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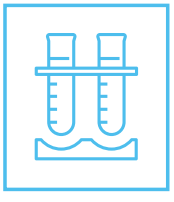

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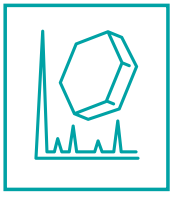

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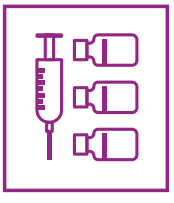

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HPAPI Market Trends

Rising demand for targeted cancer and other treatments driving HPAPI growth.

The percentage of new drug candidates that are highly potent is rising, driving the need for additional manufacturing capacity for highly potent compounds. However, producing these challenging molecules is a complex process. Specialized facilities, equipment and highly skilled personnel are required. Contract manufacturers with demonstrated success in the development and production of potent active pharmaceutical ingredients (APIs) are helping to meet this need.

WHAT DOES HIGHLY POTENT MEAN?

There is no regulatory standard defining highly potent active pharmaceutical ingredients (HPAPIs). All highly potent compounds, however, have impacts at very low concentration. In general, APIs are considered to be potent if they are pharmacologically active and exhibit biologic activity at a level of 15 micrograms (µg) per kilogram of body weight or less in humans, or are efficacious at a therapeutic dose of 1 milligram (mg) or

less per day.[1] Another pharmaceutical industry definition identifies potent compounds as having occupational exposure limits (OELs) at or below 10 µg/m3 of air as an 8-hour time-weighted average.[2] However, there is no specific consensus definition for a highly potent compound.

In addition, not all HPAPIs that are potent against diseased cells (e.g., tumor cells) are highly potent toward other cells.[2] Furthermore, potency and toxicity are not equivalent. Highly potent compounds may be effective for cancer treatment at low doses but not toxic, while traditional chemotherapy agents are not very potent at low therapeutic doses but often cause toxic side effects.

It is thus essential to characterize the hazards posed by a compound, including any potential exposure problems, whether they are acute (e.g., somnolence, respiratory arrest, adrenergic or lachrymatory effects, allergenic responses, corrosivity, irritation.) or chronic (e.g., carcinogenicity, mutagenicity, clastogenicity, sensitization), as well as the possibility for developmental or reproductive effects or toxicity with repeated dosing.[2] Critical effects of exposure must be identified and any dose–response relationships determined.

Once these attributes are understood, an OEL can be assigned and then used to conduct a risk assessment. Often, not all of this information is available at the start of a development project, and uncertainties must be considered. As a result, OEL values can vary significantly as a function of the risk assessor. A flexible approach is required to provide access to a wide range of possible practical solutions that are appropriate for the manufacturing site, will protect workers and the environment and can evolve as projects move through the development cycle and additional data is generated.[2]

POTENT GROWTH

Estimates for the size of the global HPAPI market vary, but most analysts agree that strong growth can be expected over the next 5–10 years.

Markets and Markets estimates that the global HPAPI market will expand at a compound annual growth rate (CAGR) of 8.7% from $17.72 billion in 2018 to $26.84 billion in 2023.[3] Converged Markets, meanwhile, forecasts a CAGR of 9% from 2018 to 2025, with the value of the market reaching $20 billion by the end of the period.[4] Transparency Market Research predicts that the global HPAPI market will grow at a CAGR of 8.3% to reach $25.11 billion by 2023.5 Finally, Grand View Research sees the global market expanding at a CAGR of 10.3%,6 reaching a value of $34.8 billion by 2025.7

Approximately 25% of new chemical entities are considered to be potent,[1] which can largely be attributed to the fact that about one-third of all drug candidates are oncology treatments.[2] The largest percentage of HPAPIs are used in the formation of anti-cancer drugs.[3–7] Advances in manufacturing and containment technologies and investments by manufacturers are facilitating expansion of the market. Interest in targeted therapies with reduced side effects, most notably antibody–drug conjugates (ADCs), is another key driver of demand growth for HPAPIs.

Most HPAPIs are developed or manufactured for branded drugs, but growth in generic HPAPIs is increasing as existing products lose patent protection.[3] The captive HPAPI segment is also larger than the merchant segment, but outsourcing is increasing and the latter segment is growing at a faster pace.[3] Similarly, most HPAPIs are currently small molecules, but biologic potent compounds are growing at a higher CAGR.6 Geographically, North America (specifically the U.S.) accounts for the largest share of the HPAPI market today, although demand is growing fastest in Asia.[5]

> “Outsourcing allows larger drug makers to focus on drug discovery and product launches, life cycle management and other activities.”

In addition to cancer, HPAPIs are used in hormonal imbalance drugs and drugs intended for the treatment of glaucoma. They are also used in cardiovascular drugs, central nervous system drugs and musculoskeletal drugs.[7]

TARGETED THERAPIES

Traditional drugs are designed as systemic treatments. As such, they travel and can be absorbed throughout the human body. During this process, some of the drug is degraded and some interacts at undesired sites, leading to side effects. Newer targeted therapies, on the other hand, are designed to be delivered to the specific site of action where they interact only with the diseased or cancerous cells. As a result, less drug is needed and side effects are largely avoided.[5,7]

ADCs are a prime example. The cytotoxic payloads in ADCs are HPAPIs. ADCs leverage the specificity of antibodies for certain cells—usually cancer cells. Cytotoxic “payloads”—small-molecule drugs designed to destroy cancer cells—are attached (conjugated) to the antibodies with linker technology. Once the antibody is bound to the tumor, the linker degrades, releasing the payload into the tumor.

