BIOTECH RESOURCES GROUP

CONCEPTUAL DESIGN COMPENDIUM

RLT & ADC CDMO Facility Design Compendium

Conceptual Design Framework, Commercial Landscape, Containment Strategy & EPCM Selection

Prepared for

Biotech Resources Group, LLC

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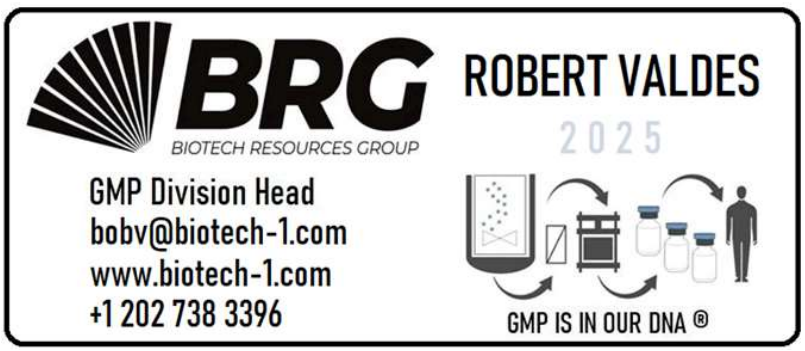
Contents



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PART I

Executive Summary

A synthesis across the RLT/ADC facility design basis, the Conceptual Design Report framework, and the EPCM shortlist and procurement strategy.

Radioligand therapeutics (RLT) and antibody-drug conjugates (ADC) are the two fastest-growing targeted-oncology manufacturing modalities in the United States, and both are structurally supply-constrained — RLT by isotope availability and decay physics, ADC by linker-payload potency and a conjugation capacity base concentrated in China-based CDMOs now directly implicated by the BIOSECURE Act (Arnold & Porter[1]). This compendium consolidates three companion work products into a single reference document for Biotech Resources Group, LLC: a technical design-basis report for end-to-end U.S. RLT and ADC CDMO facilities, a Conceptual Design Report (CDR) framework template that mirrors industry CDR structure and numbering, and a qualified EPCM shortlist with an RFI/RFP execution strategy.

Design basis is set by the commercial product landscape, not by generic biologics templates. For RLT, the approved-product set spans half-lives from roughly 46 hours (Sm-153) to 50.5 days (Sr-89), with Lu-177 (6.647 days) carrying commercial volume through Pluvicto and Lutathera (FDA Pluvicto label[2]). That half-life spread — not batch mass — drives the facility program: at least two independently schedulable hot cell suites, isotope-receipt-to-shipping adjacency measured in minutes of transit, and an approximately 20-hour receipt-to-administration cycle with built-in activity overage. For ADC, drug-antibody ratios from 2.3 to about 8 across cleavable and non-cleavable chemistries, with payload classes including calicheamicin and PBD dimers, force a worst-case OEB 5 containment design basis (OEL below roughly 1 µg/m^3) and flexible single-use conjugation and TFF/UFDF skids rather than fixed stainless equipment.

Facility scale and area program. Benchmarked against Novartis' 70,000 sq ft Indianapolis site, RayzeBio's 77,000 sq ft Indianapolis facility, and NorthStar's 52,000 sq ft Beloit CDMO (Novartis[3]; RayzeBio[4]), the RLT concept is programmed at 65,000 sq ft supporting 50,000–100,000 doses/year, with only about 6% of area in Grade A/B aseptic core and roughly 36% in unclassified radiologically controlled, utility, and QC space — a reminder that an RLT facility is predominantly infrastructure. The ADC concept is programmed at 55,000 sq ft with a discrete 3,000 sq ft OEB5 containment suite and single-pass, non-recirculated exhaust for all HPAPI-contacting air.

Two fundamentally different schedule logics. RLT is scheduled backward in hours from patient administration, with real-time release testing replacing sequential batch review; ADC is scheduled in days to weeks, gated by 14-day compendial sterility incubation, with bulk freeze decoupling conjugation from fill/finish. This single distinction cascades through adjacency, QC design, automation, and site selection for each modality.

Regulatory and geographic strategy. RLT operations are licensed under 10 CFR Parts 20, 30, and 35 either directly by the NRC or by an Agreement State; Indiana — the densest U.S. RLT cluster — remains a non-Agreement State, so licensing runs through NRC review, while Texas, California, New Jersey, North Carolina, and Pennsylvania are Agreement States with state-agency pathways (NRC[5]). Lu-177 supply is now reasonably diversified across the Netherlands, Canada, Germany, and Australia, whereas Ac-225 remains acutely scarce and tied to the DOE Tri-Lab scale-up effort (DOE Isotope Program[6]). For ADC, the defensible

U.S. market position is not price competition with China-based conjugation capacity but service to BIOSECURE-affected and single-source-exposed sponsors.

EPCM execution. No large national EPCM firm demonstrates deep, named track record in both radiopharmaceutical hot-cell manufacturing and ADC/HPAPI containment. IPS is the closest single integrated candidate (BWXT Mo-99/Tc-99m and SOFIE radiopharmaceutical projects plus a named first commercial ADC facility design); Gilbane holds the most directly relevant active radiopharma construction reference (TerraPower Isotopes' $450M Ac-225 facility in Philadelphia (Gilbane[7])); and Jacobs is the confirmed design consultant on the closest ADC/HPAPI analog. The recommended strategy is a 6–8 firm RFI narrowing to three RFP participants and two finalists, with either split-scope RLT-lead and ADC-lead awards under a single construction manager, or a requirement that integrated bidders name their radiopharma and ADC subject-matter partners explicitly. A separate, parallel RFQ should be run for health physics and shielding design, which is a fragmented boutique market and licensing-critical to the RLT schedule.

How to use this document. Part II is the technical design basis and should be read as the source of programmatic assumptions. Part III is the CDR framework to be populated with sponsor-specific data during the 15–18 week, four-gate CDR development schedule. Part IV is the procurement path. Every inline citation carries a superscript number keyed to the consolidated source list in the Appendix.

PART II

RLT & ADC Facility Design Basis

Programmatic requirements, process flows and timelines, commercial product landscape, safety and containment frameworks, site selection and geopolitics, and the CDR development schedule.

Section numbering in this Part is retained from the source technical report; in-text cross-references to "Section N" refer to these numbers.

Report Overview and Scope

Radioligand therapeutics (RLT) and antibody-drug conjugates (ADC) are the two fastest-growing targeted-oncology modalities in biopharmaceutical manufacturing, and both are structurally supply-constrained: RLT by isotope availability and decay physics, ADC by linker-payload toxicity and conjugation capacity concentrated in a small number of CDMOs, several of which are now geopolitically exposed. Novartis' commercial RLT franchise (Pluvicto, Lutathera) generated enough demand to justify a 70,000-square-foot Indianapolis facility branded as "the largest and most advanced radioligand therapy manufacturing facility in the world," with a second Indianapolis isotope-production expansion and a third West Coast site in Carlsbad, California, announced in 2024 (Novartis[3], Novartis[8]). On the ADC side, ten-plus approved products (Adcetris through Elahere, Zynlonta and beyond) have pulled a large share of global linker-payload and conjugation capacity into China-based CDMOs such as WuXi XDC and Hangzhou DAC Biotech, a concentration now directly implicated by the U.S. BIOSECURE Act (Arnold & Porter[1]; PharmaSource[9]).

This report lays out programmatic requirements, area tabulations, process flows, timelines, safety/containment frameworks, and site-selection criteria for building a U.S.-based, end-to-end CDMO facility in each modality, grounded in the commercial product landscape (Sections 5 and 6) and translated directly into design assumptions (Section 7). A companion document, the *CDR Framework Template*, mirrors the section structure of a representative Conceptual Design Report (CDR) and populates it separately for RLT and ADC facility concepts.

1. RLT CDMO Facility — Programmatic Requirements

1.1 Product and Process Basis

Commercial RLT products fall into two isotope families with fundamentally different manufacturing cadences:

- Beta emitters with multi-day half-lives — lutetium-177 (Lu-177, t½ = 6.647 days) used in Pluvicto and Lutathera, the two dominant commercial RLTs by revenue (FDA Pluvicto label[2]; FDA Lutathera label[10]).
- Alpha emitters with shorter half-lives requiring even tighter cycle control — actinium-225 (Ac-225, t½ ≈ 9.92 days total decay chain considerations, daughter isotopes Fr-221/Bi-213/Po-213 requiring additional shielding) — currently supply-constrained and produced only in pilot/clinical quantities via the DOE Tri-Lab effort (DOE Isotope Program[6]; ORNL[11]).

Because Lu-177 decays roughly 10% per day and Ac-225 similarly, the entire manufacturing-to-administration cycle time is a primary design driver — not batch size or campaign count alone. A facility with poor process-to-shipping adjacency effectively destroys drug product value through decay loss (radioactive decay is unrecoverable yield loss, unlike most biologics processes).

