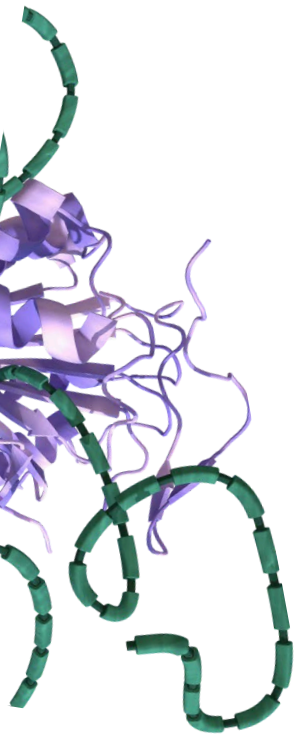
CURAPATH



GMP Manufacturing of a Polymer Drug Conjugate

Case study

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The Challenge

PDC structure & objective

The lead candidate is a macromolecular polymer–drug conjugate (PDC) composed of a polymer scaffold, an API, and a linker, designed to overcome key limitations of small-molecule therapeutics such as poor solubility, bioavailability, biocompatibility, and tissue targeting.

Regulatory complexity

PDCs are considered new chemical entities, requiring full regulatory evaluation to progress into clinical trials, which significantly increases development and approval complexity.

Manufacturing & analytical challenges

The inherent complexity of PDCs has limited market approval due to the lack of robust GMP manufacturing processes and validated analytical methods for IPCs, intermediates, and final product release.

Development hurdles identified

Feasibility studies confirmed the need for multi-step synthetic pathways with scale-up challenges, alongside the critical requirement for advanced analytical methods and stable, sterile formulations to enable parenteral drug product development.

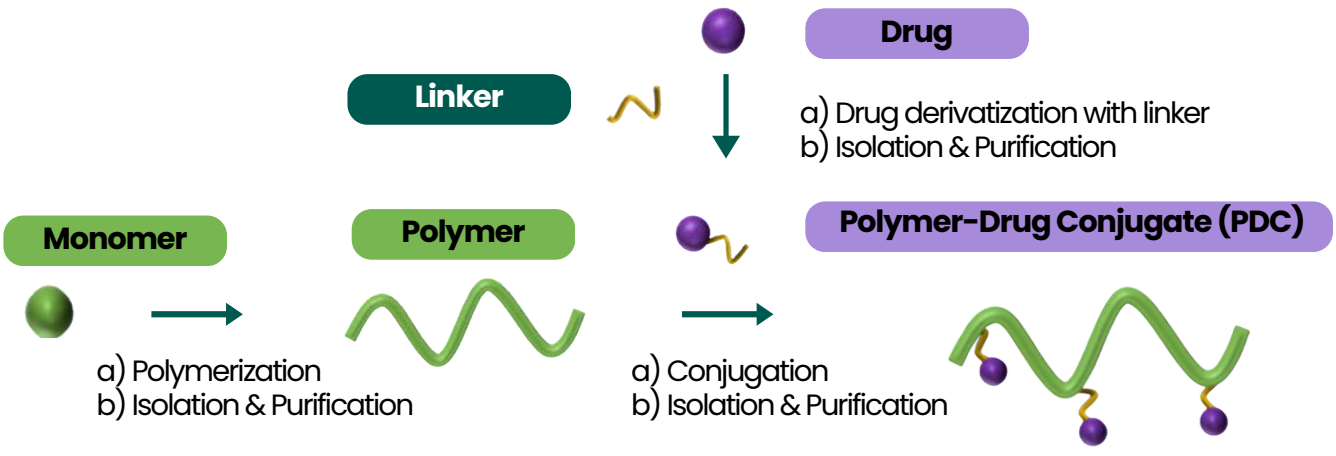


Figure 1. General Schematic representation of the synthetic and purification steps required to produce PDCs.

Curapath's Approach

Robust CMC development & control strategy

Curapath developed a comprehensive CMC strategy integrating process development and analytical methods, defining CPPs and CQAs to ensure reproducible and scalable DS & DP manufacturing within target acceptance criteria.

Process optimization & purification

Customized purification strategies were implemented at each step, prioritizing cost-effective multisolvent precipitations while addressing stability challenges of the drug–linker intermediate through optimized isolation and controlled storage conditions.

Critical conjugation step optimization

The statistical nature of the polymer–drug conjugation required extensive small-scale batch optimization to ensure reproducibility, controlled drug loading, and minimal free drug content, resulting in consistently compliant DS batches.