These attractive features are driving significant interest in ADCs, with most major and many small and mid-sized pharma companies pursuing development programs. According to Allied Market Research, the ADC market was valued at nearly $1.4 billion in 2016 and will grow at a CAGR of 12.9% from 2017 to 2023, reaching nearly $3.2 billion by the end of the period.[8]

COMPLEX MANUFACTURING

Manufacturing HPAPIs is not a simple matter. Producing ADCs, which requires conjugation of a small-molecule HPAPI to a large biomolecule, is even more daunting. The biggest challeng-

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es are preventing cross-contamination during manufacturing, protection of plant operators and the environment and protection of everyone across the supply chain that handles the final drug product.

Choosing the right containment and protection strategy, including facility design, containment equipment, procedures and personal protective equipment (PPE) can be particularly challenging.[9] The solution should be appropriate for the potent compound, the site capabilities, operator skill level and the specific process involved.

It is equally important to avoid using excessive, unnecessary containment.[10] When data is lacking, the tendency is to be conservative. However, if sufficient data is available for a risk assessment, the adequate level of controls can be determined. Implementation of unnecessarily high containment levels leads to greater costs and longer development timelines, neither of which can be afforded in today's highly competitive market.

Correct installation and setup, as well as appropriate employee training, are essential for ensuring worker protection. Ongoing OEL monitoring of all process stages is important. Proper management of waste streams containing HPAPIs is critical, as is maintenance of containment and processing systems. Manufacturers must also have relevant methods for sampling and testing that minimize the API quantity needed.[1] An understanding of regulatory requirements, including those regarding prevention of cross-contamination, is also essential.

> "[W]hile in-house HPAPI manufacturing currently accounts for the largest share of the market, outsourcing is increasing rapidly."

OUTSOURCING SUPPORT

The complexity of the facilities, equipment and processes and the high levels of operator training required to safely implement HPAPI manufacturing are significant barriers to entry for many pharmaceutical companies. Initial and ongoing investment is high. Many large drug makers have installed internal HPAPI manufacturing capabilities, though most small and medium-sized companies do not have the resources to do so.[11] In addition, some larger pharma companies have only invested in commercial-scale production systems, preferring to rely on contract service providers in earlier development stages.[11] In addition, some firms that have HPAPI capacity are closing or divesting their facilities in favor of outsourcing.[7]

As a result, while in-house HPAPI manufacturing currently accounts for the largest share of the market, outsourcing is increasing rapidly.[7] Outsourcing allows larger drug makers to focus on drug discovery and product launches, life cycle management and other activities. In addition, it can provide cost savings. Outsourcing is also often a risk-mitigation strategy.[1] For smaller firms, use of contract manufacturing services enables access to the specialized technologies needed for HPAPI production.

CHOOSING THE RIGHT CDMO

While outsourcing of HPAPI production provides many advantages, the benefits can only be realized if the contract development and manufacturing organization (CDMO) selected as an outsourcing partner has the right qualifications.

Any CDMO considered as an HPAPI production partner should have experience in the field and a long track record of successfully manufacturing and handling highly potent compounds.[12] There should be clear evidence of regulatory expertise and a positive compliance history.[1] Facilities should be designed specifically for the production of HPAPIs with containment strategies based primarily on engineering controls and administrative solutions (processes and PPE) as secondary measures.[12] An extensive operator training program is also essential. The ability to support projects from development through commercialization and extensive analytical capabilities are also important, as is proper control and containment of waste. All of these factors are indicators of long-term commitment to HPAPI production. **CP**

For a list of references visit the online version of this article at ContractPharma.com.

Michael Avraam
Global Product Manager, ChargePoint Technology

HPAPI Technology Trends

Expanding HPAPI sector driving innovation in containment technology

Use of high potency active pharmaceutical ingredients (HPAPIs) is increasing as pharmaceutical companies focus on developing more effective, better targeted medicines.

This growing interest is increasing demand for the specialist handling and containment systems needed to ensure such products can be manufactured in a manner that complies with employee safety regulations.

In addition, the trend has prompted manufacturers to search for faster, less labor intensive ways of verifying the efficacy of their containment systems.

As a result, the interpretation of containment verification data has become a major focus for internal teams at drug companies and contract manufacturing organizations (CMOs).

This article will outline some of the cutting edge handling and containment technologies being used to ensure the safety of pharmaceutical employees who work with HPAPIs. It will also outline validation and interpretation best practices industry leaders use to make sure their containment efforts are effective.

HPAPI INDUSTRY SURGE

Demand for medicines that target and treat diseases more effectively and with fewer side effects has prompted many pharmaceutical manufacturers to invest in the development of HPAPI-based medicines.

