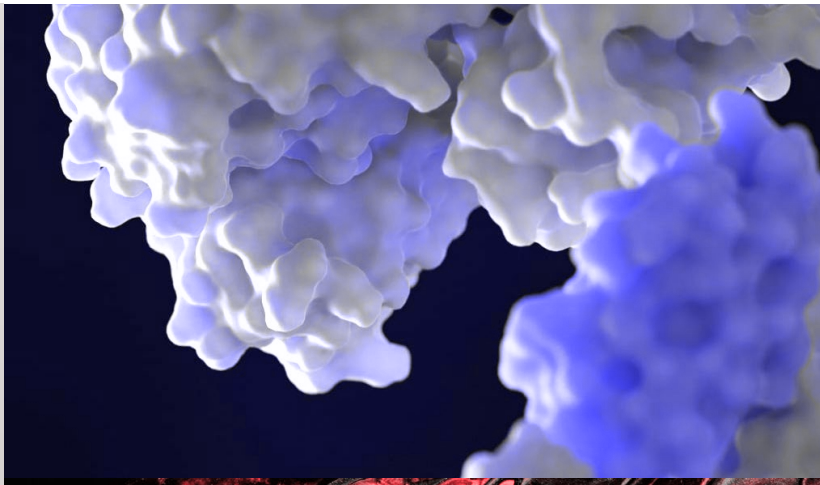
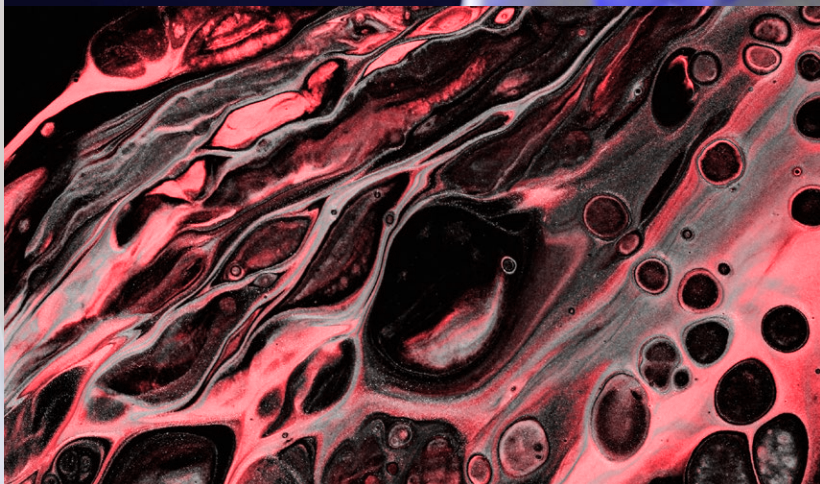
Unravelling the complexities of ADC manufacturing





Executive summary

Antibody-drug conjugates (ADCs) represent a promising frontier in targeted cancer therapy, offering the potential to revolutionize treatment approaches for a wide variety of diseases. However, their complex nature, involving the combination of monoclonal antibodies (mAbs) with potent cytotoxic payloads, presents unique challenges along the journey to market.

These challenges span from the intricate production process and the safe handling of highly potent compounds to the need for adaptable manufacturing processes that can scale to meet evolving demands.

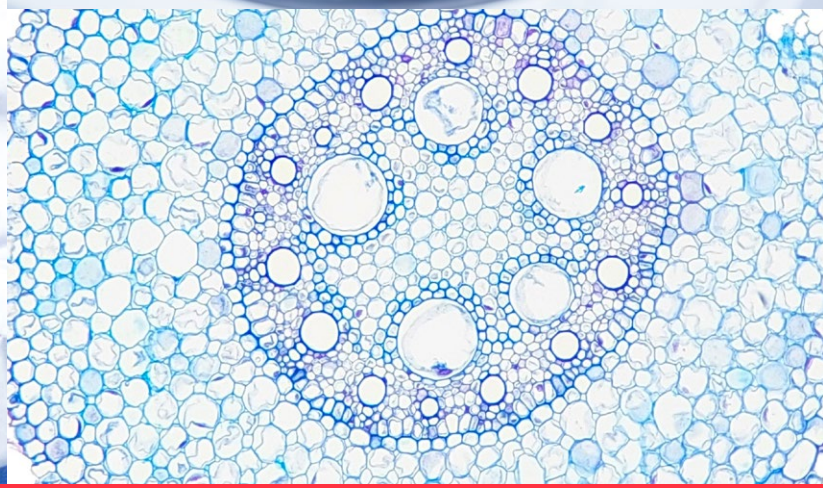
In this whitepaper, we delve into these complexities, exploring the intricacies of ADC development and manufacturing, and highlighting key considerations for ensuring the safe, efficient and compliant production of these life-saving therapies.

