are not affected by the flow through the sampler (Nasrala Alvarez et al., 2024). Figure 8 shows photographs of the current Stream Sampler Kit interfaced to three different spectrometers. The design of the sampler makes it possible to obtain a very steady powder flow even at 30 kg per hour.

The sampler is designed to avoid recirculation of the powder blend. Near infrared or Raman spectra are obtained at 180 degrees from the entrance of the powder to the sampler as shown in Figures #and #. The powder exits the stream sampler at 270 degrees from its entrance. As a result of the design, the powder blend is always entering and exiting the sampler, avoiding recirculation of any part of the powder mixture.

The sampler permits a large number of measurements of the blend uniformity through a NIR or a Raman spectrometer. These spectrometers are capable of providing spectra every 1 – 5 seconds depending on their design. The drug concentration can then be determined using multivariate calibration models (partial least squares regression a.o.). Figure 8 shows the stream sampler connected to three different spectrometers in the lab, and to the continuous mixer (MODCOS Dry Mixer 70, Glatt®, Germany).

The sampler was designed taking into consideration the principles of TOS. All parts of the batch or lot have the same opportunity of flowing into the sampler and interacting with the NIR radiation. The radiation from the spectrometers is not able to interact with the entire cross section of the flowing blend, but the sampler has been designed to minimize the thickness of the powder flow.

The development of the stream sampler has been pursued while developing a new generation of pharmaceutical scientists capable of moving PAT and TOS into commercial pharmaceutical manufacturing. The professors have not abandoned the University to pursue the development of the stream sampler. Instead, the stream sampler is currently training students from both chemistry and chemical engineering programs as shown in Figure 9, and in collaboration with a local engineering company.

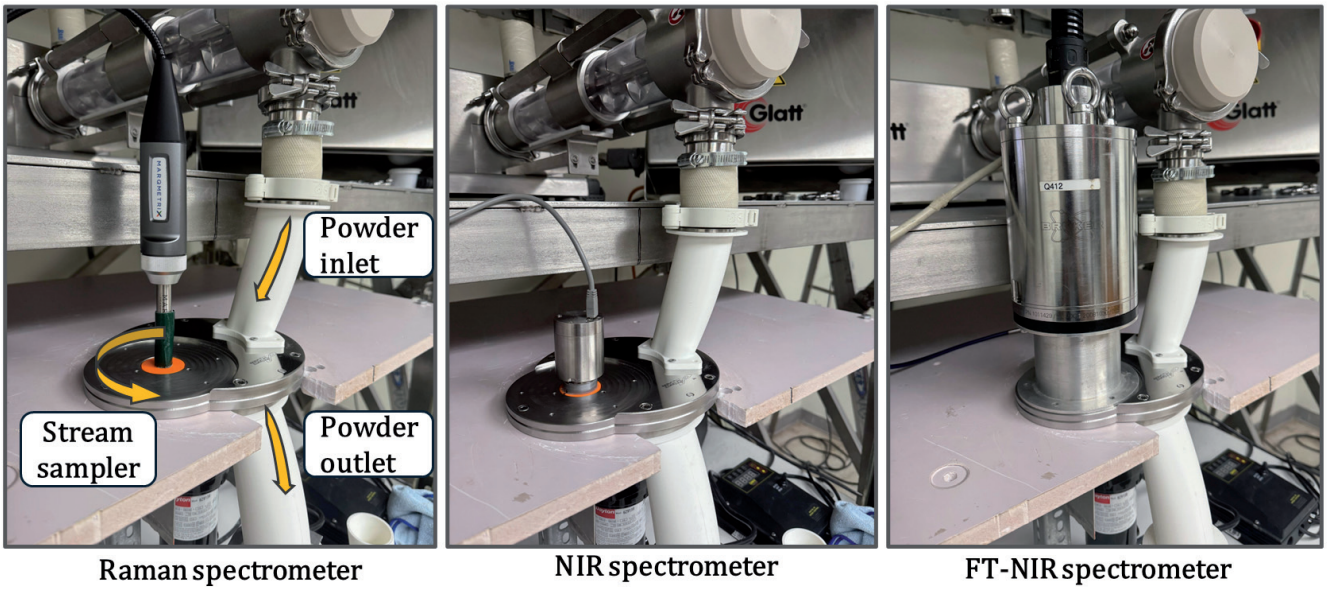

Figure 8: Stream sampler connected to three different spectrometers capable of providing real time spectra for flowing powder mixtures. Left) Marqmetrix (now Thermo) Raman spectrometer, middle) Viavi MicroNIR, and right Bruker Matrix Fourier Transform near infrared spectrometer.