Analysis by Transparency Market Research suggests by the end of 2024 the cancer segment of the HPAPI market, the largest HPAPI segment by far, will be worth close to $100 billion in value, expanding at a CAGR of 6.5%.

The term HPAPI is complicated. All active pharmaceutical ingredients have pharmacologic potency and each can be categorized on continuum of potency from low, to moderate and on to potent and highly potent.

Substances categorized as potent or highly potent must be handled in accordance with strict criteria designed to protect people using them in pharmaceutical manufacture. Generally, HPAPIs are classified as being occupational exposure band 5 (OEB 5), which means staff who work with them must be exposed to less than 1µg/m^3 within a working day. Limiting exposure to such a

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low level necessitates effective containment technologies.

CONTAINMENT TECH IN DEMAND

The use of isolators, restricted access barrier systems (RABS) and split butterfly valves (SBVs) that separate drug products from operators has grown significantly in recent years.

Part of the reason for this is closed transfer technologies like the SBV limit manual intervention and reduce the risk of cross contamination. They also limit the presence of airborne dust particulates.

CONTAINMENT IN THE MANUFACTURING ENVIRONMENT

Establishing effective containment systems in a pharmaceutical manufacturing environment is a considerable challenge because human intervention is present at almost every stage of manufacturing processes.

It is therefore vitally important that containment solutions should not hinder operability or reduce productivity.

Containment technologies such as SBVs have been developed to improve containment for processes where there is a risk of airborne exposure, including during all powder transfer stages.

These valves, when integrated with isolators or other containment technologies, allow for material to be transferred without the risk of it escaping.

VALIDATION AND ASSESSMENT

Once the desired handling and containment systems have been selected it is very important they are tested for efficacy. The best approach is to use a best practices checklist to make this assessment to prevent anything being overlooked.

The International Society for Pharmaceutical Engineering's (ISPE) SMEPAC (Standardized Measurement of Equipment Particulate Airborne Concentration) guideline is widely used. It outlines validation methodologies for a broad range of technologies and processing equipment, all of which are focused on assessing how well the system in question contains particulate matter. Specifically, it provides methodologies manufacturers can use to derive performance data that is invaluable for risk assessments.

The SMEPAC guideline is just that, a guideline rather than a set of strict requirements. Nevertheless, it provides companies with a means of benchmarking their containment capabilities and provides a way of identifying potential risks.

However, it is important to understand that the instructions and test methods set out in the guideline are conducted under controlled conditions in the laboratory. Effort must be made to understand how data generated during validation relates to real-world manufacturing.

DATA INTERPRETATION CONSIDERATIONS

The second phase of any containment technology validation process is data assessment and interpretation. Like all similar guidelines, the testing protocols set out in the SMEPAC document allow for a degree of inconsistency.

For example, manufacturers often look at containment performance data and use it to qualify the selection of the required containment technology for their production process. However, it is important that variability in the testing methods for each type of technology is taken into consideration before any decisions are made.

It is also important that validation testing takes the impact of operator intervention into consideration to ensure the containment device, some of which can be reliant on operator technique to achieve performance, is tested accordingly.

Also, it is vital to keep in mind that all containment technologies used for a particular HPAPI-based pharmaceutical manufacturing process must be validated to ensure the performance of the system as a whole. Each step where there is potential exposure must be validated and the subject of a detailed risk assessment.

The final stage of the validation process should also include the development of a preventative maintenance program based on areas of potential risk that are identified during the assessment phase. The idea is to look at the condition of each containment device and develop a maintenance plan that helps to safeguard the reliability of the containment solution.

INTEGRATION AND MONITORING

As illustrated above, validating containment technologies in a manufacturing environment where HPAPIs are used can be complex and very time consuming.

One approach used to streamline this process is to select containment technologies with capacity for both continuous operational monitoring and the ability to communicate with other systems in place on the manufacturing line.

A continuous flow of equipment operational data can shorten the time taken for revalidation of an existing line or indeed to develop a validation plan for new lines using duplicate technologies. This data can also provide insight into the wear and tear of equipment and therefore, when combined with containment testing results, allows users to secure a safe operating period or usage cycles for the valve before they begin to experience compromised performance. With this kind of monitoring, preventative maintenance can take place on a different level than before.

A continuous monitoring approach is also a good fit for the 'industry 4.0' paradigm, which is based on the idea that Wi-Fi enabled components able to transmit data cut maintenance costs and allow problems to be quickly identified.

CONCLUSION

There are a huge range of factors a pharmaceutical firm must consider when working with HPAPIs. Containment is the most important consideration from a manufacturing standpoint as preventing these highly pharmacologically active substances injuring employees is critical.

However, as stated above, it is also important the correct containment technologies and handling procedures are put in place and that all of these are validated in accordance with appropriated guidelines. Likewise, it is vital operations continue to be monitored for containment deviations after the process has been established and new wireless monitoring technology is set to make a real impact in terms of providing important operational performance data. **CP**

MICHAEL AVRAAM is the global product manager at ChargePoint Technology for the PharmaSafe range of products. He is responsible for the development and evolution of ChargePoint's split butterfly valve technology, including containment performance testing as well as developing new products and technologies.