Antibody-drug conjugates: A transformative therapeutic modality

Approximately one in five people are expected to develop cancer in their lifetime [1]. In 2024, it has been predicted that in the U.S. alone, there will be over 2,000,000 new cancer cases, attributed to a combination of factors, including population growth, aging and environmental exposures [2].

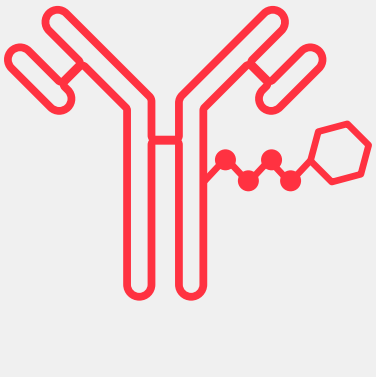
Representing a revolutionary drug modality to combat the rise in cancer cases, antibody-drug conjugates (ADCs) combine the specificity of mAbs with the potent cell-killing capabilities of cytotoxic drugs to deliver a targeted therapeutic payload directly to cancer cells. Unlike traditional chemotherapy treatment options, ADCs can specifically target cancer cells while minimizing damage to healthy tissue, enhancing therapeutic effectiveness while aiming to minimize side effects.

As a result, ADCs are increasingly being explored as monotherapies and as part of combination therapies to treat a wide variety of cancer types, including pancreatic, lung, breast, esophageal and head and neck cancers [3,4].



ADCs: A multi-component drug product

ADCs are complex biomolecules and the precise composition of an ADC will vary depending on the specific target antigen, payload and linker used. Typically, ADCs are composed of:



An antibody

The antibody subunit (commonly an IgG1 or IgG4 mAb) is the targeting element of the ADC that binds to a tumor-associated antigen with high affinity and specificity. This selective binding ensures that the drug is delivered primarily to the tumor site, minimizing damage to healthy cells.

A cytotoxic drug payload

The 'warhead' of the ADC is a highly potent cytotoxic agent. The payload is designed to be released from the ADC once it reaches the target cell. Various types of payloads can be used, including tubulin inhibitors, DNA-damaging agents and topoisomerase inhibitors.

A linker

The chemical linker attaches the antibody to the cytotoxic payload. The linker can be cleavable or non-cleavable and plays a crucial role in the stability and efficacy of the ADC, as it must be stable in circulation but release the payload upon reaching the target cell.

Although this modular design allows for a high degree of customization and tailoring of ADCs for different types of cancer, it also adds complexity to development and manufacturing processes, requiring expertise and experience in multiple disciplines.

A promising market

In May 2000, the US Food and Drug Administration (FDA) approved the first ADC, providing patients living with acute myeloid leukemia (AML) new hope [5]. Despite the promise of changing patients' lives, progress in the ADC space has been relatively slow, with only 14 ADCs seeing FDA approval from the first launch in 2000 to 2024. In part, this has been attributed to the complex nature of ADC design and the instability of early linkers that were prone to premature payload release, leading to off-target toxicities and side effects [6].

However, recent advancements have renewed interest in the ADC field. This includes improvements in linker technology, such as developing site-specific conjugation methods and pH-sensitive linkers. These innovations have led to more stable and targeted ADCs with improved therapeutic profiles, driving market growth. As of 2024, the global ADC market has an estimated value of USD $12.05 billion and is expected to reach $44.05 billion by 2029, growing at a compound annual growth rate (CAGR) of 29.57%[7].

Consequently, the number of ADCs progressing through the development pipeline is rising. In 2024, several leading pharmaceutical companies provided updates on their ADC candidates advancing through early and late-stage clinical trials across various solid tumor indications, highlighting the rapid expansion of the ADC pipeline [8-11].