1.2 Campaigns, Batch Sizes, and Annual Throughput

Benchmarking against disclosed commercial capacity:

Parameter	Basis / Benchmark	Design Assumption
Annual dose capacity (mature commercial RLT site)	Novartis Indianapolis: capacity for 250,000+ doses/year as of 2024 expansion (Novartis[3])	50,000–100,000 doses/year for a mid-scale multiproduct CDMO (fraction of a dedicated innovator site)
Batch size	Pluvicto: 1,000 MBq/mL (27 mCi/mL) concentration, ~7.4 GBq (200 mCi) per patient dose (FDA label[2])	Batch sized to fill 20–80 patient doses depending on isotope activity received per production run, driven by cyclotron/reactor delivery schedule rather than fixed batch mass
Campaigns/year	Continuous production is standard for Lu-177 RLTs (near-daily batches driven by isotope delivery cadence) vs. episodic campaigns for Ac-225 (supply-limited)	Lu-177 line: 150–250 production runs/year (3–5×/week); Ac-225 line: 12–24 campaigns/year until supply scales
Facility footprint benchmark	RayzeBio (BMS) Indianapolis: 77,000 sq ft, first-of-kind end-to-end (isotope production + drug product) facility, $160M+ invested (RayzeBio[4]); NorthStar Beloit, WI: 52,000 sq ft multi-isotope CDMO (BusinessWire[12])	50,000–80,000 sq ft total facility footprint for an end-to-end multiproduct RLT CDMO

1.3 Isotope Logistics and Decay Economics

- Lu-177 non-carrier-added (n.c.a.) supply is produced from irradiated ytterbium-176 targets at research reactors (e.g., HFR Petten, Netherlands, operated by NRG/Curium; Bruce Power in Canada) and via cyclotron routes; supply security has driven multi-sourcing strategies, including Kinectrics' new Yb-176 production specifically to reduce reliance on Russian-origin supply chains (Kinectrics[13]).
- Ac-225 is scarce: legacy supply relies on "milking" stockpiled thorium-229 (yielding roughly one curie/year at Oak Ridge National Laboratory), supplemented by an emerging accelerator-based route irradiating thorium-232 targets, developed jointly by ORNL, Brookhaven National Laboratory, and Los Alamos National Laboratory under the DOE Isotope Program's Tri-Lab effort (DOE Isotopes[6]; ORNL[11]).
- Decay-driven scheduling: because Lu-177 loses ~9.7% of activity per day, and because dose is specified as activity (MBq/mCi) at time of administration, all downstream processing — radiolabeling, purification, fill, QC release, and shipment — must be scheduled backward from a target patient-administration time, with activity overage built into the fill target. Section 4 details the hour-by-hour timeline this forces.
- Facility adjacency implication: the isotope receipt dock, hot cells, fill suite, QC lab performing radiochemical/radionuclidic purity testing, and shipping dock should be arranged in the shortest practical single-direction flow, minimizing transport time and antechamber transitions — a materially different design priority than a conventional biologics facility optimized primarily for contamination control sequencing.

1.4 Hot Cells, Shielding, and Room Counts

Hot cells are the central capital and space driver in RLT facilities:

- Each hot cell costs approximately $500,000 or more; shielded biosafety cabinets used for lower-activity operations cost more than $100,000 each (PharmOut, Facility Design Thinking[14]).
- Hot cells weigh approximately 10 tons or more per cell, are delivered on multiple pallets, and require dedicated civil design (footings, trenching) and setdown areas for installation — meaning structural and rigging requirements must be locked early in conceptual design, not left to detailed engineering (PharmOut[14]).
- Carbon/HEPA filtration for radioactive gas and particulate capture (relevant for volatile daughter products in alpha-emitter processing) requires additional technical space beyond the cleanroom footprint.
- A representative IAEA-published hypothetical Type 1 WHO-GMP radiopharmaceutical facility room list (originally developed for cyclotron-produced FDG, generalizable in principle to hot-cell RLT layouts) itemizes rooms individually — e.g., personnel entrance (4 m^2), staff offices (50 m^2 total), quarantine storage (5 m^2, ISO-classified with +10 Pa differential), material entrance, corridors, janitorial, data/archive, and multiple technical-gas storage rooms — illustrating the level of room-by-room detail expected in a CDR room list (IAEA Pub1515[15]).

Representative room count for an end-to-end multiproduct RLT CDMO (derived from the above benchmarks and scaled to a 50,000–80,000 sq ft facility):

Functional Area	Approx. Room Count	Notes
Isotope receipt / radiation dock	1–2	Shielded cask unloading, survey station
Hot cell suites (radiolabeling + purification)	4–8 hot cells across 2–4 suites	One suite typically dedicated per isotope/product line
Dispensing / precursor prep (ISO 8/CNC)	2–4	Antechambers to hot cell suites
Aseptic fill (Grade A in B/C isolators)	1–2 filling suites	Vial and/or syringe fill lines
QC radiochemistry/radionuclidic purity lab	1 lab suite (multiple rooms)	HPLC, gamma spectroscopy, dose calibrators
Microbiology/sterility QC lab	1 lab suite	Separate from radiochemistry to avoid cross-contamination of counting equipment
Decay-in-storage / waste holding	2–3 shielded rooms	Segregated by half-life for waste decay-out
Packaging / Type A shipping prep	1–2	Lead overpack assembly, dose calibration re-verification
Warehousing (unclassified)	1	Consumables, packaging materials
Utilities/mechanical (see 1.6)	Multiple plant rooms	HVAC, exhaust HEPA/carbon trains, emergency power
Administrative/QA/office	Multiple	Scaled to headcount

1.5 Area Tabulation by Classification (Illustrative, 65,000 sq ft Total)

Classification	Function	Approx. Area (sq ft)	% of Total
Grade A/B (aseptic core, isolator-enclosed)	Sterile fill, bulk formulation	4,000	6%
Grade C / ISO 7 background	Hot cell suite backgrounds, gowning transitions	9,000	14%
Grade D / ISO 8 (CNC)	Dispensing, buffer prep, QC sample receipt	8,000	12%
Unclassified — radiologically controlled	Isotope receipt, decay storage, waste handling, hot cell technical space	14,000	21%
Unclassified — QC laboratories	Radiochemistry, microbiology, stability	6,000	9%

Classification	Function	Approx. Area (sq ft)	% of Total
Unclassified — warehouse/shipping	Raw materials, packaging, Type A/B shipping prep	6,000	9%
Unclassified — utilities/mechanical	HVAC, exhaust trains, emergency power, RO/WFI if needed	10,000	15%
Unclassified — administration/QA offices/personnel	Gowning, break rooms, offices, training	8,000	12%
Total		65,000	100%

This distribution is consistent in character with the disclosed scale of NorthStar's 52,000 sq ft Beloit facility and SOFIE's 30,000 sq ft combined Totowa, NJ campus (in SOFIE's case, roughly 2,700 sq ft of GMP manufacturing space embedded within a much larger support/mechanical footprint — a ratio illustrating how much of an RLT facility is non-manufacturing infrastructure) (BusinessWire[12]; BioSpace[16]).

1.6 Utilities

RLT facilities require the standard biopharma utility set (WFI or purified water if aqueous formulation, clean steam if terminal sterilization is used, HVAC with appropriate pressure cascades) plus radiologically specific systems:

- Shielded HVAC exhaust with HEPA and, where volatile daughter isotopes are present (alpha-emitter chains), activated carbon filtration trains, sized for larger duct/plenum runs than conventional biopharma HVAC (PharmOut[14]).
- Dedicated radioactive liquid waste holding/decay tanks, engineered for the specific isotope decay schedule before discharge or solid-waste consolidation.
- Emergency power sized to maintain hot cell ventilation and monitoring instrumentation continuously (a radiological safety requirement, not just a business-continuity one).
- Area radiation monitoring network (continuous TLD/survey instrumentation) integrated into the building automation and alarm system.

1.7 Staffing

Radiopharmaceutical CDMOs require radiation safety and health-physics staffing not present in conventional biologics plants: a Radiation Safety Officer (RSO), health physicists, hot-cell-qualified operators (often cross-trained pharmacists/technologists per USP <825>-adjacent competencies), dosimetry/badge administration staff, and QC analysts trained in radiochemical and radionuclidic purity methods (HPLC with radio-detection, gamma spectroscopy, dose calibration). A representative headcount for a 50,000–80,000 sq ft, 3-shift multiproduct RLT CDMO is 120–200 FTEs, including manufacturing operators, QC/QA, RSO/health physics, facilities/engineering, warehouse/logistics, and administration.

1.8 QC Laboratories

RLT QC differs from standard biologics QC principally in radiological testing:

- Radiochemical purity (fraction of activity present as the intended labeled species, typically by radio-HPLC or radio-TLC).
- Radionuclidic purity (absence of isotopic impurities, by gamma spectroscopy).
- Specific activity and dose calibration (activity per unit volume/mass, calibrated against NIST-traceable sources).

- Standard sterility, endotoxin, pH, appearance, and container-closure integrity testing, performed in a laboratory physically separated from radiochemistry counting equipment to avoid background interference.
- Real-time release testing (RTRT) is common in commercial RLT operations given the incompatibility of lengthy compendial sterility incubation (14 days) with days-long product shelf life.

2. ADC CDMO Facility — Programmatic Requirements

2.1 Product and Process Basis

ADC manufacturing is a three-part supply chain — monoclonal antibody (mAb) drug substance, linker-payload (a highly potent, often genotoxic/cytotoxic small molecule handled as an HPAPI), and the conjugation/purification/fill process that joins them — and the commercial landscape (Section 6) spans DARs from roughly 2 (Zynlonta, Mylotarg average) to nearly 8 (Trodelvy), cleavable and non-cleavable linker chemistries, and payload classes (auristatins/MMAE-MMAF, maytansinoids DM1/DM4, calicheamicin, PBD dimers, topoisomerase-I inhibitors) (FDA labels — Adcetris[17]; Kadcyla[18]; Trodelvy[19]; Besponsa[20]; Zynlonta[21]; Elahere[22]).

2.2 Campaigns, Batch Sizes, Intermediates

Parameter	Basis	Design Assumption
mAb drug substance batch	Standard mammalian (CHO) fed-batch bioreactor scale, 2,000–20,000 L working volume depending on titer and demand	2,000–6,000 L single-use bioreactor train for CDMO flexibility across sponsors
Conjugation batch size	Driven by mAb intermediate lot size and DP fill demand	5–50 kg mAb intermediate per conjugation batch, scaled to clinical/commercial demand
Campaigns/year	ADC CDMOs typically run dedicated or tightly-cleaned multiproduct campaigns given HPAPI cross-contamination risk	8–20 campaigns/year per conjugation suite, depending on changeover/cleaning validation cycle time
Doses/campaign	Function of patient population and dosing regimen (e.g., Kadcyla 3.6 mg/kg q3wk; Enhertu 5.4 mg/kg q3wk)	Sized per sponsor program; commercial campaigns can range from thousands to tens of thousands of doses

2.3 mAb Intermediate and Linker-Payload (HPAPI, OEB 5)

- The mAb intermediate is manufactured (in-house or by a separate CDMO) to drug-substance-grade specification, then transferred — frozen or as concentrated liquid — to the conjugation site, where it is thawed and buffer-exchanged prior to reaction.
- Linker-payloads are handled as Occupational Exposure Band (OEB) 5 materials, i.e., occupational exposure limits (OELs) below approximately 1 µg/m^3 — the highest containment banding used in pharmaceutical manufacturing, requiring closed/isolator-based material transfer, single-use process paths, and dedicated or fully validated changeover between products.
- WuXi XDC, a major dedicated ADC CDMO, offers integrated GMP conjugation manufacturing spanning linker-payload handling through drug substance, illustrating the industry-standard scope of a "conjugation suite" service offering (WuXi XDC[23]; WuXi Biologics capabilities overview[24]).