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ANTIBODY-DRUG CONJUGATES: CATALYSTS FOR CHEMISTRY

Introduction

Antibody-drug conjugates (ADCs), also known as armed antibodies, are highly anticipated to be the source of next generation frontline oncolytic therapy. They marry the selective targeting properties of antibodies with the potency of cytotoxic small molecules. The antibody component targets and adheres to a selected antigenic cell-surface receptor, ideally only expressed on the target cancer cell. Once bound, the ADC is internalized through endocytosis, and the cytotoxic payload is then released in the lysosomal cellular compartment providing precise, selective delivery to cancerous cells.[1] With the development and subsequent marketing approval of Mylotarg® (2000)1, Adcetris® (2011) and Kadcyla® (2013), there was exponential growth in ADC research and development; a trend that has continued with the approvals of Besponsa (2017), Lumoxiti (2018), and Polivy (2019) (Figure 1). Estimates place the global ADC market at $10 billion annually after 2024 with seven to 10 new commercial ADC launches projected in the next decade.[2] No doubt, this explosive track will create opportunities for CROs and CDMO with the expertise necessary to work with these entities. The development of ADCs brings many challenges, however. Multiple disciplines across drug development must engage to successfully discover, develop, evaluate and eventually manufacture a therapeutically relevant ADC.

To illustrate, large macromolecular ADCs have a complex architecture whose assembly, manufacture and analysis presents challenges for organizations without significant experience in biological conjugation, optimization and the development of the important chemical linkers that are critical for effectively tethering the small molecule payload to the antibody. As such, ADCs are good candidates for outsourcing to experienced CROs, particularly the technically demanding processes of preparing the linker payload and developing an optimized conjugation process.

AMRI offers expertise for ADC discovery and development and provides a broad library of natural products, many of which are potent and biologically active and have great potential as ADC payloads. AMRI also has expertise in antibody suitability testing and prioritization, general process research on ADCs, MS analysis and characterization of ADCs, the production of pyrogen-free, sterile ADC for in vivo, preclinical studies as well as pharmacokinetic and pharmacodynamic analysis.

AMRI's capability is not limited to discovery – our expertise also spans development through drug product development and GMP fill-finish. The company has conducted numerous projects involving the synthesis of linker-warhead conjugates under cGMP guidelines for the eventual manufacture of ADCs for clinical trials. Expertise in both discovery and development is rare in the CRO industry. Notably, AMRI partnered with Seattle Genetics for the cGMP manufacturing of the proprietary drug linker section of Adcetris®. AMRI also supported the development of Adcetris® lyophilized drug product, including the supply of multiple clinical batches.

In this article, we discuss the complexities of developing linkers – chemical moieties which attach a drug payload to an antibody, and the considerations that need to be made when identifying a CRO for ADC research and development.

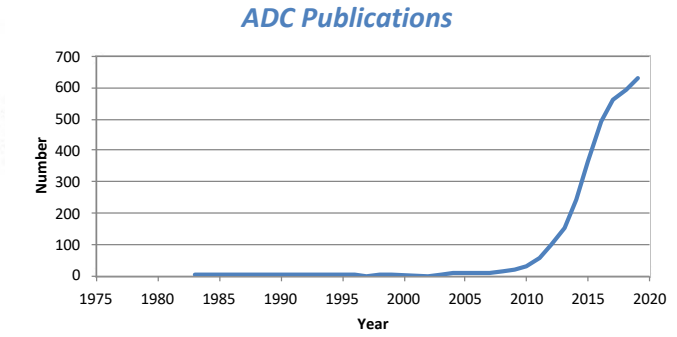

Figure 1:
Results from SciFinder search for "antibody drug conjugate"

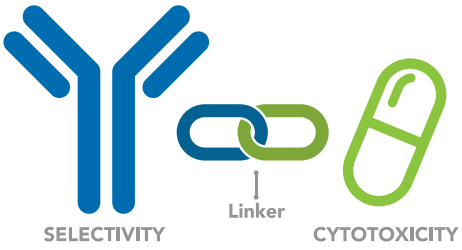

Figure 2: The anatomy of an ADC

ADC Anatomy

Structurally, ADCs consist of an antibody, typically a humanized monoclonal (mAb) of the IgG class, a chemical linker of variable composition and a terminal payload, most frequently a cytotoxin (Figure 2). The payload and linker are miniscule in size compared to the 150 kDa mAb. Multiple linker-payload units are affixed to an antibody, typically up to eight. The ratio of linked drug to antibody (drug antibody ratio or DAR) is a critical factor to consider when designing an ADC. Early ADC research found that high DAR was associated with increased clearance and the potential for aggregation.[3] Equally, increased toxicity may be a likely outcome of high DAR ADCs. Antibodies with site-specific conjugation chemistries are being developed to carefully control DAR and improve ADC homogeneity.[4,5,6] Modification strategies include introduction of cysteine residues (example HC-A114C, Genentech[7]), glutamine residues[8], peptide tags[9], unnatural amino acids[10] and chemoenzymatic functionalization at the conserved heavy chain glycosylation sites at Asn297[11].

