Enabling a Healthier World

Lonza Biologics

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Accelerating the Path to Clinical Filing Applications with Rapid Toxicology Material Delivery

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The application for investigational new drug (IND) and Clinical Trial Application (CTA) is a key step in initiating clinical trials/first-in-human (FIH) trials for a drug candidate. Furthermore, its approval can help companies secure additional funding and facilitate pipeline generation.

However, pre-clinical toxicology studies can present a bottleneck for companies on the path to FIH. Accelerating their timelines through rapid toxicology material delivery can be an effective way to reduce a drug candidate's time to enter the clinic.

Pre-clinical toxicology studies aim to provide safety data on a drug candidate, so that any potential risks are well-understood before the candidate enters clinical trials in humans.

Indeed, data from toxicology studies are required for drug developers to apply for FIH initiation. Attaining regulatory approval means a pre-clinical drug candidate has been approved for FIH trials.

The importance of early toxicology studies for health authority application and securing funding

In early-stage drug development, a health authority application for FIH is not only indicative of a drug candidate's quality and therapeutic potential. In some cases, it also helps companies secure further funding needed to bring the candidate into the clinic, after demonstration of its safety.

"One of the main benefits of rapid initiation of toxicology studies is that it enables the customer to de-risk investment opportunities," explains Alejandro Fernandez-Martell, Principal Scientist, Global Process Development at Lonza. "This is particularly important for early stage biotech companies, because they might have financial milestones linked to the initiation or even completion of pre-clinical toxicology studies."

"Early execution of pre-clinical toxicology provides confidence to investors," Fernandez-Martell continues. "This can be pivotal in securing the next investment round."

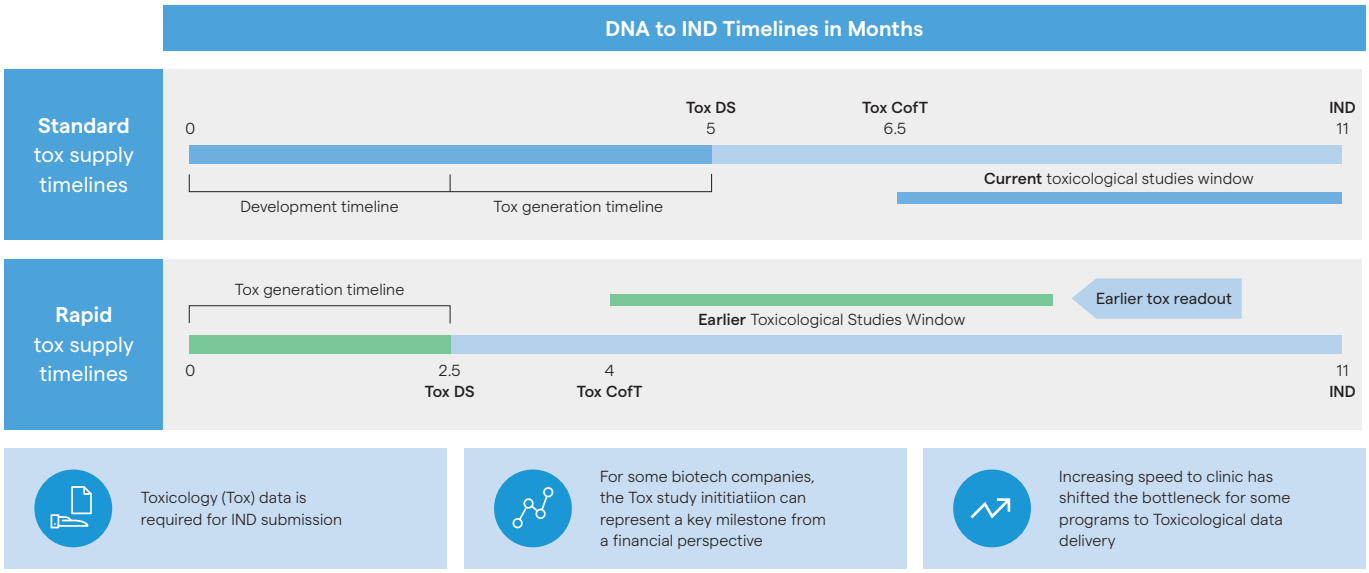

Figure 1
Lonza's new accelerated tox offering for mAbs.

Removing the bottleneck in toxicology material delivery

Today, monoclonal antibodies (mAbs) are an effective, widely used treatment form for a range of conditions, including inflammatory disease and cancer. These therapeutic proteins, or biologics, are made in living cells from a DNA template. Moving from this DNA stage to the final protein product used to take a considerable amount of time, but this has changed.

Within the framework of accelerated timelines, however, toxicology (tox) studies are now often a rate-limiting step in preparing a health authority application for FIH.

"We've shortened the DNA-to-IND timeline significantly for mAbs. But, this can create a bottleneck when it comes to generating tox data – everything for an FIH application may be in place except for the tox data, because the studies are still running" explains James Berrie, Technical Director, Global Process Development at Lonza. "However, we're finding ways to debottleneck the process through early initiation of tox studies."

In standard DNA-to-IND offerings, toxicology animal testing, including data analysis and generating a report, needs to be completed within four to five months. Lonza has advanced strategies deployable to meet these deadlines for a timely FIH application.

"Lonza's new accelerated tox offering can generate toxicology material within two and a half months post-transfection, so our customers can initiate toxicology studies sooner," Fernandez-Martell elaborates (Figure 1). "This gives them an additional two to three months to complete tox studies, minimizing potential delays to the regulatory application."