2.4 Conjugation Suite, TFF/UFDF

- The conjugation reaction (reduction/reoxidation or direct coupling of linker-payload to antibody, depending on chemistry) occurs in single-use, closed, isolator-contained reactors sized to the mAb intermediate batch.
- Downstream purification uses tangential flow filtration (TFF)/ultrafiltration-diafiltration (UFDF) to remove unconjugated ("free") payload and exchange into final formulation buffer — a critical step given regulatory and safety limits on free-payload content in drug substance.
- In-process analytics (DAR by hydrophobic interaction chromatography [HIC] or reversed-phase HPLC, aggregation, free-drug content) gate advancement to bulk formulation.

2.5 Area Tabulation by Classification (Illustrative, 55,000 sq ft Conjugation + Fill Facility)

Classification	Function	Approx. Area (sq ft)	% of Total
Grade A/B (isolator-enclosed aseptic core)	Aseptic vial filling, lyophilization loading	5,000	9%
Grade C / ISO 7	Conjugation suite background, TFF/UFDF suite	8,000	15%
Grade D / ISO 8 (CNC)	mAb thaw/buffer exchange, compounding	6,000	11%
OEB5 HPAPI containment suite	Linker-payload dispensing, weighing, isolator transfer	3,000	5%
Unclassified — QC laboratories	Analytical (DAR, purity, potency), microbiology	6,000	11%
Unclassified — warehouse/cold storage	mAb intermediate frozen storage, DP cold-chain staging	7,000	13%
Unclassified — utilities/mechanical	HVAC (including dedicated exhaust for HPAPI), WFI, clean steam	10,000	18%
Unclassified — administration/QA/gowning/personnel	Offices, gowning, decon/degown corridors	10,000	18%
Total		55,000	100%

2.6 Utilities

ADC facilities require conventional biologics utilities (WFI, clean steam, single-use process water) plus containment-driven systems: dedicated HEPA-filtered exhaust for HPAPI handling areas (often single-pass, non-recirculated air), closed-loop decontamination systems (e.g., vaporized hydrogen peroxide or validated chemical decon for isolators), and segregated cytotoxic liquid/solid waste streams requiring validated chemical deactivation (e.g., sodium hypochlorite or hydrolysis) before disposal.

2.7 Staffing

An ADC CDMO of this scale typically requires 150–250 FTEs, including upstream/downstream (if internalizing mAb production) or intermediate-receipt operations staff, conjugation/purification operators trained in OEB5 containment practice, fill/finish operators, industrial hygiene/occupational toxicology staff (distinct from RLT's radiation safety function), QC analytical staff (bioanalytical + small-molecule payload methods), QA, and facilities/engineering.

3. Process Flow Diagrams

3.1 RLT End-to-End Process Flow

The RLT process is fundamentally a hot-cell-centric flow: isotope receipt → dispensing → radiolabeling (conjugation of isotope to targeting ligand) → purification → sterile filtration/bulk formulation → aseptic fill → QC release → time-critical shipment. Unlike most biologics, there is no bulk-freeze step for commercial Lu-177/Ac-225 RLTs — because decay makes frozen intermediate storage impractical, product is formulated as a ready-to-use liquid, filled, and released within hours.

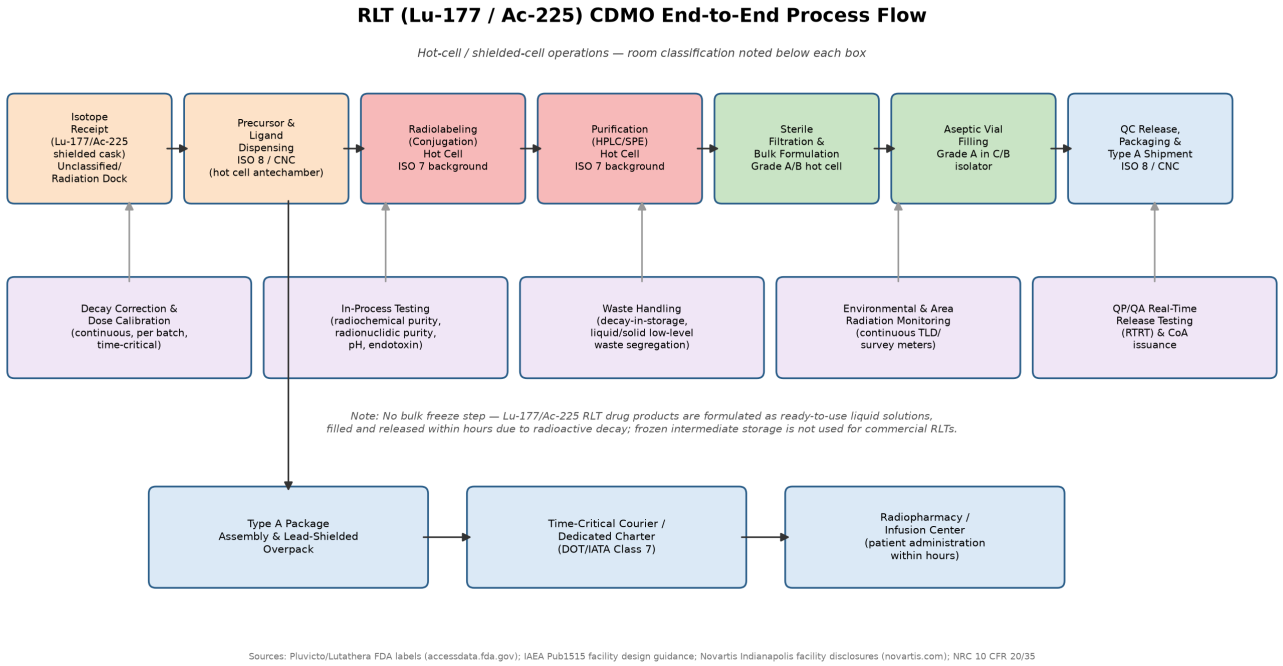

Figure 1. RLT CDMO end-to-end process flow diagram showing isotope receipt through distribution

Key adjacency-driving features of the flow:

- Isotope receipt and radiation dock must sit close to hot cell suites to minimize the "clock" started by isotope calibration.
- Decay correction and dose calibration run continuously and in parallel with production, not as a discrete downstream step — dose calibrators are typically embedded at multiple points (post-labeling, pre-fill, post-fill).
- Waste handling (decay-in-storage) is a parallel, continuously operating function segregating waste by isotope half-life for hold-then-release disposal.
- QP/QA real-time release testing (RTRT) replaces sequential batch-record review common in conventional biologics, again driven by the incompatibility of long compendial testing with short shelf life.

3.2 ADC End-to-End Process Flow

The ADC process bridges biologics-style upstream/downstream unit operations (mAb intermediate handling, TFF/UFDF) with small-molecule HPAPI handling (linker-payload dispensing under OEB5 containment) and, unlike RLT, does include a bulk-freeze step, because ADC drug substance is chemically stable for extended frozen storage (weeks to months) at -20°C or -70°C, allowing conjugation and fill/finish to be decoupled in time and even in location.

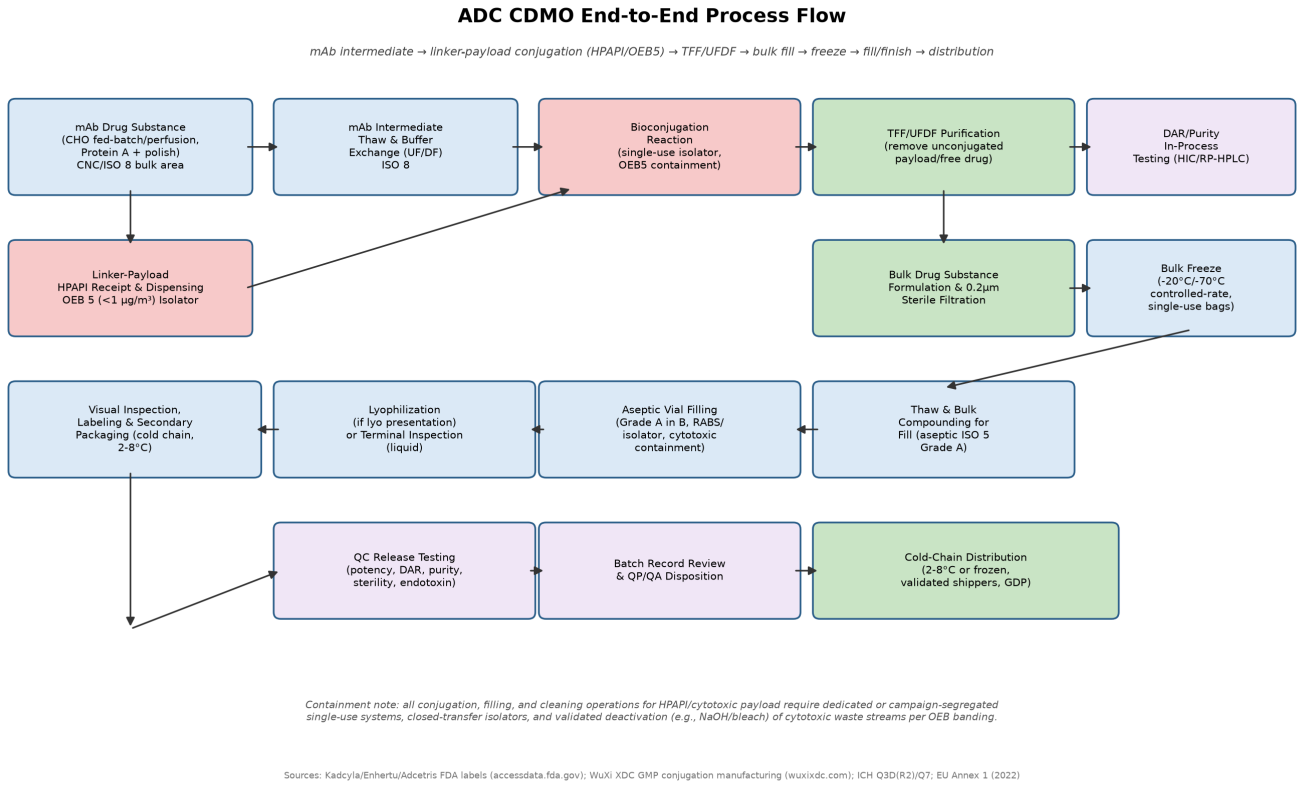

Figure 2. ADC CDMO end-to-end process flow diagram showing mAb intermediate through distribution

Key features:

- Containment boundary crosses the conjugation reactor: everything from linker-payload dispensing through TFF/UFDF and bulk formulation sits inside the OEB5/cytotoxic containment boundary; downstream of bulk freeze and thaw-for-fill, containment requirements relax somewhat (conjugated drug substance is generally less hazardous than free payload but still handled with cytotoxic precautions through fill).
- Bulk freeze decouples conjugation from fill/finish — a scheduling and site-selection-relevant feature, since conjugation and fill/finish can occur at different CDMO sites (a common commercial pattern, e.g., ADC drug substance conjugated at one CDMO and shipped frozen to a separate fill/finish specialist).
- Lyophilization is a common but not universal presentation choice among approved ADCs (several are lyophilized powder for reconstitution; others are supplied as liquid concentrate).

