TRANSLATING EXTRACTABLES AND LEACHABLES RISK ASSESSMENT FROM A LOCAL INITIATIVE INTO A GLOBAL PLAN

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Every pharmaceutical manufacturer strives to perform their production under the highest quality standards possible and adhere to guidelines set by regulatory bodies. Despite these efforts, the true test in achieving these goals is passing a regulatory audit. Any issues or deficiencies resulting from an audit must be addressed expeditiously, even if resolution to the issues means needing to turn to outside experts.

SGS Life Science Services was approached by a large multinational pharmaceutical company as the result of an audit of one of their European manufacturing plants. This particular plant was used in the manufacture of over 40 of their key products, mainly injectables, and hence comprised the highest risk for extractables and leachables. Furthermore, since processes in this location were also used in their plants in other regions (North America and Asia), addressing these issue had far reaching implications beyond just the European operation. Therefore, they were looking for a partner who could evaluate extractables and leachables in their production processes.

Although the company had approached SGS, their intention was to undergo a selection process that involved two other service providers. All three service providers were invited to meet with a selection panel of 20 of their scientists. SGS learned that their production processes involved many filtration and separation steps. As such, there were many points for extractables and leachables to be potentially introduced into various products. While the regulators were interested in potential extractables and leachables in the final 40 products, SGS uncovered that the client's concerns went further during these initial meetings. They wanted to examine their entire production processes. Therefore, the challenge was not simply testing final products, but rather to assess risks and to determine on which risks to focus. Consequently, analytical performance was just one of their selection criteria. In the end, the client was also seeking a conceptual approach to exposure and risk assessment. SGS was selected as the outsourcing partner not only based on technical competence and understanding their need to evaluate risk across the entire production processes, but because of the ability to deliver a global solution. While the audit and need to assess extractables and leachables originated in one European site, their plan was to deploy the testing plan in other European, North American and Asian plants as well. Because of its global network, SGS Life Science Services has the ability to perform harmonized testing in other SGS labs across all regions.

SGS performed the risk assessments in a stepwise fashion. Upon determination of the most critical materials and processes, extractables experiments were performed, followed by essential toxicological evaluations. This was then followed by defining and validating leachables methods for their products.

The final output of the entire process was the on-time delivery of the dossier for the client's extractables and leachables assessment. Given that this study was initiated by a regulatory audit, strict delivery timelines and payment penalties were in place since the client's ability to deliver products to the market was on the line.

INNOVATIVE APPROACHES

There were a few innovative approaches that helped deliver solutions to the customer.

One of the client's additional objectives was to develop and maintain their own global extractables and leachables database on materials within their supply chain (tubes, fittings, etc.), or involved in production. Surprisingly, none of their suppliers could provide information on potential extractables and leachables, exposures, or risks. The reason is that suppliers typically test their materials, but based on their own specifications (e.g. water based testing with pH adjusted). However regulatory authorities require at least three solvents and exhaustive extraction. Because SGS performs extractables and leachables in multiple sites, we maintain and leveraged our own database on these potential compounds in helping the client establish their own database.

Next, SGS has knowledge from different disciplines (production and analytics) and is then able to apply this experience

in addressing the topic of potential unknowns with toxicological relevance with very low threshold values. Organic impurities and toxic compounds were tested via GC and HPLC, inorganic compounds by ICP MS, and further contaminants were evaluated by specific methods already established within our lab network.

Finally, the client had immediate need to roll out the methodology in five other European manufacturing sites and one in North America. The initial work was performed by two German SGS sites (Taunusstein and Berlin) and utilized equipment that is standardized across our network, such that the validated methodology could easily be deployed in other regions.

