Analyze That episode 7 transcript

From Molecule to Medicine: How Quality Is Built into Drug Development

An Interview with Dr. Anil Kane
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This transcript has been lightly edited for clarity, readability, and length. The content reflects the original discussion and technical intent of the speakers.

Keith: I was curious—before I dive right into it—what brought you to this field of science? Speaking to a lot of scientists, what I've found is that when they were starting, going way back even to coming out of undergrad, there were always options. One person I spoke to had a choice between biomedical engineering and food development science, and they went the food development route. I'm just curious, what were your choices when you were picking a field?

Anil: I was actually intrigued by the field of paramedical sciences, and pharmacy and pharmaceutics really caught my attention. Within the pharmaceutical world, the drug development piece really caught my attention. I wanted to learn more, and that's where I started—my education background being a pharmacist—and then jumped into the pharmaceutical industry. I've been in drug development throughout my career.

Keith: So when you were a pharmacist, what setting were you working in? Was it a hospital setting?

Anil: No, actually there are different branches of pharmacy. One is industrial pharmacy, where we do research and development. The second arm could be clinical pharmacy, where one could work in a hospital setting, etc. I chose industrial pharmacy—research and development in an industry setting—to develop medicines and drugs for a variety of different indications. So that's the path I chose.

Keith: I see, so you chose the more upstream path.

Anil: That's correct.

Keith: How many years have you been in this industry?

Anil: That's a great question. I've lost track of time. It's been more than 35 years in the pharmaceutical industry. It's a long time, and it has been extremely rewarding—great learning. As one can imagine, in every field, things have changed drastically from the time we all started to now, because things have evolved and technology has changed. That has changed the world in the way we think, the way we do things, and it's getting more and more interesting.

Orf: When somebody says, "I don't know how long I've been in the industry," you just know they've been in it a really long time.

Keith: Well, I guess right there we can jump into the nitty-gritty of what we came to talk about today. What I wanted to discuss was how quality is built into drug development from early design through manufacturing. I'm really glad to have your background to speak to this. So I'll start with this: what does quality really mean in drug development?

Anil: In drug development and in the pharmaceutical world, quality is an integral part of everything that we are required to do and expected to do. Let me elaborate. Quality is something that is given—there is no choice, there is no compromise—and quality is expected.

Let me take a step back. In drug development, the entire journey of drug development from concept through the clinical phases and all the way to approval to the patient takes anywhere between five to twelve years, and quality is an integral part of every step of the way of the drug development journey. It starts from designing the right strategy in development and decision-making. The quality of input will directly impact the quality of decision-making and the quality of output. This is science, so this is data-driven decision-making.

In the entire drug development scenario, the decisions are go/no-go decisions are made based on data sets. There is a hypothesis, there is a practicality, there is data generation, and based on that data, a scientist would decide to proceed in one direction or choose another path to meet their goals and milestones. This quality of input—the data set—is extremely important at every step of the drug development process.

Keith: Is there a difference between how quality is perceived earlier in development versus later in development?

Anil: Yes, there is certainly a difference in the sense that there are phase-appropriate quality decisions to be made. Let me take some examples to illustrate the point. As I was mentioning, a small molecule coming out of drug discovery and choosing the lead candidate that has the potential to treat an immunological condition, or a type of cancer, this cancer could be different types of cancer, the cancer could be stomach cancer, intestinal cancer, lung cancer, or another target—right from lead candidate selection, we

would have quality decisions. We would have test methodologies. We would have phase-appropriate analytical techniques to generate the right data set.

For small molecules or large molecules coming out of drug discovery, it is essential that we adopt good, robust, phase-appropriate working test methods and analytical methods that will give us the right feedback to help with decision-making. That's where I say the robustness of the methods.

Now, these analytical methods and techniques need not be fully validated as one would require at a late-stage development or a late-stage commercialization process that meets regulatory guidances and expectations. However, these analytical test methods have to be phase-appropriate, and the working methods must be robust enough to give us the feedback to make the right quality decisions—a go or no-go—or to give us the right interpretation or inference as to how the molecule is behaving. Is it stable? Does it absorb in the bloodstream in small animals, in human subjects, and in clinical phases?

That's where the quality of input and the quality of interpretation, and the data set are important. That's where I would differentiate between phase-appropriate analytical techniques to give phase-appropriate quality decisions, and would differentiate between early-stage decision-making and late-stage clinical and commercialization stages to make those different quality decisions.

Orf: So it sounds to me like when you're saying quality, it's almost a measurement of effectiveness. Does the molecule do what you want it to do? How would your team build in whatever analytical methods or testing methods to check or verify those things as your molecule is developing and moving through the process?