4. Process Timelines

4.1 RLT: Hour-by-Hour Timeline Driven by Isotope Decay

Because Lu-177 loses roughly 9.7% of activity per day (t½ = 6.647 days) and Ac-225-chain isotopes decay on a comparable timescale, RLT manufacturing is scheduled in hours, not days, from isotope receipt to patient administration.

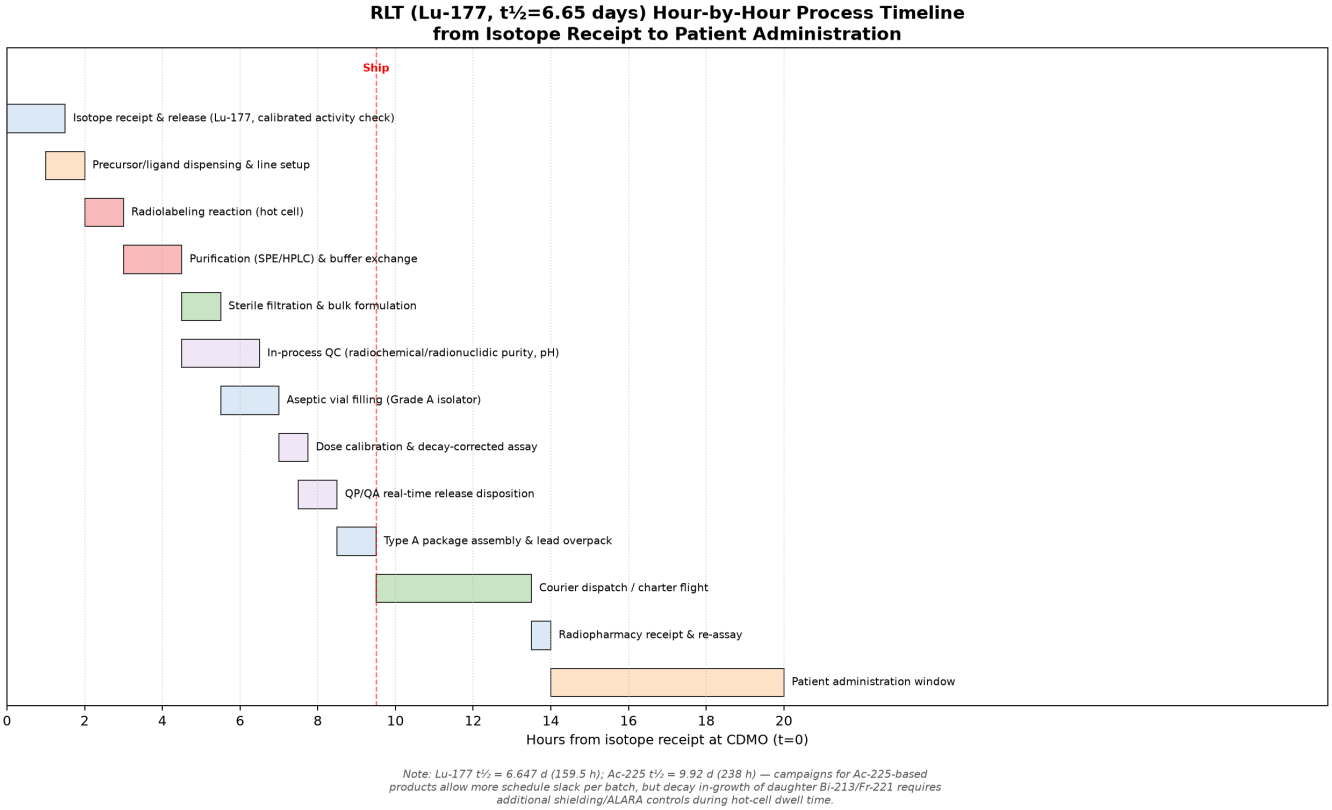

Figure 3. RLT hour-by-hour process timeline from isotope receipt to patient administration

The approximately 20-hour receipt-to-administration window shown reflects industry practice of building an "activity overage" into the fill target so that the labeled activity at time of administration meets the labeled claim (e.g., Pluvicto's 1,000 MBq/mL at time of administration) despite in-transit decay (FDA Pluvicto label[2]). Facilities located farther from major radiopharmacy/infusion-center hubs must build in additional overage, directly consuming yield and margin — a key economic argument for regional/hub-and-spoke RLT manufacturing rather than a single centralized site serving the whole country.

4.2 ADC: Day-Level Timeline

ADC manufacturing timescales are measured in days to weeks rather than hours, since the conjugated drug substance and drug product are chemically (not radioactively) stable.

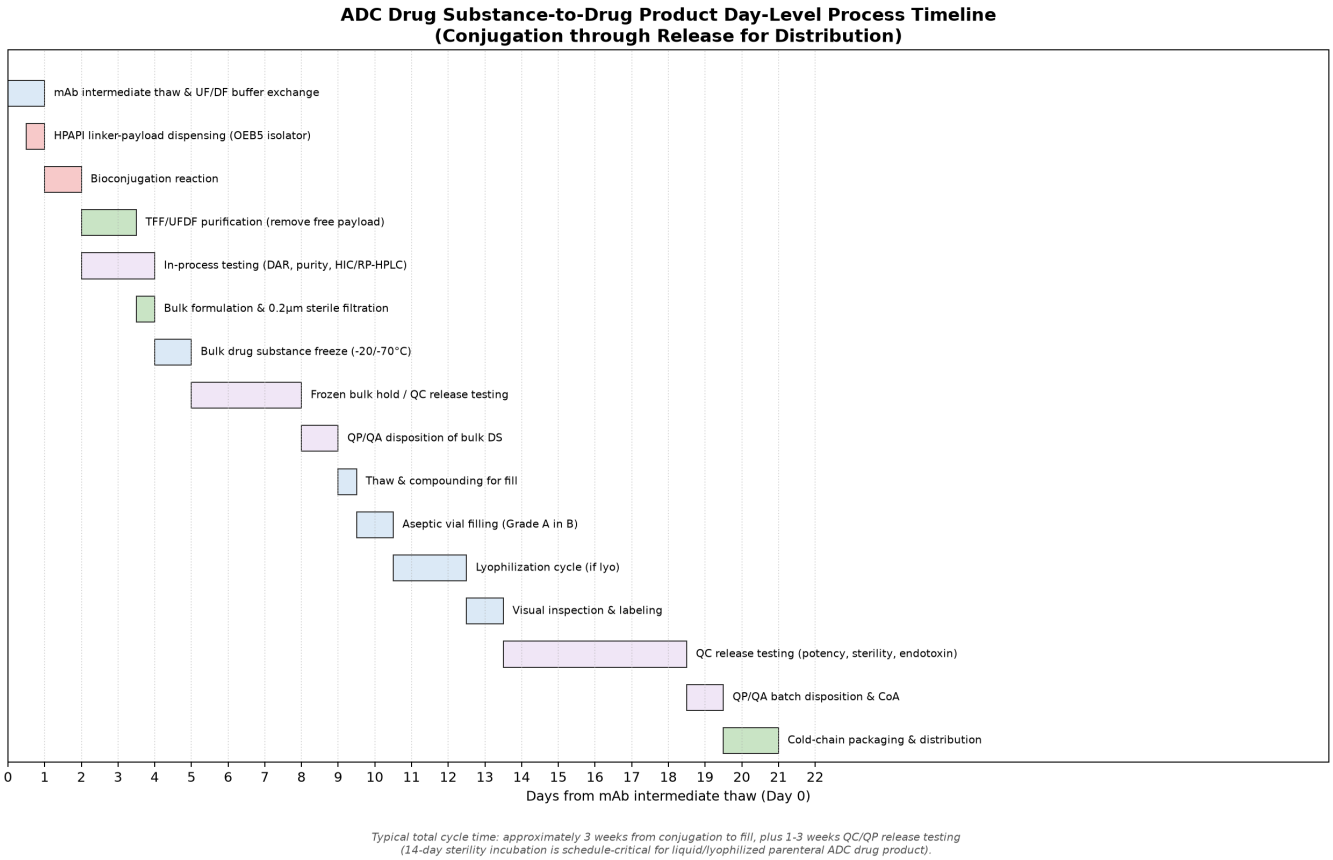

Figure 4. ADC day-level process timeline from mAb intermediate thaw to distribution

The dominant schedule constraint is not decay but compendial sterility testing (14-day incubation) gating final QP/QA disposition — a fundamentally different timeline driver than RLT, and one that argues for building sufficient frozen bulk drug substance inventory buffer to decouple conjugation campaign cadence from fill/finish and release cadence.