Although ADCs entering the development pipeline have the potential to drastically change the lives of patients, helping ensure their successful delivery to market relies on overcoming various development and manufacturing challenges.

Overcoming the challenges of ADC manufacturing

The complex nature of ADCs presents unique challenges throughout the manufacturing journey

From ensuring the stability and efficacy of these intricate molecules to navigating stringent regulatory requirements, success in the ADC space demands a deep understanding of the obstacles and a commitment to finding innovative solutions that enable the flexibility needed to successfully bring ADCs to market.

1) The multifaceted nature of ADC production

Producing ADCs is an inherently complex endeavor, requiring the seamless integration of multiple components and processes. As ADCs consist of three distinct elements (the antibody, the cytotoxic payload, and the chemical linker), each component demands specialized expertise and infrastructure for development and manufacturing.

One of the most significant challenges in ADC production stems from the complexity of ADC chemistries resulting in poor yields due to issues with:

Linker performance

Optimizing the linker chemistry to achieve the desired stability, solubility and controlled payload release is complex, impacting conjugation efficiency and yields. Important parameters to optimize include conjugation site, linker length, chemistry (e.g. maleimide vs disulfide), cleavable vs non-cleavable linkage, and proximal linker steric hindrance [12].

Payload compatibility

Identifying a potent cytotoxic payload that is stable during conjugation and has suitable physicochemical properties can be challenging [13].

Conjugation site

Site-specific conjugation is preferred for homogeneous ADCs, but it is difficult to achieve high yields, especially for cysteine conjugation which requires partial antibody reduction [14].

Aggregation and hydrophobicity

The hydrophobic nature of many payloads and linkers can cause aggregation, leading to product loss during purification [14].

Overcoming these hurdles requires extensive process development to maximize yields and, whenever possible, simplify the processes themselves.

When manufacturing complex multi-subunit therapies like ADCs, it is not only critical to have access to the broad expertise needed to successfully produce each component and the final drug product, but these experts communicate with each other transparently.

From the initial design and engineering of the antibody to the synthesis of the payload and linker, and finally, the precise conjugation process, each step requires meticulous coordination.

Access to end-to-end ADC manufacturing capabilities can streamline these complexities with all teams working closely together to ensure decisions made upstream are accounted for downstream in production.

Early considerations for antibody tech transfer success

When transferring the antibody component of an ADC to the drug product manufacturing facility, all teams involved must collaborate closely together early in the project to help ensure a seamless tech transfer while maintaining high quality and safety.

Key considerations include:

- The compatibility of the antibody formulation and container with downstream manufacturing processes, e.g., the chemical compatibility of DMSO with single-use consumables during the ADC coupling process.
- Whether platform formulations used for standard mAbs will be compatible, as each ADC drug substance will have unique needs.
- Cleanroom conditions and reaction vessel suitability must be carefully evaluated to avoid compromising the integrity and efficacy of the final product.

Additionally, an integrated network that encompasses all stages of manufacturing can help eliminate the challenges associated with working with multiple facilities and vendors. This integrated approach fosters efficient communication, aims to provide seamless transitions and tech transfer between stages, and ultimately helps accelerate time to market.

Questions to ask before initiating ADC tech transfer

During ADC production, it is essential to consider dosing requirements, as they can have a cascading effect on various aspects of the manufacturing process. It is crucial to ensure that the facility's capabilities align with the specific requirements of the ADC.

Is there close collaboration with pharmaceutical sciences?

Close collaboration with the pharmaceutical sciences group is vital to obtain early estimates of the final drug product scale. This information is essential for designing the drug substance process, taking into account factors like the concentration of the active ingredient in the formulated solutions. By aligning these processes early on, potential bottlenecks and delays can be avoided during tech transfer.

Can the contract manufacturing organization (CMO) support single-partner material sourcing?

Streamlining tech transfer is significantly easier when all materials are sourced from a single partner, rather than relying on multiple external vendors. This approach simplifies logistics, reduces the risk of supply chain disruptions and ensures consistent quality control throughout the development and manufacturing process.

Are there standardized processes?

Standardizing processes can significantly accelerate the tech transfer of a new ADC product. By leveraging existing knowledge and infrastructure, the time and resources required for validation and qualification can be minimized, ultimately helping expedite the product's path to market.