IMPROVING OUR CLIENTS BUSINESS PERFORMANCE

There were a few changes with how the client dealt with the materials used in production as a result of the project. At the beginning of the project, the client was unsure of their suppliers and the quality of materials they were receiving from them. From the client's perspective, they are continually being approached by different suppliers and they have to balance risk of changing suppliers that could result in costs savings with the additional effort to assess these new supplies for extractables. During the exposure assessment phase, one outcome was that supplies with different plastic materials would be limited and where possible, the same materials should be used to minimize any potential extractables and leachables. Furthermore, the client also made the decision to minimize number of suppliers of plastic materials and focus just on those suppliers that specialize in pharmaceutical-grade materials when possible. One additional outcome of the project was that for some the supplies, pre-preparation procedures (e.g. rinsing steps prior to use in the production line) were developed to reduce extractables and leachables. By implementing this measure in the production procedure, it was possible to limit waste in production and minimize the effort for in-process controls. With the knowledge gained from the project, the client now has a better understanding of the risk profiles associated with all materials in their production process. Finally, with the robust set of data delivered by SGS on-time, the client passed the follow-up audit – an indicator of success.

PROJECT DELIVERY

At beginning of the project, the structure of the project was unclear. After placing the project with SGS, we worked together with the client to address areas that were not covered upfront. For instance, pre-preparation procedures needed to be defined and consequently implemented. Additionally, availability and delivery of the materials from vendors was uncertain and SGS needed to show high flexibility in the planning based on material availability. In order to address these and other issues needed to deliver the project on time, the project was managed by two project managers: one from SGS and one from the client. The responsibility and ownership of the project was shared by these two project managers.

When looking at extractables and leachables, the approach is quite different for each one. For extractables, determination is an R&D type of activity and hence is performed under GMP-like conditions because strict GMP is not required. However, the extractables experiments were performed using SOPs and proven Best Practices. Leachables, on the other hand, must be performed under GMP. In this project, there were many products and each product had a different leachables profile. So, given the strict delivery parameters, one factor that helped SGS win the bid was our agreement to payment penalty terms within the contract based upon our confidence and ability to deliver within the given timelines.

CHALLENGES

As with any project, challenges are expected to arise. One which was unique to this particular project was that the client had an in-house extractables and leachables expert in one of its US sites. This issue had to be handled with respect and sensitivity since the internal expert was well known in scientific circles on the topic of extractables and leachables. Their approach in the US site primarily utilized NMR for unknown determination in addition to MS. In many cases, NMR is the method of choice for identification. However, information delivered by MS like accurate mass/elementary composition, molecular mass and fragmentation pattern provides structural information of the unknown which in most instances will allow for a proper characterisation. Performing NMR requires either more material for analysis or will require additional concentration steps. An alternative would be for the client to invest in high-end NRM systems that would require capital, and the necessary expertise to operate the instrument. The European site (our client), on the other hand, wanted a more pragmatic approach in order to deliver the file on time. They favored using LC/MS Q ToF mass spectrometry that could perform testing on samples without concentration and operate in ultra-trace levels. Additionally, since deploying methodology arising from the project was planned, harmonizing a LC/MS Q ToF approach was more practical than potentially using NMR. In the end, SGS was able to use this Q ToF – MS/MS procedure as the basis for harmonized SOPs for the client's extractables testing.

KEY FACTORS TO SUCCESS

There were a few key factors that stand out that allowed SGS to win this competitive bid and deliver a successful project. First, SGS had established its expertise in the extractables and leachables arena via its participation in various extractables and leachables conferences. SGS often presents data at these conferences and engages regulatory bodies on discussion. As a result SGS was able to demonstrate to the client its complete command of the subject matter. In addition, SGS's global compliance with regulatory authorities contributed greatly to the project's success since the client wanted to deploy the methodology in multiple regions.

Finally, the most significant factor was how SGS used its technical expertise to help the client shape the project beyond just the extractables and leachables assessment of the 40 finished products. What began as potentially routine analysis extended beyond what was discussed in the initial meeting. In the end, the project extended to include

an in-depth examination of their entire production process in the context of extractables and leachables. This satisfied not only the evaluation of the existing products in production, but also allowed the client eliminate future concerns by developing and implementing a strategy in managing the materials used in their production.

Learn more about SGS's extractables and leachables testing services.
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