5. Commercial RLT Products — Landscape and Design Implications

Product (INN)	Isotope	Half-Life	First Approval	Indication	Dosing	Manufacturer / Site(s)	Source
Pluvicto (lutetium Lu 177 vipivotide tetraxetan)	Lu-177	6.647 days	2022	PSMA-positive metastatic castration-resistant prostate cancer	7.4 GBq (200 mCi) IV every 6 weeks, up to 6 doses; 1,000 MBq/mL (27 mCi/mL)	Novartis (ex-AAA); Millburn, NJ and Indianapolis, IN (largest site, 70,000 sq ft)	FDA label[2]; Novartis[3]
Lutathera (lutetium Lu 177 dotatate)	Lu-177	6.647 days	2018	Gastroenteropancreatic neuroendocrine tumors (GEP-NETs)	7.4 GBq (200 mCi) IV every 8 weeks (±1 week), 4 doses, cumulative 29.6 GBq; co-administered with amino acid solution and octreotide 30 mg IM	Novartis	FDA label[10]
Azedra (iobenguane I-131)	I-131	8.021 days	2018	Pheochromocytoma / paraganglioma	Dosimetric 185–222 MBq or 3.7 MBq/kg; therapeutic 18,500 MBq (500 mCi) or 296 MBq/kg, 2 doses ≥90 days apart, cumulative 37 GBq	Progenics/Lantheus	FDA label[25]
Xofigo (radium-223 dichloride)	Ra-223	11.4 days	2013	Castration-resistant prostate cancer with symptomatic bone metastases	55 kBq/kg IV every 4 weeks × 6 injections	Bayer	FDA label[26]
Quadramet (samarium-153 lexidronam)	Sm-153	1.93 days (46.3 h)	1997 (EU 1998)	Osteoblastic bone pain palliation	37 MBq/kg IV	Originally Cytogen/Berlex; EU marketing authorization	EMA SmPC[27]
Metastron (strontium-89 chloride)	Sr-89	50.5 days	1993	Bone pain from osteoblastic metastases	148 MBq (4 mCi) or 1.5–2.2 MBq/kg; repeat not before 90 days; 28-day shelf life from calibration	GE Healthcare	FDA label[28]
Zevalin (ibritumomab tiuxetan)	In-111 (imaging) / Y-90 (therapy)	In-111: 67.3 h; Y-90: 64.1 h	2002	Relapsed/refractory follicular non-Hodgkin lymphoma	Y-90: 0.4 mCi/kg (14.8 MBq/kg), or 0.3 mCi/kg if thrombocytopenic	Spectrum Pharmaceuticals	FDA label[29]

Design implications drawn directly from this table:

- Half-life spread (46 hours to 50+ days) demands facility flexibility, not a single fixed cycle time. A multiproduct RLT CDMO must design adjacency and hot-cell allocation to accommodate both fast-decay isotopes (Sm-153, In-111/Y-90 conjugates) that demand hour-scale turnaround, and slower-decay isotopes (Sr-89, Ra-223) that tolerate a multi-day production-to-ship window — arguing for at least two independently schedulable hot cell suites rather than one shared suite.
- Fixed multi-dose regimens with defined cumulative activity limits (e.g., Lutathera's 29.6 GBq cumulative cap, Pluvicto's up to 6 doses) imply a CDMO must plan campaign cadence around approximately 6–8-week reorder cycles per patient cohort, informing warehouse and scheduling software requirements captured in the CDR's Process Architecture section.
- The concentration of commercial RLT capacity in a small number of purpose-built mega-sites (Novartis Indianapolis, RayzeBio Indianapolis, NorthStar Beloit) reflects the extreme capital intensity of hot cells and the advantage of co-locating isotope production with drug product manufacturing — directly supporting Section 1's facility-scale assumptions and Section 9 (site selection) preference for isotope-adjacent locations.

6. Commercial ADC Products — Landscape and Design Implications

Product (INN)	Target	Payload	Linker	Approx. DAR	First Approval	Dosing	Sponsor / Key Manufacturing	Source
Adcetris (brentuximab vedotin)	CD30	MMAE	Protease-cleavable (vc)	~4	2011	1.2–1.8 mg/kg every 2–3 weeks	Seagen/Pfizer	FDA label[17]
Kadcyla (ado-trastuzumab emtansine)	HER2	DM1 (maytansinoid)	MCC, non-cleavable thioether	3.5	2013	3.6 mg/kg every 3 weeks	Genentech/Roche	Genentech label[18]
Enhertu (fam-trastuzumab deruxtecan)	HER2	Exatecan-derivative (DXd, topoisomerase I inhibitor)	Cleavable tetrapeptide	~8	2019; expanded indications through 2026	5.4 mg/kg every 3 weeks	Daiichi Sankyo / AstraZeneca	FDA[30]
Trodelvy (sacituzumab govitecan)	Trop-2	SN-38 (topoisomerase I inhibitor)	CL2A, hydrolysable/cleavable	~7.6	2020	10 mg/kg on days 1 and 8 of 21-day cycle	Gilead (ex-Immunomedics)	FDA label[19]
Padcev (enfortumab vedotin)	Nectin-4	MMAE	vc-cleavable	~3.8–4	2019	Per label regimen	Astellas/Seagen	Astellas label[31]
Polivy (polatuzumab vedotin)	CD79b	MMAE	mc-vc-PAB, cleavable	3.5	2019	1.8 mg/kg every 21 days × 6 cycles	Genentech/Roche	FDA label[32]
Besponsa (inotuzumab ozogamicin)	CD22	N-acetyl-gamma-calicheamicin	Acid-cleavable (AcBut)	~6 (range 2–8)	2017	mg/m^2-based cycle regimen	Pfizer	FDA label[20]
Mylotarg (gemtuzumab ozogamicin)	CD33	N-acetyl-gamma-calicheamicin	Cleavable	~2–3 average (range 0–6)	2000 (withdrawn 2010, re-approved 2017)	mg/m^2-based	Pfizer	FDA label[33]
Elahere (mirvetuximab soravtansine)	Folate receptor alpha	DM4 (maytansinoid)	Sulfo-SPDB, cleavable	3.4	2022	6 mg/kg (adjusted ideal body weight) every 3 weeks	ImmunoGen/AbbVie	FDA label[22]
Tivdak (tisotumab vedotin)	Tissue Factor	MMAE	vc-cleavable	~4	2021	2 mg/kg every 3 weeks, capped at 200 mg	Seagen/Genmab	FDA label[34]
Zynlonta (loncastuximab tesirine)	CD19	SG3199 (PBD dimer)	Protease-cleavable (val-ala)	2.3	2021	0.15 mg/kg tapering to 0.075 mg/kg every 3 weeks	ADC Therapeutics	FDA label[21]
Blenrep (belantamab mafodotin)	BCMA	MMAF	Maleimidocaproyl, non-cleavable	Not specified in accelerated-approval summary	2020 accelerated approval; withdrawn 2022; regulatory status revisited 2023–2025	Per label regimen	GSK	FDA[35]
Disitamab vedotin (Aidixi / RC48)	HER2	MMAE	Cleavable	~4	China NMPA, multiple indications	Per NMPA label	RemeGen	ADC Review[36]

Design implications drawn directly from this table:

- The DAR range (2.3 to ~8) and payload diversity (auristatins, maytansinoids, calicheamicin, PBD dimers, camptothecin derivatives) mean a multiproduct ADC CDMO conjugation suite must be designed around flexible single-use reaction and TFF/UFDF skids rather than fixed stainless equipment, to avoid extensive requalification between sponsor programs.
- Non-cleavable linker chemistries (Kadcyla's MCC-thioether, Blenrep's maleimidocaproyl) imply lower free-payload risk downstream of conjugation relative to cleavable-linker products, which is a defensible basis for tiered containment (i.e., not every unit operation downstream of conjugation needs to be held to OEB5 standard) — but the conjugation and purification steps themselves must be designed to the worst-case (highest-potency, cleavable-linker) payload the facility is qualified to handle.
- Multiple approved products' payloads (calicheamicin in Besponsa/Mylotarg, PBD dimer in Zynlonta) are extremely potent DNA-damaging or DNA-crosslinking agents, reinforcing that OEB5/HPAPI-grade containment (sub-1 µg/m^3 OEL) is the appropriate design basis for a general-purpose ADC CDMO conjugation suite rather than a lower band suitable only for less potent programs.
- The China-centric concentration of dedicated ADC conjugation CDMO capacity (WuXi XDC, with linker-payload licensing from Hangzhou DAC Biotech feeding into WuXi Biologics deals) is a direct commercial-landscape justification for building U.S. end-to-end ADC CDMO capacity, addressed further in Section 9.

7. Linking Commercial Product Data to Facility Design and Capacity Assumptions

The product tables in Sections 5 and 6 are not incidental context — they are the empirical basis for the programmatic assumptions in Sections 1 and 2:

For RLT:

1. The half-life range across approved products (46 hours to 50+ days) directly sets the requirement for at least two independently schedulable hot cell suites (Section 1.4) rather than a single shared suite, because a facility optimized only for Lu-177's 6.6-day half-life would over- or under-design cycle time for faster (Zevalin/Y-90, Quadramet) or slower (Metastron, Xofigo) decaying products.
2. Fixed cumulative-dose regimens (Lutathera's 29.6 GBq over four doses at 8-week intervals; Pluvicto's up to six doses at 6-week intervals) directly inform the campaign-cadence and warehouse/scheduling assumptions in Section 1.2 and the CDR's Process Architecture section.
3. The scale of disclosed commercial facilities (Novartis Indianapolis 70,000 sq ft targeting 250,000+ doses/year; RayzeBio 77,000 sq ft; NorthStar 52,000 sq ft) directly calibrates the illustrative 65,000 sq ft/50,000–100,000 doses/year design point used in Section 1.2 and the area tabulation in Section 1.5.
4. Isotope receipt-to-administration decay economics (illustrated by Pluvicto's explicit MBq/mL concentration specification at time of administration) directly justify the hour-by-hour timeline in Section 4.1 and the adjacency-driven layout implied in Section 3.1.

For ADC:

1. The DAR and payload diversity across 12 approved products directly justifies the flexible, single-use-skid conjugation suite design assumption in Section 2.4, since a CDMO serving multiple sponsors cannot commit to fixed equipment optimized for one payload chemistry.