Anil: Understanding the molecule's properties at an early stage is extremely critical and important, whether it's a small molecule coming out of medicinal chemistry and synthetic organic chemistry, or a biologic drug substance developed using cell line development. Understanding the molecule and performing a complete characterization is extremely critical. This is where the right analytical techniques come in—to understand the properties of the molecule and generate what we call an enabling data set.

Right from selection of the right polymorph, selection of the right salt to select the lead candidate, moving into preclinical decision-making, toxicology studies, and then first-in-human clinical studies—that's where the quality comes in. Having the right analytical techniques, the right working methods, to understand the molecule, its criticalities, and its stability profile. Will the molecule be absorbed by small animal rodents or larger animals in preclinical toxicology studies? Will it be absorbed in first-in-human subjects?

The right analytical techniques and bioanalytical techniques are extremely important to give this feedback. Does it get absorbed? Is it distributed? Does it reach the plasma levels to give its therapeutic efficacy? In early stage, these are stage-gate decision-

making processes wherein the right analytical techniques and quality of input—the data that is generated at every step—will help drive the right decision-making.

In today's day and age, with the pressures of bringing new drugs to clinical proof of efficacy and to the patients, there is no time to go back to the drawing board. Hence, getting it right the first time and having the right data set to make the right decisions at the right time is extremely critical. We rely on the methods that are generated, and we have started to rely on predictive modeling tools as well.

Keith: Can you touch on some of these advanced techniques? You're talking about predictive modeling tools. I'd like to hear a little more about some of those advanced techniques.

Anil: Modeling tools have been around for several years now. If we recall, it used to be called neural networks—building algorithms and learning modules. Today, we're calling it artificial intelligence and machine learning. As we were saying, the right data set is required to build these learning modules. With faster computing techniques and technologies, we are now able to build robust learning modules, and with these robust learning algorithms, we are now able to use them as the basis for prediction in several areas.

This could be in selecting the right candidate in early stage, the salt selection, predicting its solubility, its absorption profile, predicting its bioavailability, selecting the right excipients, polymers, and ingredients that will help improve the effectiveness of these molecules, predicting the right technology, or predicting the stability profile in a much shorter timeframe. All of these are applications of the predictive modeling tools that have evolved.

We have started to leverage these predictive modeling tools to bring efficiencies of time, to make speedier decision-making. These models also help reduce the overall cost of drug development, especially in early stages where time is more critical than at other stages. There is then no requirement for—or no place for—trial and error. With these predictive modeling and AI/ML learning tools, we are now better equipped to narrow down the options and progress selected molecules towards clinical stage and then towards later clinical stages, to bring the most effective molecules towards approval and to the patients.

Orf: So predictive modeling is great, but at some point you have to know whether or not what you predicted actually happened. What kind of advanced analytical instrumentation would you be using? Something like basic chromatography or melting point and boiling point isn't going to tell you if you got that functional group in the right place, or if it even exists at all. Could you go into what sort of more advanced analytical instrumentation would help you figure out if your predictions came true?

Anil: Absolutely. Predictive modeling helps reduce the trial-and-error methods and narrow down the options from a data set of tens of molecules or hundreds of molecules to a few limited number of candidates or technologies that we want to pursue. That's

where we would focus the true experimentation to confirm that the predictive modeling is giving us real-time data—whether it's experimentation of selecting the right polymorph using X-ray crystallography, particle size determination, Raman spectroscopy, near infrared, or any of these analytical techniques that give us information about the right molecule.

Selection of the right technology. We would confirm whether we can convert a crystalline drug substance to an amorphous drug substance using powder X-ray diffraction or differential scanning calorimetry. All these techniques then give us confirmation that our predictive modeling has resulted in the right selection of potential candidates where we can focus and bring speed in taking those effective molecules to late-stage clinical success.

Keith: This is very complex. You're involved in drug companies, or you help drug companies execute on this process. Are there parts of this process that some companies choose to keep in-house and outsource other parts of it?

Anil: At Thermo Fisher Scientific, within our Pharma Services Group, we are very frequently contracted for the entire end-to-end drug development services. We are brought into the discussions early on, where our sponsor companies—whether these are the larger biopharma companies, mid-size, or even biotech companies who may not have in-house expertise, capabilities, or infrastructure—would outsource their drug development to us at the Thermo Fisher Scientific Pharma Services Group.

We would adopt all these decision-making processes from early development to mid-development, clinical development, all the way to late and commercialization processes. For biotech companies, they may not have in-house expertise and infrastructure, so we would be supporting them in almost every step of the way, as per our discussions and contractual agreements and the expertise that they expect from us—from early development, clinical development, clinical trials, as well as bringing these drugs to market and to the patients.

For bigger biopharma companies, they would have in-house expertise, infrastructure, and capabilities as well. This is where they would want to leverage where the best place is to position a project. What kind of partnership is best to bring speed, efficiency, and success in bringing molecules to approval and to market in the most cost-effective way? This is an ongoing discussion.