The linker moiety is deceptively simple in concept, normally represented in graphics as a mere bridge connecting the payload to the antibody. In practice, the linker is one of the most important factors in the overall performance of the ADC. The linker-payload requires highly skilled scientists to design and construct, as multiple complex chemistry reactions are required to attach the payload to the linker and then the linker-payload to the antibody.

The linkers themselves are demanding to design and develop. Several classes of linkers are cleaved to release the active form of the payload once the ADC is inside the cell. In contrast to this deliberate intracellular frailty, high plasma stability is essential to avoid premature release of the payload and indiscriminate cell killing. Notably, antibodies can circulate in the bloodstream for several days. Therefore, linkers need to match this level of plasma stability. Currently, the range of payloads for ADCs is quite limited with tubulin inhibitors auristatins (MMAE and MMAF) and maytansinoids (DM1 and DM4) comprising 80% of the payloads in clinical development.[12] The paucity of diversity in both mechanism and payload identity is an opportunity for the future development of ADCs, but until new payloads are developed, varying linker chemistry can modulate the physicochemical properties of the ADC. Natural product samples have been a rich source of highly potent, cytotoxic compounds including antibiotics (e.g. penicillins) and anti-cancer (e.g. vinca alkaloid) drugs, but their production, isolation, structural elucidation and incorporation into a druglinker reagent for production of an ADC requires specialized resources (strain and sample libraries), experience, capabilities and expertise.

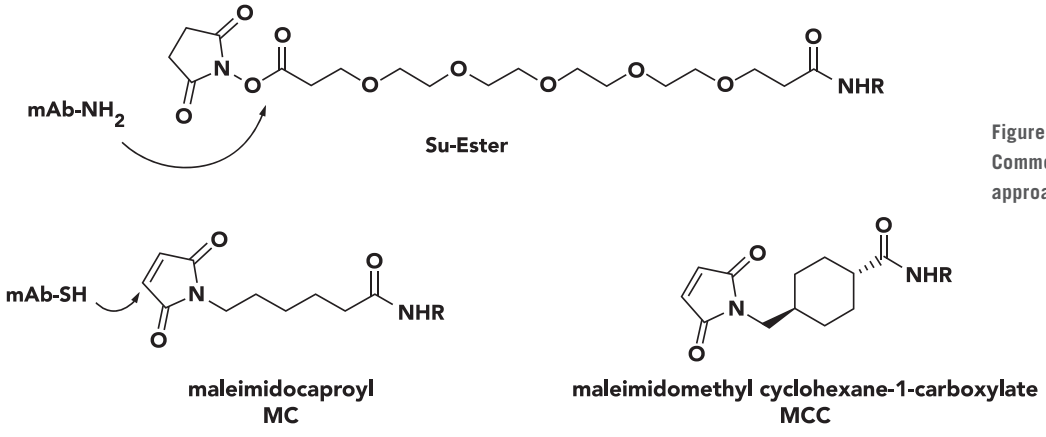

Figure 3: Common conjugation approaches

Linker Chemistry – Antibody Side

Conjugation chemistry to antibodies has historically relied on the sulfhydryl or amino groups found in the natural amino acids. Linker-payload reagents with a terminal antibody-side maleimide or activated ester are frequently encountered (Figure 3). Conjugation chemistry to these groups can be controlled but are random in that the product ADC consists of multiple species. Heterogenous ADCs are more difficult to manufacture due to batch variability, and biologically, individual ADC species offer different profiles of target activity, toxicity and clearance. More recently, site-specific conjugation strategies have opened up the options to include engineered thiols, non-natural amino acids, aldehydes and other groups in the antibody.[13,14] These strategies provide greater control of DAR, simplify the manufacturing process, improve ADC homogeneity[6,8] and can lead to improvements in efficacy and therapeutic index[7].

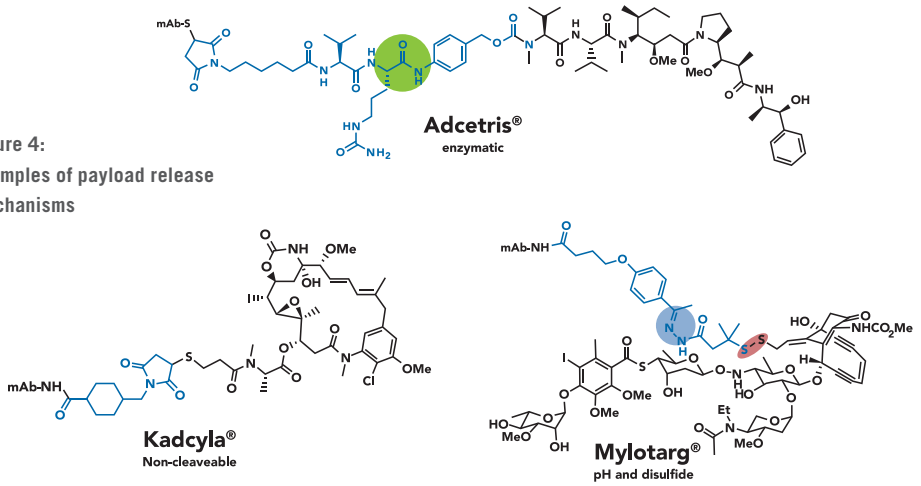

Figure 4:
Examples of payload release mechanisms

Linker Chemistry – Payload Side

In the case of the auristatins and maytansinoids, amine or thiol groups, respectively, connect the payloads to the linker. A thiol-bearing spacer was introduced in maytansine to incorporate a release mechanism. New technologies that use other functional groups, such as hydroxyl, are sought to open up new payload options and linker chemistries.