2. The presence of multiple extremely potent DNA-damaging payloads (calicheamicin, PBD dimer) in the approved-product set justifies designing the general-purpose containment boundary to OEB5/sub-1 µg/m^3 standard (Section 2.3) even though not every individual program requires that level.
3. Dosing regimens requiring repeat cycles (e.g., Polivy's six 21-day cycles, Kadcyla's every-3-week regimen) inform the campaign-cadence assumption of 8–20 campaigns/year per conjugation suite in Section 2.2.
4. The commercial concentration of dedicated conjugation capacity in China-based CDMOs (Section 6) is the direct empirical basis for the site-selection and geopolitical analysis in Section 9, since it identifies conjugation (not mAb production, which is broadly distributed globally) as the specific bottleneck a new U.S. facility should target.

8. Safety and Containment

8.1 RLT: Radiation Safety Framework

Regulatory basis. U.S. radiopharmaceutical manufacturing is governed by the Nuclear Regulatory Commission (NRC) or, in "Agreement States," by state-level regulators operating under authority delegated by the NRC:

- 10 CFR Part 20 — Standards for Protection Against Radiation, codifying the ALARA (As Low As Reasonably Achievable) principle as the operative dose-minimization standard for facility design and operations (eCFR Part 20[37]).
- 10 CFR Part 30 — Rules of General Applicability to Domestic Licensing of Byproduct Material (eCFR Part 30[38]).
- 10 CFR Part 35 — Medical Use of Byproduct Material, directly applicable to radiopharmaceutical manufacturing and dispensing (eCFR Part 35[39]).
- Agreement States hold delegated authority to license and inspect byproduct, source, and special nuclear materials used within their borders; applicants in Agreement States file with the state, not the NRC. As of the most recent NRC listing, non-Agreement States/territories include Alaska, Delaware, Hawaii, Idaho, Indiana (denoted with an asterisk on the NRC's list, indicating a pending or special status), Michigan, Missouri, Montana, Puerto Rico, South Dakota, U.S. Pacific Territories, U.S. Virgin Islands, Washington DC, and West Virginia — all other states are Agreement States (NRC Agreement States[5]). Notably, Indiana — host to the largest concentration of commercial RLT manufacturing (Novartis, RayzeBio) — is *not* currently a full Agreement State, and industry sources indicate Indiana has submitted a letter of intent to the NRC seeking Agreement State-like authority over certain radioactive materials, a live regulatory consideration for site selection.
- Low-level radioactive waste disposal in the U.S. is concentrated in four licensed facilities operating under regional compact agreements: EnergySolutions Barnwell (South Carolina, Atlantic compact, Class A/B/C), US Ecology Richland (Washington, Northwest/Rocky Mountain compacts, Class A/B/C), EnergySolutions Clive (Utah, all U.S. regions, Class A only), and Waste Control Specialists (Texas, Texas compact, Class A/B/C) (NRC[5]). Waste disposal logistics and compact eligibility are a non-trivial site-selection factor.

Shielding and hot cell design. Shielding calculations (half-value layer/tenth-value layer methodology) size lead, tungsten, or concrete shielding thickness to isotope energy and activity; hot cells for Lu-177/Ac-225-scale activities are typically lead- or tungsten-lined steel enclosures weighing roughly 10 tons or more each, requiring dedicated structural design (PharmOut[14]).

Decay-in-storage is the standard low-level waste management approach for short-half-life isotopes: waste is segregated by isotope/half-life and held in shielded storage until activity decays to background or clearance levels, avoiding the need for off-site disposal for the shortest-lived waste streams.

Packaging and transport. Radioactive shipments are classified under DOT/IATA as Class 7 (radioactive material), with Type A packaging for lower-activity shipments and Type B packaging (rigorously tested to withstand accident conditions) for higher-activity shipments, per 49 CFR 173.427 and 172.310 (Cornell Law/eCFR 49 CFR 173.427[40]). IAEA facility design guidance and EANM/SNMMI radiopharmacy practice guidance (cGRPP) inform receiving-end handling requirements that a CDMO's shipping design must anticipate (IAEA Pub1515[15]; EANM guidance[41]).

8.2 ADC: Containment and Cross-Contamination Control Framework

OEB/OEL banding. ADC linker-payloads are classified by Occupational Exposure Band (OEB), typically OEB 5 (OEL below approximately 1 µg/m^3) given the cytotoxic, often DNA-damaging mechanism of action of approved payloads (calicheamicin, PBD dimers, maytansinoids, auristatins, topoisomerase-I inhibitors). This is the highest containment tier used in routine pharmaceutical manufacturing and drives isolator-based, closed-transfer material handling throughout dispensing, conjugation, and purification.

Containment isolators and single-use systems. Industry practice (reflected in dedicated ADC CDMO service offerings such as WuXi XDC's GMP conjugation manufacturing) is to conduct linker-payload dispensing, conjugation, and initial purification within closed isolators using single-use process paths, both to protect personnel and to minimize cross-contamination risk between sponsor programs sharing a multiproduct facility (WuXi XDC[23]).

Decontamination and cytotoxic waste. Surfaces, isolators, and equipment exposed to HPAPI payload require validated chemical decontamination (commonly oxidative, e.g., sodium hypochlorite, or hydrolytic deactivation depending on payload chemistry) before maintenance access or product changeover; liquid and solid cytotoxic waste streams require segregated collection and validated deactivation before disposal as hazardous waste.

Dedicated vs. multiproduct facility rules. Regulatory expectation (reinforced by ICH Q7 for APIs and by general cGMP cross-contamination principles) is that highly potent/cytotoxic products either use dedicated facilities/equipment or rely on rigorously validated cleaning and containment with quantitative carryover limits set using health-based exposure limits (HBELs) — a framework formalized in ICH Q3D(R2) for elemental impurities (analogous risk-based logic applies to organic HPAPI carryover) (ICH Q3D(R2)[42]) and ICH Q7 for API GMP more broadly (ICH Q7[43]).

EU GMP Annex 1 (2022 revision) — while an EU rather than U.S. instrument, Annex 1's revised contamination control strategy (CCS) framework for sterile products is widely adopted as best practice by U.S.-based CDMOs serving global markets, particularly around environmental monitoring, single-use system qualification, and isolator/RABS design for aseptic fill of both RLT and ADC drug products (European Commission, EU GMP Annex 1[44]).

9. Geopolitical and Site-Selection Analysis

9.1 RLT Isotope Supply Chain Geography

Region/Country	Role in RLT Supply Chain	Key Facilities/Programs	Source
Netherlands	Major Mo-99 and Lu-177 production hub	HFR Petten (NRG), converting to low-enriched uranium (LEU) targets; Curium's new Petten Lu-177 facility (2 production lines, 52 weeks redundant capacity, using in-licensed Eczacıbaşı-Monrol technology)	NucNet[45]; GlobeNewswire/Curium[46]
Canada	Growing Lu-177 and other medical isotope producer; historical Mo-99 leadership	Bruce Power (Lu-177, regulatory approval received); TRIUMF and other cyclotron facilities	Bruce Power[47]; ANS[48]
Germany	n.c.a. Lu-177 commercial supplier with multiple global supply agreements	ITM Isotope Technologies Munich	ITM press releases[49]
Australia	Licensed Lu-177 producer; strong nuclear medicine research infrastructure	ANSTO	ANSTO[50]
United States	Growing commercial RLT drug product manufacturing hub; DOE-led Ac-225 production scale-up	Novartis/RayzeBio/NorthStar (Indianapolis, IN; Beloit, WI); DOE Tri-Lab (ORNL, Brookhaven, Los Alamos) for Ac-225	Novartis[3]; DOE Isotopes[6]
South Korea	Emerging radiopharmaceutical export ambitions; targeting 100% isotope self-sufficiency by 2030 and export industry by 2035	Government-backed initiative; reported Novartis investment interest	KoreaBizWire[51]; Pulse[52]
Kinectrics (Canada, cross-cutting)	Yb-176 target material production to diversify away from Russian-origin supply	Kinectrics facility	Kinectrics[13]

Implication: Lu-177 supply is now reasonably diversified across the Netherlands, Canada, Germany, and Australia, reducing single-point-of-failure risk relative to a few years ago. Ac-225 remains acutely scarce, with the U.S. DOE Tri-Lab effort (Oak Ridge's thorium-229 "milking" plus emerging accelerator-based thorium-232 irradiation routes, supported by Brookhaven and Los Alamos hot-cell buildout) representing one of the only credible scale-up paths — a structural argument for co-locating a U.S. Ac-225-capable RLT CDMO near DOE national laboratory infrastructure or building direct supply relationships with the Tri-Lab program rather than assuming commercial-scale open-market Ac-225 availability in the near term (DOE Isotopes[6]; ORNL[11]).

9.2 ADC Payload/CDMO Supply Chain Geography and BIOSECURE Act

ADC linker-payload synthesis and GMP conjugation capacity is heavily concentrated in China:

- WuXi XDC operates dedicated ADC-focused facilities offering GMP conjugation manufacturing and mAb intermediate production (WuXi XDC[23]; WuXi XDC locations[53]).
- Hangzhou DAC Biotech is a significant linker-payload technology licensor, with licensing deals feeding into WuXi Biologics' and other sponsors' ADC programs (e.g., Aadi Bioscience's exclusive licensing agreement covering the CPT113 linker-payload) (PharmaSource[9]).
- Other ADC CDMO capacity exists at MabPlex (commercial ADC drug product fill-finish line) and Western players including Lonza, AGC Biologics, Catalent, Piramal, and BioDlink, but the highest-profile dedicated ADC conjugation specialists remain China-concentrated (MabPlex[54]).