Certainly, we have seen multiple models of partnership where some sponsors may want to keep certain portions of the work in-house but outsource to partners like our teams, where they would leverage the expertise and experience set in various stages of the drug development journey.

Keith: Thank you for that. The next thing I want to know—you spoke a lot about some of these methods, what quality is, how we implement it—but now I want to understand: when we implement quality measures early in development, what kind of payoff does it

have later on downstream in development? What about the early quality measures makes the later process better?

Anil: Quality is fundamental and integral in the entire development process. As I mentioned earlier, understanding the molecule and performing full drug substance characterization is key. This forms a fundamental foundation—the pillar—for designing the right strategy in the drug development process or drug product development process. We impart Quality by Design, as the term goes—QbD, as an acronym that is used in the pharmaceutical world. There is phase-appropriate Quality by Design.

We would bring in the Quality by Design experts, protocols, and procedures at different stages in the drug development process—early stage, mid-stage, clinical stage, as well as late stage towards approval. There are different aspects of Quality by Design that we would be working on throughout the entire drug development journey: to select the right candidate, to select the right formulation, select the right analytical techniques, to have the right method validation parameters, to understand the criticalities of these different parameters, and understand the impact of these parameters on the output. Is the method robust?

Is the product design robust? Can it be validated? Can this be a quality product that will be made consistently to meet the quality specifications? Have we understood the edge of failure? Have we understood the ranges where the product would be stable enough?

Every drug product that we make in this industry has a certain amount of shelf life or expiry dating. We would generate the required stability data for every drug product. To understand the stability profile, we would use all these quality metrics and quality parameters.

There are quality specifications that the product is required to meet at every stage of the process. The regulatory agencies—such as the US FDA, the European EMA, the Brazilian ANVISA, the Japanese PMDA, and the Korean MFDS, to name some of these major regulatory agencies—expect quality to be built into the product and the processes. Quality is an integral part of the drug development journey, and this ensures the safety of the patients, as these drugs need to treat certain diseases or indications for which they have been developed and be safe throughout the intake of these drugs. The safety aspect and the effectiveness aspect are essential elements of quality that are expected in a pharmaceutical drug product.

Orf: Have you noticed or seen some actual real-world examples where building in this quality early—making sure that your molecule is what you think it is and does what you think it will do—has avoided or eliminated some sort of late-stage unexpected surprise that is detrimental to drug development? Does the early-stage work smooth things out a lot, or is it still an equal chance that things might go wrong towards the end?

Anil: Absolutely. Quality of data and quality of decision-making are extremely important. As I mentioned earlier, we want to catch the problems early. Generating the right data set—the scientific information—helps with better quality interpretation. Understanding

the right quality parameters, making the right decisions, and solving problems early on is extremely important.

Now, if these quality decisions or the quality of the data set is not accurate enough, there are chances that a product could be unstable. We would not have understood these challenges. The product may not have the right stability parameters. The product may not be scalable or manufacturable, or may not be absorbed in the body to give the right effectiveness. To avoid this attrition or the inefficiencies in the drug development process—which is an expensive proposition—we want to avoid these situations by catching the problems early, by understanding the molecule, generating the right data set, by designing the product, its processes, its scalability, manufacturability, and stability early on.

This is where quality decisions have a big impact on the quality of output, thereby saving time and cost in this expensive process of bringing effective molecules to the patients.

Keith: So Anil, what are you and your team most excited about in the near future?

Anil: We are really excited about the application of artificial intelligence, machine learning, and the use of learning modules, learning algorithms, and neural networks. All of these are very similar in meaning, which is the utilization of predictive modeling to give us information faster, to make quality decisions sooner, and to bring drugs to clinical proof of concept, to clinical success, and to bring these effective drugs to patients faster.

I think AI and ML have applications at a variety of different stages throughout the drug development journey. They also have applications in clinical trials, where we at Thermo Fisher Scientific have been exploring every possible opportunity to adopt and implement AI/ML tools to bring these medicines to patients faster. We really look forward to those successes, which will help the pharmaceutical and the healthcare industry.

Keith: What does it mean for the patient when we develop drugs faster, with less costly surprises? In a real patient's life, why does it matter?

Anil: It would really matter because there are patients waiting for these effective medicines to treat their situations, disease states, and ailments. There are several indications where today there are no approved drugs. We want to bring safer drugs to these patients and effective drugs to these patients, and bring a better quality of life so that they are treated faster.

Just as we want to bring efficiency in drug development, in healthcare there is also diagnostics. These disease states, conditions, and ailments need to be diagnosed sooner to be treated sooner. This will bring a better quality of life for all of us, and the patients would be treated faster. That's the goal.

Keith: Thank you, Anil.