Figure 9: Graduate student Dhavalkumar Patel explaining the system. Left to right: graduate student Maraliz Rivera Santiago (Chemical Engineering), and undergraduate students:Edwin Tañon Flores (Chemistry), Daianne L. Negrón Martínez (Chemical Engineering) Carlos Feliciano López, (Chemistry) and Diego Rodriguez Perez (Chemical Engineering).

16. Quality and Sampling in the Pharmaceutical Industry

The recent Covid pandemic crisis (2020–2022) showed the extreme importance of pharmaceutical manufacturing and of having a pharmaceutical industry able to respond to a global, regional or local health crisis. The right pharmaceutical products need to be accessible to patients the world over.

Since 2001, leading regulatory agencies have emphasized the need to guarantee the quality of pharmaceutical products through the QbD concept (quality by design) instead of quality by testing (European Medicines Agency, 2017). One of the tenets of this initiative is that science and regulatory agencies must protect patients (Woodcock, 2014). Even the most knowledgeable pharmaceutical scientist cannot evaluate the quality of a pharmaceutical product when lying in the intensive care unit: Scientific understanding and regulatory agencies are needed.

Quality by Design also requires sampling by design. Representativity depends on the sampling process. Representative samples only occur as a result of a representative sampling process (Danish Standard 3077, 2024).

17. Process Analytical Technology system solution in pharma

The developments described in this article were selected to showcase key examples of PAT solutions while also taking care of the specific analytical and IDE/IEE issues facing pharmaceutical systems. The still remaining issue is the partial thickness coverage (IDE/IEE) of the stream flow. However, there are still other TOS principles and ideas that need to be considered in pharmaceutical manufacturing. Additional research is needed.

18. Future goals

The next big goal is to include TOS in analytical chemistry books. It is very difficult for an analytical chemist whose entire training has been in wet chemistry and instrumental analytical methods to comprehend and visualize a sampling error. Chemists often believe that method validations already cover sampling errors. TOS needs to be incorporated into analytical chemistry textbooks to foster curiosity towards sampling errors early in the career of young chemists. These textbook chapters are the next big challenge.

The recent Euroanalysis2025 conference in Barcelona provided the opportunity to deliver three lectures on TOS: Claudia Paoletti presented on "The new frontiers in food and feed risk assessment", Kim Esbensen on: "Why analysis needs the Theory of Sampling (TOS) – the importance of the 'before analysis' domain", and the present author on "Innovation & Collaboration for Process Analytical Technology & Advanced Pharmaceutical Manufacturing". The audience's response to these presentations was encouragingly positive. The audience recognized that sampling is essential and that the concepts and ideas discussed in the three presentations need to be included more in analytical chemistry. A textbook chapter would certainly help develop TOS within the analytical community and spark genuine scientific curiosity.

The challenges and rewards of representative sampling need to be highlighted. Sampling has to be shown to be scientifically, technologically and economically attractive in spite of all the hard work needed. TOS cannot afford to be viewed as but a set of mandated high-level rules that must be followed, or a as a set of articles on the theme "I told you so, you should have followed TOS". The web site of the International Pierre Gy Sampling Association (IPGSA) and the new journal Sampling Science and Technology (SST) will certainly contribute to meeting this challenge. The reader is invited to join in this endeavor.

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This article is possible thanks to the efforts of over 30 graduate students who have contributed to the research since 1999. The collaboration with Dr. Rafael Méndez of the UPRM Chemical Engineering department has been essential for this study. As a result of this support, we now have a research lab dedicated to the training of both chemistry and chemical engineering students, and a commercial Stream Sampling Kit for use in the pharmaceutical industry The article is dedicated to the first students work on sampling together with the present author on this journey: Manuel Popo Amú, Angel Martínez Hernández, and Saly Romero-Torres. Manuel, the one of the author's first graduate students, was a devoted family man who recently passed away in his native Colombia. Angel Martínez Hernández obtained his M.S. in Chemistry in our group and is successfully leading the manufacture of pharmaceutical products. Saly Romero-Torres, a devoted mother and community leader, was the first undergraduate student to select our group and is currently a chemometrics and data science expert who leads her own consulting company.

Dhavalkumar Patel is thanked for the wonderful work with the figures.

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