Scale-up, GMP transfer & validation

The optimized process was successfully transferred to larger GMP-like (GLP-Tox) batches for DP formulation and preclinical studies, followed by GMP implementation with tailored IPCs and validated analytical methods, demonstrating strong batch-to-batch reproducibility & stability.

RELEASE TEST ITEMS OF DS			BATCH 1	BATCH 2	BATCH 3	BATCH 4
PARAMETER	**METHOD**	**ACCEPTANCE CRITERI**	**R&D**	**R&D**	**GLP-TO X**	**GMP**
APPEARANCE	Visual	Solid	Solid	Solid	Solid	Solid
COLOR	Visual	White	White	White	White	White
IDENTITY	NMR	Conforms to Std	Conforms	Conforms	Conforms	Conforms
DRUG LOADING (% OF TARGET)	NMR	+/- 5% of target	48%	1%	22%	13%
PURITY	HPLC-UV	97-103%	99%	98%	100%	102%
FREE DRUG	HPLC-MS	<0.1%	4%	8%	5%	7%
IMPURITY 1	HPLC-MS	<0.1%	3%	<0.05%	<0.08%	2%
COUNTERION 1	Ion Chromatography	<0.20	7%	10%	N/D	N/D
WATER CONTENT	Karl Fisher	<10%	80%	72%	75%	55%
SOLVENT 1	GC-FID	<0.5%	7%	<0.10%	3%	<0.02%
SOLVENT 2	GC-FID	<0.3%	<0.02%	<0.02%	<0.02%	<0.02%
SOLVENT 3	GC-FID	<0.1%	N/D	N/D	N/D	N/D
ENDOTOXINS	Eur. Pharm/USP	<75 EU/g	<70 EU/g	<40 EU/g	<20 EU/g	<10 EU/g
TAMC	Eur. Pharm/USP	<250 CFU/g	N/A	100 EU/g	40 CFU/g	70 CFU/g
TYMC	Eur. Pharm/USP	<25 CFU/g	N/A	<20 EU/g	<15 CFU/g	<10 CFU/g

Table 1. Key release test items of DS and the obtained data from different R&D, GLP-Tox, and GMP batches.*

**For simplicity, only a few analyzed parameters are included i.e. Number of Analyzed counterions: 5, Number of Analyzed impurities from reagents and byproducts: 8. N/D: Not detected, N/A: Not applicable.*

Curapath's comprehensive end-to-end approach also encompassed the development and scale-up of DPs, starting from the formulation of the DS to the fill & finish (F&F) stage. For this particular PDC, this involved meticulous process development, following a similar workflow than the DS. The DP formulation development from the technical batch DS, as previously commented, was followed by a rigorous qualification of the sterility assurance level. Subsequently, the DP was aseptically F&F into vials.

This process not only ensured the highest quality and purity of the PDC DP, but also optimized its scalability for large-scale manufacturing, facilitating a seamless transition from development to clinical and potentially commercial production.

In adherence to the quality standards set by the International Council for Harmonization (ICH-Q), comprehensive stability studies were also conducted for both the DS and the DP GMP batches, including long-term and accelerated storage conditions. These studies are essential for assessing the durability and reliability of pharmaceutical products over time, ensuring their safety and efficacy throughout their shelf-life.

To streamline the approval process through the regulatory bodies, Curapath also provided strong support for regulatory CMC coverage. Through the generation of the regulatory-ready CMC dossier for investigational new drug (IND) application, Curapath demonstrated that the PDC manufactured batches were adequately characterized and produced under a robust, controlled, and reproducible manufacturing process.

RA based & Phase Appropriate CMC Development for novel excipients & Nanoparticle Drug Products

Tech Transfer

30-60 days

- Scientific Review
- Tech Transfer
- GAP assessment
- Comparability studies.

Preclinical

80-150 days

- Syn. Route Development
- Formulation Development
- Definition of TPP & key CQAs
- Method Development
- Pilot Scale-up (to Kg)
- Non-Clinical Material Supply .

IND Enabling

120 days

- Process characterization
- Preliminary control strategy
- Method Qualification
- Impurity profiling
- Formal ICH Stability
- GMP Clinical Trial Supply
- Regulatory CMC package.

Phase I-II

120-200 days

- Inventory management
- Continued process Characterization
- Updated Control Strategy
- GMP CTM supply (1-6Kg batch)
- Continous Regulatory Support.