2) Advancements in the ADC space are bringing further complexity

The field of ADC development is rapidly evolving, with groundbreaking advancements introducing new complexities at every stage of production.

To remain at the forefront of innovation, it is essential for ADC developers and manufacturers to understand and adapt to these challenges, which include:

Complex conjugation methods

Conjugation methods - particularly site-specific conjugation - are becoming increasingly intricate, often involving multiple steps with purification processes in between.

This complexity demands specialized expertise and meticulous attention to detail to ensure the precise, efficient and consistent attachment of payloads to antibodies.

Diverse payload options

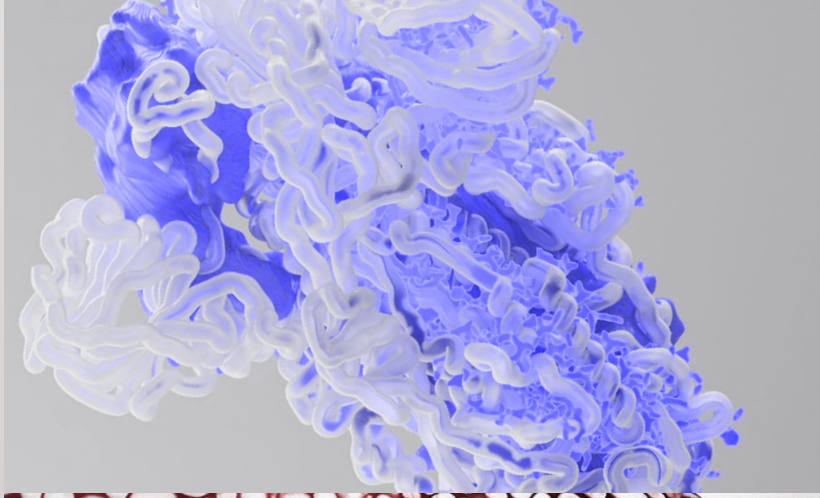
Beyond traditional cytotoxins, the ADC landscape now encompasses a wide array of payloads, including immunomodulators, statins and DNA-damaging agents [15,16]. Supporting these diverse payloads requires a deep understanding of their unique properties and the capabilities to tailor conjugation strategies accordingly.

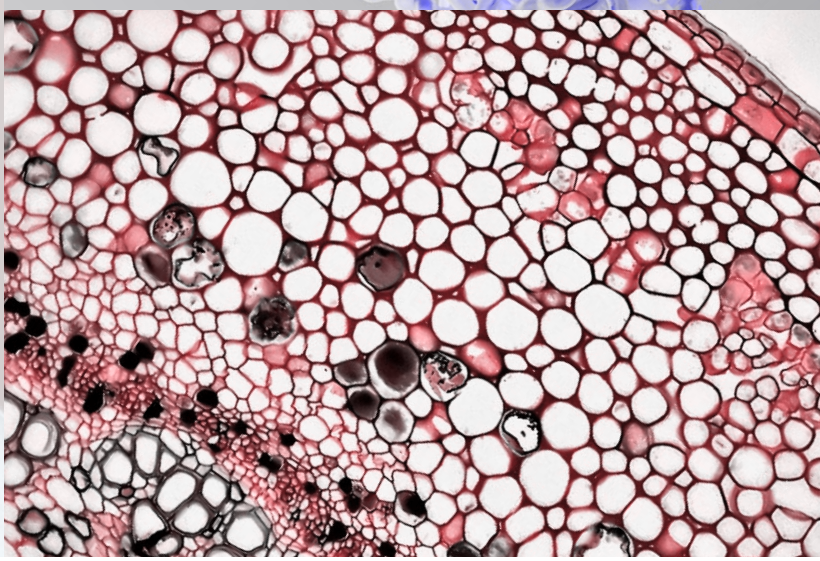
Antibody engineering advancements

As a result of advances in antibody engineering, specifically engineered antibodies, antibody fragments and alternatives to IgG are increasingly considered for use in ADC production to replace the traditional mAb [17,18]. These innovations can have unique upstream requirements, such as the need for microbial culture systems as opposed to mammalian, further complicating ADC manufacturing.

To navigate these complexities and support the development of innovative ADC therapies, flexibility is paramount. Partnering with a CDMO that boasts a team of experts with experience in developing an extensive library of linkers and payloads, as well as various conjugation chemistries, can significantly streamline the development process. This expertise is invaluable when identifying the most promising ADC candidate and optimizing the conjugation strategy.

