Coping with challenges in drug development

DRUG DEVELOPMENT AND MANUFACTURING Checklists could significantly avoid delays and difficulties in drug development.

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The challenges involved in drug development are growing, and regulatory requirements are becoming more complex. Formal GMP requirements for sterile manufacturing can cause delays or force companies to seek additional funding. Partnering with an experienced Contract Development and Manufacturing Organization (CDMO) can help prevent such issues from occurring. This report highlights some key aspects to consider from a CDMO perspective before starting a clinical manufacturing project.

A realistic timeline

The key to success is early planning. First and foremost is to create a realistic timeline in advance of a formal submission of an investigational new drug file (IND), or an investigational medicinal product dossier (IMPD) to an authority. Discuss this schedule in detail before setting dates with a Contract Research Organization (CRO) or clinical trial site. Be sure that all the parameters required by regulatory authorities are determined, such as class of compound, formulation, and presentation. Requirements regarding sterile filling, stability, bioavailability, and patient safety should also be clarified. Establishing GMP production also demands in-depth manufacturing knowledge of the active substance and the ultimate drug product. Moreover, certain quality requirements should be established from the start, such as the level of containment, local site registration documentation, solubilization of API, and unique properties or process requirements, such as the addition of organic solvents, nitrogen overlay, or

Automatic vial filling at Vetter's US site in Chicago

suspension filling. The more complex the substance, the more complicated the filling process. Discuss issues early with the CDMO so as to avoid delays.

Primary packaging selection to reduce risk and cost

It is important to know from the start if the drug will be filled in a standard package or a customised one and be sure to check if the device system or format can be filled at a CDMO. An experienced partner will know what generates additional costs or delays in manufacturing and can support you with valuable recommendation, for example, for the choice of stoppers. Also, consider sourcing of components and excipients. Experienced partners will have established suppliers for common excipients, which may differ from the ones used in the laboratory setting. Large-scale GMP procedures require formal proof of quality manufacturing, with documented and certified specification limits. This is done using formal audits, which will have to be performed in order to establish that the clinical manufacturing project is being handled correctly. Another option is to cooperate with the CDMO's existing sources. Because the location of the filling can also become an issue, before starting, ask how best to import and export your API and various components to the country where the manufacturing will occur. Usually, manufacturing in the same country where the trial is to take place is the simplest solution. If this is not possible, investigate how to get regulatory approval in your trial country, and extensive international customs documentation will be needed for shipping. Compounding and filling may change the value of the product with respect to exporting.

Legal and quality issues

The agreement should include an understanding of all of the manufacturer's quality requirements for GMP filling. An agreement by the partner to commit resources and set a date for a formal audit by an CDMO is preferable. Confidentiality and development service agreements also have special requirements. Risk management, liability, and IP ownership are all issues that need to be understood and agreed upon prior to starting any work, so

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Clinical manufacturing on time and within budget: Items for consideration

- Contact regulatory authorities before planning time lines.
- Know your drug product details. What will you need for GMP production and clinical trials by country?
- Importing and exporting API and filled drug product. What should you know about shipping and customs?
- Are you using common packaging materials, and can they be processed and sourced for clinical and commercial supply?
- Talk to your CDMO as early as possible, and share as much data as possible.
- Have you planned enough time for legal agreements?

that both parties have a common understanding. The process can become even more complicated as additional third parties are involved.

As we have seen, elaborating a detailed checklist is an important key to successful GMP clinical manufacturing. In summation, the first requirement is a realistic timeline. Second, be well-versed in all the regulatory provisions. Finally, be aware of any risks involved, e.g., nonstandard packaging solutions or loss of API. A good CDMO should be able to walk a development team through a project outlining the timelines and critical issues that need to be considered at each stage. ■

Parasite prevents autoimmunity

ALLERGY A protein used by tropical parasitic worms to survive in humans could be key to the reduction of allergic and autoimmune disorders in the western world, where parasitic infections are rare. In November, researchers from CRNS in Nice, German Twincore GmbH (Hannover), and the University of Queensland reported that administration of a recombinant version of the immunodampening AIP-2 protein from the tropical hookworm *Ancylostoma caninum* suppressed airway inflammation in a mouse model of asthma.

Following administration, the team headed by Alex Loukas observed reduced expression of costimulatory markers on human dendritic cells (DCs), and suppressed *ex vivo* proliferation of T cells from human subjects with house dust mite allergy. In mice, AIP-2 was primarily captured by mesenteric $CD103^+$ DCs, and the suppression of airway inflammation was dependent on both DCs and $Foxp3^+$ regulatory T cells (Tregs) that originated in the mesenteric lymph nodes (MLNs) and accumulated in distant mucosal sites. Transplantation of MLNs from AIP-2–treated mice into naïve hosts revealed a lymphoid tissue conditioning that promoted Treg induction and long-term maintenance. The authors believe that recombinant AIP-2 could serve as a novel, curative therapeutic for allergic asthma and other inflammatory diseases.

A patent on uses of AIP-2 to fight autoimmune diseases had been filed by Swiss Mondobiotech AG, which went bankrupt in 2012. ■

Pictures: CDC