Pivotal Phase, Commercial supply

300-500 days

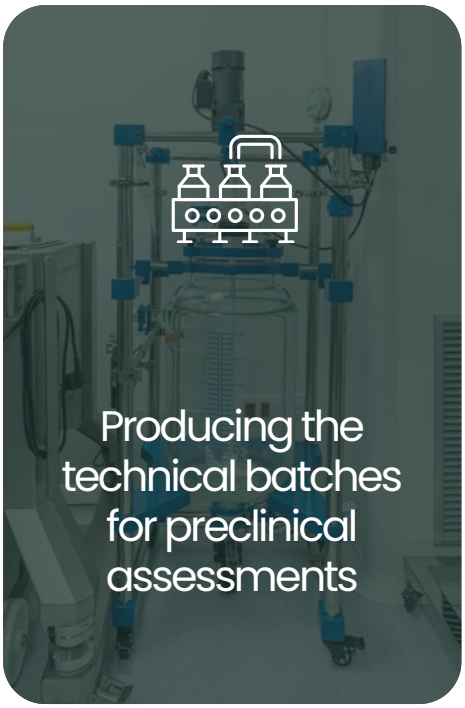
- Process Validation
- Method Validation
- Final Control Strategy
- Formal ICH Stability
- BLA filling support
- GMP CTM Supply
- Commercial Supply.

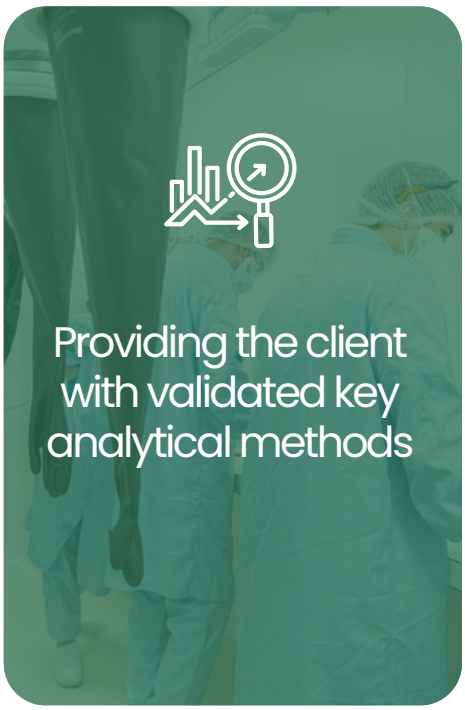
Figure 2. Schematic representation of Curapath's End-to-End approach for PDCs, from Proof of Concept (POC) to Commercial supply.

Outcome

Curapath has developed and optimized a multi-step manufacturing process for a complex PDC. The process has been efficiently scaled-up from mg-scale to kg-scale, covering preclinical and clinical batches in less than 12 months.

This manufacturing process includes a robust formulation and GMP-compliant F&F, ending with a final sterilization step. This ensures that the resulting DP meets the rigorous requirements for safe parenteral administration in humans. Overall, Curapath has supported the client, for both DS and DP, in the journey towards clinical trials by:





As a result, the client has submitted the IND documentation, which has been approved for starting the Phase 1 clinical trial.

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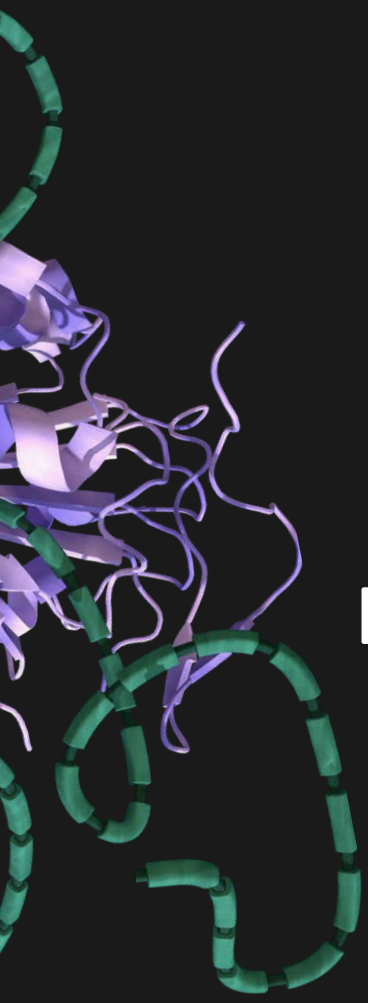

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