Payload Release – Cleavable and Non-Cleavable Linkers Innovation

Linkers are categorized as cleavable or non-cleavable. Non-cleavable linkers do not fragment. Instead, proteases digest the antibody protein backbone leaving the linkerpayload tagged with a terminal amino acid residue. Kadcyla® is an example of this type (Figure 4). Cleavable linkers fragment depending upon the environment within a cell. The three common cleavage mechanisms are enzymatic, disulfide and pH. Adcetris® uses a valine-citrulline para-aminobenzyl alcohol motif as part of the linker. Amide bond cleavage of the substrate by a protease results in release of the parent payload after 1,6 – elimination of the *p*-aminobenzyl carbamate moiety.[14] Mylotarg® uses a two-step cleavage method using both pH and disulfide triggers. The acyl hydrazide within the linker is thought to first hydrolyze under the low pH environment of the lysosome (pH ~5). The disulfide is then reduced by glutathione, which is abundant in cancer cells.[14]

ADC Drug Product Development and Fill Finish

Like many biological products, ADCs require careful handling in low-shear, closed systems to ensure retention of biological activity and avoid microbial contamination. Validated single-use systems, low-shear mixing and filling systems utilizing peristaltic pump processes, as well as cold chain product management capabilities are key to maintaining control.

ADC drug products require dedicated cleanroom facilities designed to handle highly potent compounds. Additionally, expertise in liquid and lyophilized product development is required to support the ADC drug product development, as both frozen and lyophilized products are created at various stages in the process, supporting the clinical investigation.

ADC CROs

CROs vary in their competence to deliver quality ADC research. Experienced staff is crucial, as working with both payloads and linkers present challenges. Linkers, which are designed to release their payloads, are sensitive by design and subject to degradation. Poly-functional payloads can possess complex stereochemistry or issues of regiochemistry, requiring selective transformations and non-routine purifications. In addition, payloads are usually highly potent compounds and available in very limited quantities, requiring expert handling during linker-payload reagent synthesis and conjugation reaction process research. Chemists with expertise in small-scale, natural product chemistry and biologists with protein chemistry expertise are well-suited for ADC work.

ADCs straddle the “small molecule/large molecule border” and require expertise in both areas, which are typically not integrated. It is rare to find a CRO with the expertise and analytical capabilities to work effectively in each of these arenas, but finding such a partner can dramatically reduce the burdens of technology transfer. Beyond analytical concerns, this difference is most often seen in purification of the ADC, where advanced techniques in small molecules (crystallization and affinity chromatography) and large molecules (adsorption chromatography and size-exclusion dialysis) differ greatly.

CROs should have proper support facilities such as high potency suites with laminar flow hoods for safe handling of highly potent cytotoxins, protein expression and engineering laboratories for antibody engineering and production and high resolution mass spectrometry for comprehensive analysis of monoclonal antibodies and ADCs. AMRI has state-of-the-art investigational and development tools to support lyophilized product development and a successful track record of transition from lab to GMP fill-finish of liquid and lyophilized ADC products.

Conclusion

As the ADC space matures, novel antibodies, linkers and payloads will be developed to keep pace with the goal to deliver effective medicines with improved safety. Increased pressure to create homogenous ADCs will drive new conjugation approaches to control DAR. ADC discovery will catalyze the development of new chemistry and create opportunities for CROs and CDMOs with the expertise required to work with these entities. With deep expertise in payload and linker chemistry, protein production, ADC process development and sterile, pyrogen-free manufacture of ADCs, along with state-of-the-art facilities across drug discovery, development and drug product, AMRI has the capabilities to meet the needs of our customers who are pursuing ADC drug discovery and development.

About AMRI?