BIOSECURE Act. As of the most current reporting, the BIOSECURE Act — restricting U.S. federal agencies from contracting with, or granting/lending to, companies reliant on biotechnology equipment or services from named "biotechnology companies of concern" (including WuXi AppTec and WuXi Biologics under the

Department of War's Section 1260H list, plus a new OMB-developed list using national-security criteria such as government/military/intelligence ties and improper handling of sensitive biological data) — is reported as law, with implementation expected to be gradual and restrictions unlikely to take full effect before approximately 2028, with grandfathering provisions delaying compliance for existing contracts into the early 2030s pending OMB guidance and revised federal acquisition rules (Amritt[55]; Arnold & Porter[1]). Separately reported coverage describes an "8-year deadline" framing for U.S.-China CDMO decoupling in some legislative drafts, and a 2026 Pentagon ruling reportedly affecting WuXi AppTec specifically (PharmaSource[56]; PharmaManufacturing[57]; C&EN[58]). Countries positioned as likely beneficiaries of U.S. sponsors diversifying away from China-based CDMOs include India, elsewhere in Europe, Japan, South Korea, and Israel, provided those alternative providers can demonstrate compliance, data governance, and independence from foreign government influence (Amritt[55]).

Implication for facility design: A new U.S. ADC CDMO's most defensible strategic position is not competing broadly against low-cost China-based conjugation capacity on price, but specifically targeting (a) BIOSECURE-affected sponsors needing non-China-dependent supply chains for federally funded or defense-adjacent programs, and (b) sponsors seeking to de-risk single-source dependency on WuXi-linked linker-payload technology, regardless of BIOSECURE's exact implementation timeline.

9.3 Broader Country/Region Comparison for Site Selection

Location	RLT Suitability	ADC Suitability	Key Considerations
United States	Strong — largest commercial RLT market, Indianapolis isotope cluster, DOE Ac-225 program, NRC/Agreement State framework mature	Strong for BIOSECURE-driven reshoring; existing biologics CDMO base (Lonza, Catalent, AGC, etc.) can add conjugation capability	IRA drug-pricing provisions and domestic manufacturing incentives favor U.S.-based commercial production; NRC/Agreement State licensing pathway well understood; largest end-market (patient population under Medicare/commercial insurance)
Canada	Strong — Bruce Power Lu-177, Kinectrics Yb-176 target production, TRIUMF cyclotron infrastructure	Moderate — biologics CDMO base exists but limited dedicated ADC conjugation specialists	Proximity to U.S. market; different regulator (Health Canada/CNSC) but strong bilateral trade relationship; potential tariff/USMCA considerations
EU (Netherlands/Belgium)	Strong — HFR Petten, Curium Lu-177 facility, strong EANM guidance ecosystem	Strong — many established biologics CDMOs; Belgium/Netherlands host significant biomanufacturing clusters	EU Annex 1 and evolving "EU Pharma Package" reforms set a high bar but are well-documented; isotope logistics favor EU-domestic RLT production for EU market
Switzerland	Moderate — strong biopharma R&D presence (Novartis HQ) but limited domestic isotope production	Strong — deep biologics manufacturing expertise, high-quality talent pool	High cost base; strong IP protection and regulatory sophistication; Swissmedic well-regarded but outside EU regulatory harmonization
Ireland	Limited — no significant domestic isotope production	Strong — major biologics manufacturing hub (multiple large-scale mAb sites) with EU market access	Favorable corporate tax regime; EU regulatory alignment; strong existing biologics workforce transferable to ADC conjugation with retraining
Japan	Moderate — growing radiopharmaceutical interest, strong nuclear medicine research base	Strong — sophisticated biologics/CDMO sector, strict but predictable PMDA regulation	High-quality manufacturing culture; potential isotope self-sufficiency ambitions; distance from U.S. market a logistics factor for time-critical RLT export
South Korea	Growing — explicit government strategy targeting radiopharmaceutical export leadership and full isotope self-sufficiency by 2030	Moderate-to-growing — expanding biologics CDMO sector (Samsung Biologics, others)	Government-backed strategic investment; reported Novartis interest in a Korean radiopharma plant; export-oriented policy alignment
Australia	Strong — ANSTO Lu-177 licensing, established nuclear medicine infrastructure	Limited — smaller biologics CDMO base	Geographic isolation from major Northern Hemisphere markets is a significant RLT logistics constraint given decay economics
India	Limited for isotope production; growing pharmaceutical manufacturing base broadly	Strong emerging position — explicitly named as a likely BIOSECURE beneficiary for biologics/CDMO reshoring	Cost-competitive; improving regulatory sophistication (CDSCO); named specifically as well-positioned if compliance/data-governance credentials are demonstrated
China	Growing domestic capability but not a preferred site for Western-market-facing RLT given regulatory/political exposure	Currently dominant in ADC linker-payload/conjugation (WuXi XDC, Hangzhou DAC) but structurally exposed to BIOSECURE Act and broader US-China biotech decoupling risk	Highest current ADC conjugation capacity concentration globally, but the single largest geopolitical risk factor for Western sponsors post-BIOSECURE

9.4 Site-Selection Criteria and Scoring Matrix (Illustrative)

Criterion	Weight	RLT Considerations	ADC Considerations
Proximity to isotope source (reactor/cyclotron) or payload/linker supply	25%	Distance to Lu-177/Ac-225 production source drives decay-loss economics directly	Distance to linker-payload synthesis source drives lead time and inventory risk
Regulatory environment	20%	Agreement State vs. NRC-direct licensing complexity and timeline	FDA cGMP track record; state-level environmental/hazardous-waste permitting for cytotoxic operations
Airport/logistics access	20%	Direct flights/charter availability critical given hour-scale shipping windows	Less time-critical, but cold-chain logistics infrastructure still matters
Workforce availability	15%	Health physics, radiopharmacy-trained technologists (a narrow talent pool)	Biologics + potent-compound handling talent (broader pool, but OEB5 experience is narrower)
Utility/infrastructure cost and capacity	10%	Power reliability for continuous monitoring/ventilation systems	Standard biologics utility demand; HPAPI-rated HVAC design experience among local A/E firms
Incentives/tax environment	10%	State/local incentives for isotope/radiopharma manufacturing (e.g., Indiana's cluster-building efforts)	IRA/state manufacturing incentives; potential eligibility for BIOSECURE-driven reshoring incentives

9.5 U.S. State-Level Considerations

Within the United States, state-level factors materially affect RLT site selection in particular:

- Agreement State status determines whether a facility licenses radioactive material directly through the NRC or through a state regulator; most U.S. states are Agreement States, but notable non-Agreement States/territories include Alaska, Delaware, Hawaii, Idaho, Indiana, Michigan, Missouri, Montana, Puerto Rico, South Dakota, Washington DC, and West Virginia (NRC[5]). Indiana's non-Agreement-State status is a notable friction point given that it hosts the largest concentration of U.S. commercial RLT manufacturing — reportedly prompting the state to seek expanded authority.
- Proximity to reactors/cyclotrons favors regions near research reactor infrastructure or established cyclotron networks for shorter isotope transit times.
- Low-level radioactive waste compact membership determines which of the four licensed U.S. disposal facilities (South Carolina, Washington, Utah, Texas) a given site's waste stream can access, which varies materially by state and waste class (NRC[5]).
- Airport/logistics access is a first-order RLT site-selection criterion given the hour-scale shipping windows illustrated in Section 4.1 — proximity to a major cargo/charter-capable airport with reliable schedule reliability materially affects achievable geographic market radius without unacceptable decay loss.

10. Conceptual Design Report (CDR) Development Schedule (15–18 Weeks)

A conceptual design report for a facility of this complexity follows an industry-standard Front-End Loading (FEL-1/FEL-2 equivalent) stage-gated process, typically executed over 15–18 weeks with four formal gates.

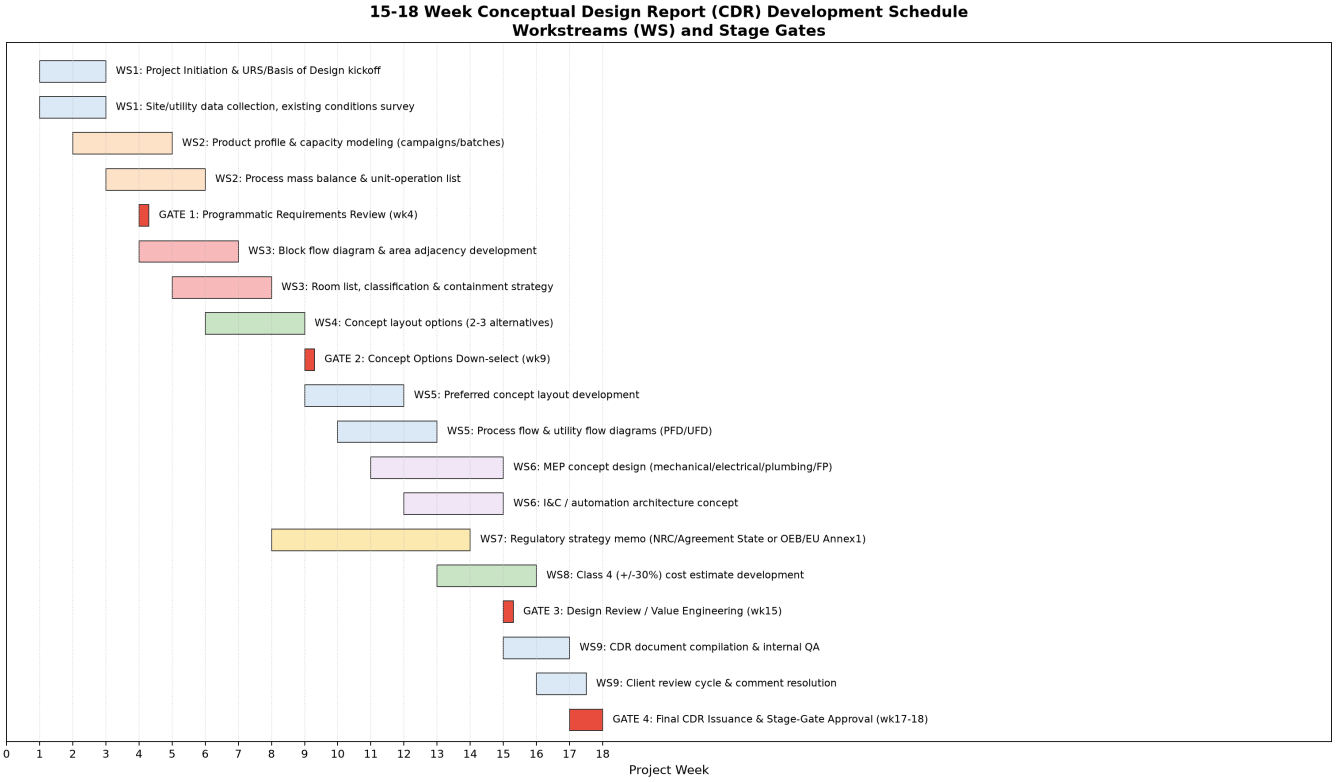

Figure 5. 15-18 week CDR development schedule Gantt chart with workstreams and stage gates