By embracing these advancements and partnering with a CMO equipped to handle the complexities of modern ADC development, drug developers can more confidently push the boundaries of innovation, ultimately delivering more effective and targeted therapies to patients.





3) Ensuring seamless scalability

The diverse nature of ADCs necessitates a flexible and scalable manufacturing approach.

Different products, targeting various indications and utilizing different payloads, will require varying production volumes. For instance, ADCs targeting solid tumors or employing topoisomerase inhibitors with lower potency often demand larger scales to achieve the necessary dose per patient.

Additionally, as projects progress, production volume needs will change and even after commercialization it will be crucial to understand the projected annual demand for the ADC. This information, obtained through close communication with business groups, informs decisions regarding equipment selection, facility design and overall production capacity.

Anticipating potential fluctuations in demand also allows developers and manufacturers to plan more accurately for scalability. This might involve considering strategies such as scale-out, where additional production lines or facilities are added to meet growing needs.

By proactively addressing scalability, developers and manufacturers can ensure a smooth transition from clinical to commercial production, avoiding costly delays and disruptions.

The use of single-use equipment can help enhance flexibility and scalability. Single-use systems eliminate the need for cleaning and sterilization, reducing turnaround times and minimizing the risk of cross-contamination. This agility is particularly valuable for ADCs, where the diversity of products and varying batch sizes necessitate adaptable manufacturing solutions.

To accommodate evolving project needs, ADC innovators must look to CMOs partners offering access to appropriately sized equipment and those that leverage single-use equipment. By offering the flexibility to support different products as they scale, CMOs can help to ensure each ADC project receives the optimal manufacturing setup, maximizing efficiency and minimizing waste.

4) Handling highly potent compounds

The potent nature of ADCs, particularly those incorporating cytotoxic payloads, introduces significant safety and operational challenges throughout the production process.

Handling highly potent compounds necessitates specialized equipment and meticulous facility design to ensure the safety of personnel and the environment. Engineering controls such as pressurization systems and isolators are essential to contain the product and prevent operator exposure. Segregating manufacturing areas and establishing dedicated facilities for cytotoxic compound production are needed to further mitigate potential risks.

Before starting an ADC project, thorough toxicology assessments are crucial, especially during clinical manufacturing when the full extent of a compound's toxicity may be unknown. Understanding the toxicological profile of the payload allows for the implementation of appropriate containment strategies and manufacturing processes. Collaboration with industrial hygiene experts is essential to establish a robust monitoring program, including surface and air sampling around operators, as well as health-based monitoring to ensure worker safety.

Additionally, personnel working with highly potent compounds will require comprehensive training on specific procedures and safety protocols. This training should cover the proper handling and disposal of hazardous materials, emergency response procedures and the use of personal protective equipment (PPE).

Preventing cross-contamination

To develop effective cleaning procedures, it is important to understand the stability and degradation pathways of highly potent compounds. In some cases, dedicated studies may be necessary to gather this information. Until a fully validated cleaning process is established, dedicating equipment to a specific payload can prevent cross-contamination and ensure product integrity.

By addressing these challenges proactively, ADC innovators can create a safe and controlled environment for the production of ADCs, ensuring the highest standards of quality and safety while accelerating these life-saving therapies to patients.

5) Meeting stringent regulatory requirements

When ADCs first entered the development pipeline, they saw unique challenges in regulatory compliance stemming from a lack of familiarity with their novel mechanisms of action and complex characterization.

Regulatory agencies are now increasingly familiar with ADCs. Regulatory guidance around ADC production emphasizes the need for aseptic process simulations, gowning and environmental monitoring to enhance product quality and sterility, as well as the need for comprehensive quality control strategies, validated analytical methods and specific containment measures.

However, recent updates to regulatory guidelines are adding complexity to ensuring compliance. For example, revisions to Annex 1 of the EU GMP guidelines are set to impact ADC production, requiring stricter contamination control measures through robust facility design, environmental controls and aseptic processing.

These changes necessitate state-of-the-art facilities, rigorous quality systems and a deep understanding of evolving regulations to ensure the safe and effective manufacture of ADCs.