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1. Perez, H.L., Cardarelli, P.M., Deshpande, S., Gangwar, S., Schroeder, G.M., Vite, G.D. and Borzilleri, R.M. *Antibody–drug conjugates:* Current Status and Future Directions. Drug Discov Today. (2014). 19(7): 869-881.
2. *Looking Ahead to 2020: Global Antibody-Drug Market Prediction.* ADC Review. August 17, 2015.
3. Kamath, A.V. and Iyer, S. *Preclinical Pharmacokinetic Considerations for the Development of Antibody Drug Conjugates.* Pharm Res. (2015). 32(11): 3470–3479.
4. Sochaj, A.M., Swiderska, K.W. and Otlewski, J. *Current methods for the synthesis of homogeneous antibody–drug conjugates.* Biotechnology Advances. (2015). 33(6): 775–784.
5. Panowski, S., Bhakta, S., Raab, H., Polakis, P. and Junutula, J.R. *Site-specific Antibody Drug Conjugates for Cancer Therapy.* mAbs. (2014). 6(1): 1–12.
6. Zhou, Q. and Kim, J. *Advances in the Development of Site-Specific Antibody-Drug Conjugation.* Anti-Cancer Agents in Medicinal Chemistry. (2015). 15(7): 828-836.
7. Junutula, J.R., Raab, H., Clark, S., Bhakta, S., Leipold, D.D., Weir, S., Chen, Y., Simpson, M., Tsai, S.P., Dennis, M.S., Lu, Y., Meng, Y.G., Ng, C., Yang, J., Lee, C.C., Duenas, E., Gorrell, J., Katta, V., Kim, A., McDorman, K., Flagella, K., Venook, R., Roos, S., Spencer, S.D., Lee Wong, W., Lowman, H.B., Vandlen, R., Sliwkowski, M.X., Scheller, R.H., Polakis, P. and Mallet, W. *Site-specific Conjugation of a Cytotoxic Drug to an antibody Improves the Therapeutic Index.* Nat. Biotechnology (2008), 26, 925-932.
8. Dennler, P., Chiotellis, A., Fischer, E., Bregeon, D., Belmant, C., Gauthier, L., Lhospice, F., Romagne, F. and Schibli, R. *Transglutaminase-based chemoenzymatic conjugation approach yields homogeneous antibody-drug conjugates.* Bioconjug. Chem. (2014). 25(3): 569-578.
9. Ramakrishnan, B., Boeggeman, E. and Qasba, P.K. *Novel method for in vitro O-glycosylation of proteins: application for conjugation.* Bioconj. Chem. (2007). 18(6): 1912-1918.
10. Hallam, T.J., Wold, E., Wahl, A. and Smider V.V. *Antibody conjugates with unnatural amino acids.* Mol. Pharm. (2015). 12(6): 1848-1862.
11. Okeley, N.M., Toki, B.E., Zhang X et al. *Metabolic engineering of monoclonal antibody carbohydrates for antibody-drug conjugation.* Bioconj. Chem. (2013). 24(10): 1650-1655.
12. Rostami, S., Qazi, I. and Sikorski, R. *The Clinical Landscape of Antibody-Drug Conjugates.* ADC Review. August 1, 2014.
13. Jain, N., Smith, S.W., Ghone, S. and Tomczuk, B. Current ADC Linker Chemistry. Pharm Res. (2015). 32(11): 3526–3540.
14. Kim, E.G. and Kim, K.M. *Strategies and Advancement in Antibody-Drug Conjugate Optimization for Targeted Cancer Therapeutics.* Biomol Ther. (2015). 23(6): 493–509.

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High Potency APIs:
Some Bad News, Some Good News

The growing use of HPAPIs has created some challenges in the lab, while at the same time offering advantages as well.

Some of the newer drugs are extremely potent, allowing for lower level dosage forms—often in the <<1% API range—to be administered. From a patient's standpoint, this means lowered side effects, smaller dosage forms that are easier to swallow for geriatric patients and children, and possibly lower costs. Producing the dosage forms comes with a new set of parameters.

Since it is summer, I will start with the good news. First, with lowered doses, the overall number and volume of excipients are also lower, allowing smaller equipment to be used. When using less material, less space in the warehouse is needed. Fewer shipments of excipients also means fewer samples for QC to assay. Also, smaller tablets/capsules require smaller containers, meaning lower shipping costs and less warehouse storage space for finished products.

Unfortunately, there are also a few downsides to potent, mini-doses. Being more potent, and potentially hazardous, than normal drugs, the handling—weighing, transporting, adding to blenders, sampling, and so forth—may need be done with breathing apparatus, gloves, and gown. This is not to imply that any API is totally harmless, but inhaling small amounts of or touching something like acetaminophen is hardly life threatening. This adds time and expense and potential liability issues arise.

In addition, cleaning and validation thereof can be tricky with extremely low dose products. If we have an SOP stating that "less than one dose may remain on X-cm2 of surface," then the onus is on proper sampling and extremely sensitive analytical methods to remain in compliance. Microgram residual levels of API could, theoretically, put the equipment out of compliance.

Lastly, if the API, as with many newer actives, is poorly soluble and needs to be in an amorphous form to be bioavailable, spectroscopic methods for determining crystalline form are strained by extremely low levels of material. After-the-fact analysis will prevent an OOS product from delivery, but not be of much use for control of production.

At this point, I will point out that, in any group in which I had a voice, we referred to the above and insurmountable opportunities. I am fond of stating, "If it were easy, you wouldn't need a consultant." Without trivializing any of the above downsides, many, if not all, could be addressed by a well-designed PAT/QbD system and, better yet, by a continuous manufacturing system.

Starting with the so-called simplest part of the production process, weighing, we need to address the two potential points of concern: toxicity and accuracy. Without dwelling on physiology, it should be evident that, if the dose is very small, the chemical/biological activity of the API is enhanced. As the dose moves from, say,

25-100 mg per tablet to, perhaps, one 10-25 micrograms per dose, it is rather simple math to see that the drug could be as much as 10,000 times as potent as the typical material handled in production.

This could mean mandatory safety precautions well in excess of "normal," including full "monkey suit" and breathing apparatus. This costs time and money as well as potential hazards for the operators. Also, without implying anything negative, plant operators are not analytical chemists. Weighing kilo-sized portions is far simpler than weighing gram-sized portions. The chance of sub or super-potent final products is enhanced by the far smaller mass of API needed to be weight and carefully transferred to the mixing apparatus.