"We are also developing accelerated tox delivery processes for high concentration mAb formulations and more complex molecular formats," says Berrie. "As these formats become widely used in a variety of therapy spaces, expediting their development is increasingly important."

Ensuring toxicology material availability

The execution of toxicology studies require a certain amount of drug substance to generate usable data.

"Titer is an essential aspect of rapid toxicology delivery," says Berrie, "because drug substance is required not only for the tox studies themselves, but also for multiple supporting activities that facilitate rapid timelines in tox material delivery. A minimum titer ensures sufficient material is available for all these processes."

"For more complex non-platform processes, material might be required for formulation evaluation. Material is also needed to manufacture drug substance into drug product to provide stability data for the regulatory submission" Berrie explains.

Lonza's GS piggyBac® system can generate consistent, predictable high-yield cell lines and support a rapid stable pool generation. GS piggyBac® utilizes an engineered transposase enzyme to insert genes of interest into transcriptionally active regions of the host genome.

"Prior to process development, we perform *in silico* manufacturability assessment to identify specific patterns that help

our customers make informed decisions about the liability of certain molecules" Fernandez-Martell continues.

"We prioritized some of our analytical method development stages, so that the tox material is available when needed," explains Fernandez-Martell. "This helps guide small-scale development before rapidly scaling up to a production scale."

Delivering rapid toxicology material with Lonza's platform

Lonza utilizes multiple methods and processes in their platform approach to deliver toxicology materials quickly. For more complex modalities, the company uses an analytical toolbox approach.

"Our Drug Product Services (DPS) function can help identify which formulation is the most suitable for standard mAbs," Fernandez-Martell continues. "Reducing timelines also requires handling multiple processes simultaneously. To this end, we are developing purification steps which run the development and actual DSP pilot processing of mAbs almost in parallel."

"Another important change is our ability to deliver tox drug substance (DS) material supply from stable pools instead of clonal material," says Fernandez-Martell.

Clonal cell lines are derived from a single progenitor cell that is cloned to produce more cells. On the other hand, a pool of stable clones refers to a genetically engineered population of heterogeneous cells. Stable pools are a frequently used approach in early-stage process development, and are then used in toxicology studies. In most cases, they can also be a starting point for generating clonal cell lines.

"To make optimal use of stable pools for toxicology material generation, the tox material generated using pools needs to be comparable to the clonal material intended for first-in-human studies," Fernandez-Martell explains. "Using pool material helps us bring innovative therapeutic drugs to first-in-human trials faster. Furthermore, with the correct evaluations, we can demonstrate the product comparability between pool-for-tox strategy and clonal GMP batch."

Meeting industry demand of today

Lonza's tox work with stable pool cells started over two decades ago and has been growing steadily. Pool material supply helps initiate drug development early and create material for later development stages. Stable pool material also helps reduce development timelines, which proved valuable during the pandemic.

"Companies have adopted accelerated CMC workflows to enable speed to clinic. Some companies moved to pooled material for tox rather than clonal, not only in response to the Covid pandemic but beyond. In the past, moving from DNA to IND could take years. Now, the expectation has been reduced from years to months," Fernandez-Martell explains. "These timelines are likely becoming the new industry norm."

"Expectations for rapid timelines were driven by progress in delivering mAbs quickly. Now, rapid tox delivery is expected for highly complex molecules and high concentration biotherapeutics products as well," explains Fernandez-Martell.

According to Fernandez-Martell, the use of devices such as pre-filled syringes and autoinjectors for subcutaneous administration is propelling the development of high concentrated products in chronic immunological diseases. Furthermore, the majority of new mAb projects now focus on high concentration formulations, suggesting high concentration biopharmaceuticals will continue to grow in the future.

"Relatively high concentrations bring additional risks to a platform approach, particularly from a platform formulation and analytical perspective; however faster timelines have been developed for these therapeutics", explains Berrie.

In response to current industry demands for speed to FIH, regulators are looking to adapt regulatory guidance. For example 'breakthrough status' designation and the FDA recently issued draft guidance around platform technology designation. For a technology in drug development and manufacturing to qualify for platform status, it must provide a standardized approach to facilitate the development or production of more than one drug or biologic.

"The idea behind this is to speed up development, review, and delivery to the clinic for applicants," explains Berrie. "Granting platform status to a drug in development can bring it to patients faster, as platform technologies do not need to go through a full regulatory review potentially. In turn, this places further pressure on the need for debottlenecking toxicology material delivery."

The horizon of tox studies

The emergence of personalized therapeutics and the shift towards AI-generated drug candidates are changing how toxicology studies will be approached in the future. Personalized therapies use drug material tailored to, and possibly derived from, each individual patient – such as cell and gene therapies. Additionally, AI-generated candidates may become so tailored to a human target that testing in an animal model may not be feasible in some cases.

As a result, *in silico* predictability and technologies based on the patient's own immune system, such as human iPS cell-derived 3D organoids, may replace traditional toxicology studies as a precursor to clinical trials. Furthermore, targeting technologies such as analysis of expression databases can help de-risk candidates and characterize drug effects more fully. These approaches are also likely to play an important role in debottlenecking timelines to FIH and aligning clinical material with patient needs as quickly as possible.

These advances are on the horizon, but they have yet to come into widespread use. Until that becomes a reality, the supply of tox material is for now a fundamental part of the path to IND both in terms of new molecular formats and complex biologics. Lonza's ability to provide Tox material supply to initiate toxicology studies early, already enables customers to remove bottlenecks on the road to FIH for more traditional biologics and will continue to be an important asset in drug development in the future as Lonza further seeks ways to reduce time to toxicology material supply.

Contact us to discuss how Lonza's rapid delivery of toxicology material can benefit your program on the road to FIH trials today.

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