To ensure ADC reaches as many patients as possible, a well-defined launch and filing strategy is essential. This involves coordinating regulatory submissions in different regions, managing potential variations in requirements, and optimizing the timing of market entry. A knowledgeable CMO can help navigate these complexities and maximize the global reach of the therapy.

Preparing for the future of ADCs

The success of approved ADCs and the expanding market underscore the immense potential of these targeted therapies in the future, so long as developers and manufacturers adopt effective approaches to overcoming the challenges outlined.

With a surge in investment and growing global demand, the future of ADC manufacturing is undeniably bright. As the industry continues to mature, the initial high costs associated with specialized facilities and equipment can be expected to decrease as processes become standardized, making ADCs more accessible to a wider patient population.

The integration of artificial intelligence (AI) and machine learning (ML) is poised to revolutionize the ADC space further. These technologies offer the potential to streamline and optimize various aspects of development and manufacturing, from designing and developing processes like freeze-drying to automating tasks such as report writing in tech transfer. AI-powered platforms are already being leveraged to accelerate target identification and drug response prediction for ADCs, ultimately de-risking the production process and reducing costs [19].

As the ADC market continues to evolve, we can anticipate a greater focus on personalized medicine, with the development of ADCs tailored to individual patient needs. Additionally, advancements in linker and payload technologies will likely expand the range of targetable diseases and improve therapeutic outcomes. The use of AI and ML in optimizing these complex chemistries will undoubtedly play a crucial role in achieving these goals.

By partnering with a forward-thinking CMO that embraces innovation, drug developers can more confidently navigate the complexities of the ADC landscape and accelerate these life-changing therapies to patients worldwide.

Leaders in ADC manufacturing with a legacy of success.

At Pfizer CentreOne, we are ready to help you unravel the complexities of ADC manufacturing and support your therapeutic as it progresses toward the patients waiting.

Our state-of-the-art Pearl River facility, the hub for Pfizer's highly potent and cytotoxic bioconjugate manufacturing, brings a legacy of experience in manufacturing oncology therapies and vaccines, combined with over two decades of expertise in ADCs.

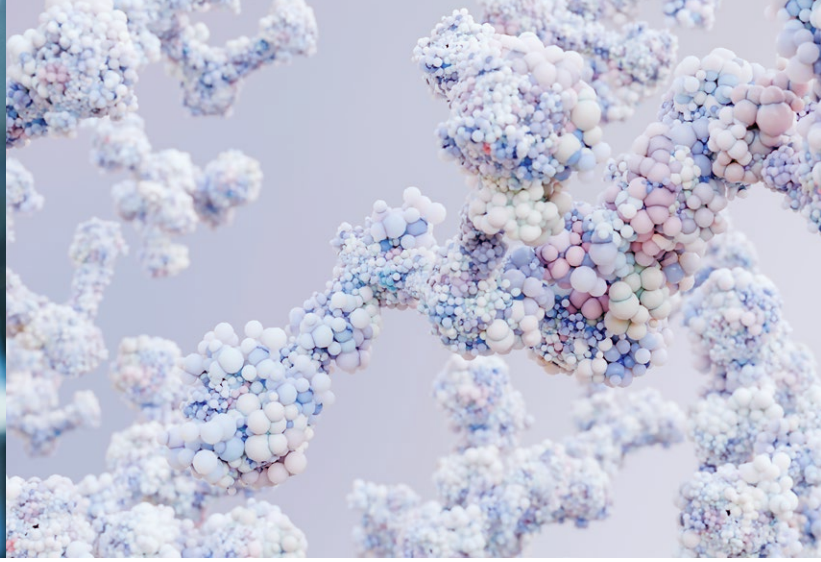
Leveraging approximately 94,000 square feet of manufacturing space specifically designed for cytotoxic drug processing, the Pearl River site can support your project with capabilities including:

- Fermentation
- Recovery
- Chemical synthesis
- Purification
- Formulation

With a track record of outstanding safety performance, successful tech transfers, and on-time delivery, we are committed to partnering with you to help accelerate your ADC program, overcome challenges, and deliver life-changing therapies to patients waiting. Because for patients, time is life.

For more information about Pfizer CentreOne and its ADC services, contact us to start the conversation.

Visit us at **www.pfizercentreone.com**



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A CMO for therapies that define legacies

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