The precise amount needed for the product is added with mechanical accuracy in a CM process, eliminating most errors in high or low doses. The fact that the API is in an enclosed vessel also protects operators, aside from the initial loading of the bin, from exposure to the drug. Two potential problems, solved with one device.

Content uniformity can be a more difficult target to "hit" with miniscule dosage levels, as well. Physically, the number of particles of excipient so greatly outnumber the particles of API that any minor heterogeneity is amplified. The "good enough" approach for larger doses (10-50% w/w) is not good enough for a case where the number of particles of drug may almost be counted in the tablet/capsule. Just a small amount of API, either high or low, could lead to super- or sub-potent doses. Again, traditional methods of testing—stopping the blender, using a sample thief, sending samples to QC, waiting, then deciding to pass or fail—may not be sufficient for low dose products. More samples may need to be taken and analyzed to assure homogeneity, although, as a physical chemist, I know powders cannot truly be homogeneous, just well-blended.

This is a case where the current in-process (PAT) "standby," near-infrared spectroscopy (NRS), may not suffice. The acknowledged lower level of NIRS is roughly 1% API. That would leave LIF (Light-Induced Fluorescence) as the technology of choice. Briefly, LIF (where the "L" was originally for LASER) is a very simple concept: a bright beam of light, a laser-diode or SLED (superluminescent light-emitting diode), is shone on the powder mix, causing the complex organics (the API, in this case) to fluoresce. As the blending proceeds, the level of fluorescence is measured and when the levels are constant, the mix is declared complete.

Since fluorescence is a very sensitive technique, it has been routinely used in lieu of NIR for years when the API level approached 1% or below. While many of the units are non-specific, very little of the blend, aside from the API, fluoresce. By contrast, NIR and Raman can see all organics and some multivariate equation is needed to see only the API during the blending. This makes the calculation of the end-point of the blend rather simple: without fancy, complicated and potentially time-consuming to validate math, the signal merely needs to level out, within predetermined limits, and the blending is complete. Of course, as with any step in a GMP-compliant process, this will need to be validated with compendial technology (e.g., HPLC).

Cleaning the production machinery is never fun, simple, or obvious. The operator in charge of cleaning needs to be sure that all the water-soluble and water-insoluble components are removed from the surfaces of the equipment. The process usually involves multiple steps, involving solvents, detergents, and purified water. Then, someone needs to swab the surface with appropriate solvents, attempting to determine that there is little to no material remaining. The spec for cleanliness is some level of dose, perhaps less than one unit dose, over a set area (often 10 cm2), determined buy some analytical method. While merely time-consuming for larger doses, the aforementioned very small dose levels make the process quite difficult.

Two alternatives may be employed to make the low dose cleaning faster and more effective. First, for a batch process—either classic GMP or PAT controlled—the manual swabbing of the equipment could be followed by use of an Ion Mobility (IM) unit. This device, a later version of the ones found at airports, works by vaporizing the materials removed from the surface of the equipment, giving them an electrical charge, and running them through a column to a detector. The principle is much like a time-of-flight mass spectrometer, but does not require a vacuum or fancy software.

The components of the wash solution acquire a single charge and travel along the tube, arriving by increasing molecular weight. The recorded signal resembles a chromatograph, where the arrival time gives the molecular mass and the signal strength gives the amount present. The entire analysis takes roughly 20 milliseconds.

In addition to being faster and possibly more accurate than the standard "sample and sent to the lab" approach, the operator knows, within seconds, whether he/she needs to perform further cleaning or that the unit can be placed back into service immediately. This step, alone, increases the availability of process equipment, cutting back on the need for more hardware on hand.

The second way to assure cleanliness is achieved in a continuous manufacturing set-up. After the product has been completed, a common excipient—salt, lactose, or microcrystalline cellulose—is run through the system until clean as per validation. The subsequent product blend excipient blend may then be used to clean out the cleaning powder, prior to initiating the actual product blend.

This benefit also obviates the need for the operator who does the cleaning to take precautions, such as mask, gloves, and even full covering for highly toxic drugs. In addition, this does away with the dismantling of the CM unit and the washing step, again, allowing the unit to be used in short order, cutting the needed inventory of process lines.

As for the last difficulty, morphology, there is one possible solution for measuring in real time: time-gated Raman. Overall both Raman and NIR are very good for determining polymorphic forms of API and excipients, such as sugars. However, we have already established that the level of API makes NIR problematic and, at lower levels, normal Raman's fluorescence background makes it a poor choice for analysis. In a previous column, I showcased a product where the LASER that strikes the sample is pulsed nanosecond bursts and the emitted light is samples in picosecond time frames, allowing the Raman spectrum to be enhanced. This would be a good tool to try for determining the polymorphic state of the API, especially is it needed to be amorphous for solubility's sake.

So, it appears that a number of answers to problems in analysis or procedure not only make handling and analysis possible, but they speed up and help with the quality of the product, itself. And, for an added bonus, they free up the process equipment more rapidly for subsequent batches. Win-win-win, I would say. **CP**

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