Week(s)	Workstream	Key Activities	Deliverables
1–2	WS1: Project Initiation	Kickoff, URS/Basis of Design confirmation, existing-conditions site/utility survey	Project charter, URS draft, site data package
2–4	WS2: Programmatic Requirements	Product profile and capacity modeling (campaigns, batch sizes, doses/campaign), process mass balance, unit-operation list	Capacity model, unit operations table (mirrors CDR §3.1–3.2)
4	Gate 1	Programmatic Requirements Review	Sponsor sign-off on capacity/product basis before layout work begins
4–6	WS3: Containment & Classification Strategy	Block flow diagram, area adjacency study, room list, GMP classification assignment, containment/segregation strategy	Block flow diagram, preliminary room list, classification matrix (mirrors CDR §3.3–3.5)
6–9	WS4: Concept Options	Development of 2–3 alternative concept layouts	Concept layout drawings, options comparison (mirrors CDR §4.0)
9	Gate 2	Concept Options Down-Select	Sponsor selects preferred concept for further development
9–13	WS5–WS6: Preferred Concept & MEP	Preferred layout development, process/utility flow diagrams, MEP (mechanical/electrical/plumbing/fire protection) concept design, I&C/automation architecture concept	PFDs/UFDs, MEP concept package, I&C architecture (mirrors CDR §5.0–6.0)
8–13	WS7: Regulatory Strategy	NRC/Agreement State licensing strategy memo (RLT) or OEB/EU Annex 1/state hazardous-waste permitting strategy (ADC)	Regulatory strategy memo
13–15	WS8: Cost Estimate	Class 4 (+/-30%) cost estimate development and reconciliation	Cost estimate package (mirrors CDR §7.0)

Week(s)	Workstream	Key Activities	Deliverables
15	Gate 3	Design Review / Value Engineering	Cross-functional review, VE recommendations incorporated
15–17	WS9: CDR Compilation	Document compilation, internal QA, appendix assembly (process/architectural/mechanical/electrical sections)	Draft CDR document (mirrors CDR §8.0 appendix structure)
16–17.5	WS9: Client Review	Client review cycle, comment resolution	Comment-resolution log, revised CDR
17–18	Gate 4	Final CDR Issuance & Stage-Gate Approval	Approved CDR, authorization to proceed to FEED/detailed design

This structure is consistent with published Front-End Loading practice, under which FEL-1 (conceptual/scoping) typically runs 4–8 weeks and FEL-2 (feasibility/concept selection, corresponding to the bulk of a CDR) runs 8–12 weeks on mid-to-large capital projects, with cost estimate confidence progressing from roughly ±40–50% at FEL-1 to ±25% by the end of FEL-2 (Umbrex, Front-End Loading[59]; Genoil FEL[60]). ISPE's Baseline Guide Volume 6 (Biopharmaceutical Manufacturing Facilities, 3rd Edition) formalizes an analogous "Conceptual Design Stage Gate Model" as a dedicated appendix, alongside a sample rooms list — directly paralleling the room-list and classification-matrix deliverables called out in the schedule above (ISPE Baseline Guide Vol 6 TOC[61]).

Conclusion

Both RLT and ADC manufacturing sit at the intersection of high commercial demand growth and structurally concentrated, geopolitically exposed supply chains — isotopes and hot cells for RLT; linker-payload chemistry and conjugation capacity for ADC. The commercial product landscape (Sections 5 and 6) is not incidental background; it is the direct empirical basis for every capacity, area, staffing, and timeline assumption in this report, from the two-hot-cell-suite minimum driven by half-life diversity to the OEB5 containment standard driven by payload potency diversity. Facility design decisions — particularly site selection, hot cell/containment suite count, and adjacency between isotope/payload receipt and time-critical downstream steps — should be treated as direct derivatives of the commercial dosing regimens, decay kinetics, and DAR/linker chemistries actually in commercial use today, not generic biologics facility templates adapted after the fact. The companion CDR Framework Template applies this same evidence-based approach within the specific section structure, numbering, and level of detail of the reference Conceptual Design Report template.

PART III

Conceptual Design Report Framework

A CDR framework template mirroring the section structure and numbering of a representative industry Conceptual Design Report, populated separately for an RLT facility concept and an ADC facility concept.

The template's native 1.0–8.0 numbering is preserved verbatim in the content; PDF headings in this Part are prefixed "CDR §" to avoid collision with Part II section numbers.

Framework mirrors the section structure, numbering, and level of detail of a representative industry Conceptual Design Report (IPS Biopharmaceutical Technical Consulting, "BiBo P03 Project — Large Scale Biopharmaceutical CDMO Integrated Platform Phase II," Dec. 17, 2021), adapted and populated separately for an RLT facility concept and an ADC facility concept. Bracketed items marked [TBD — Project-Specific] indicate fields that must be finalized with sponsor/site-specific data during actual CDR development; all other content reflects design-basis assumptions derived from commercial RLT/ADC product data, ISPE Baseline Guide practice, and current U.S. regulatory frameworks, cited inline.

CDR §1.0 Project Overview

CDR §1.1 Foreword

[RLT Facility] [Consulting Firm] has been retained by [Sponsor/CDMO Owner] to provide conceptual design services for a new end-to-end radioligand therapeutics (RLT) contract development and manufacturing (CDMO) facility located at [Site, State, USA]. The scope of this design phase addresses the Owner's objectives by outlining the fundamental programmatic requirements for the new facility through identification of design philosophies, hot-cell and containment layout development, radiological and process utility analysis, and order-of-magnitude (Class 4, ±30%) cost estimating. The design basis reflects benchmarking against operating commercial RLT facilities, including Novartis' Indianapolis site (70,000 sq ft, described by the sponsor as "the largest and most advanced radioligand therapy manufacturing facility in the world") and RayzeBio's Indianapolis site (77,000 sq ft, first-of-kind co-located isotope production and drug product manufacturing) (Novartis[3]; RayzeBio[4]).

[ADC Facility] [Consulting Firm] has been retained by [Sponsor/CDMO Owner] to provide conceptual design services for a new end-to-end antibody-drug conjugate (ADC) contract development and manufacturing (CDMO) facility located at [Site, State, USA]. The scope of this design phase addresses the Owner's objectives by outlining the fundamental programmatic requirements for the new facility through identification of design philosophies, HPAPI/OEB5 containment layout development, conjugation and TFF/UFDF process architecture, utility analysis, and order-of-magnitude (Class 4, ±30%) cost estimating. The design basis reflects benchmarking against the commercial ADC product landscape (12 approved products spanning DAR 2.3–8, multiple payload/linker chemistries) and the current concentration of dedicated conjugation capacity in China-based CDMOs (WuXi XDC, Hangzhou DAC Biotech), which this facility is intended to address as a U.S.-domestic alternative in light of the BIOSECURE Act (WuXi XDC[23]; Arnold & Porter[1]).

CDR §1.2 Executive Summary

CDR §1.2.1 Facility Design Overview

[RLT Facility] The Owner has identified [Site] for construction of a new radioligand therapeutics CDMO facility. The campus is planned to contain manufacturing (hot cell suites for radiolabeling and purification), aseptic fill/finish, QC laboratories (radiochemistry, radionuclidic purity, microbiology), radiologically controlled warehousing and decay-in-storage waste handling, central utilities, and administration. The design scope includes:

- Lu-177 radiolabeling/purification suite (multiproduct, hot-cell based)
- Ac-225 radiolabeling/purification suite (dedicated or campaign-segregated, given alpha-emitter daughter-product shielding requirements)
- Aseptic fill suite (Grade A in B/C isolators)
- QC laboratories (radiochemistry, microbiology, stability)
- Radiologically controlled warehouse, decay-in-storage waste holding, and Type A/B shipping preparation area
- Central utilities including shielded exhaust/HEPA-carbon filtration trains and emergency power

This scope is the basis for this report.

[ADC Facility] The Owner has identified [Site] for construction of a new antibody-drug conjugate CDMO facility. The campus is planned to contain manufacturing (mAb intermediate receipt, bioconjugation, TFF/UFDF purification), aseptic fill/finish (including optional lyophilization), QC laboratories (bioanalytical/DAR, microbiology), HPAPI-rated warehousing and cytotoxic waste handling, central utilities, and administration. The design scope includes:

- HPAPI linker-payload receipt, dispensing, and OEB5 containment suite
- Bioconjugation suite (single-use, isolator-enclosed reactors)
- TFF/UFDF purification suite
- Bulk drug substance formulation, sterile filtration, and freeze
- Aseptic fill suite (Grade A in B, vial and/or lyophilization)
- QC laboratories (DAR/purity bioanalytical, microbiology, stability)
- HPAPI-rated warehouse, cold-chain storage, and cytotoxic waste deactivation area
- Central utilities including dedicated single-pass HEPA exhaust for containment areas

This scope is the basis for this report.

CDR §2.0 Project Definition

CDR §2.1 Business Mission

[RLT Facility] To establish U.S.-domestic, end-to-end radioligand therapeutics contract manufacturing capacity capable of serving multiple sponsor programs across the commercial Lu-177 and emerging Ac-225 product classes, reducing single-site dependency risk in a market currently concentrated in a small number of purpose-built facilities (Novartis, RayzeBio, NorthStar) (BusinessWire[12]).

[ADC Facility] To establish U.S.-domestic, end-to-end ADC contract manufacturing capacity spanning HPAPI linker-payload handling through conjugation, purification, and fill/finish, offering sponsors an alternative to

China-concentrated conjugation capacity in light of BIOSECURE Act-driven supply-chain reshoring pressure (Amritt[55]).

CDR §2.2 Project Objectives

CDR §2.2.1 Business

- [RLT] Achieve commercial-scale annual dose capacity of 50,000–100,000 doses/year across multiproduct Lu-177 lines, with a scalable Ac-225 suite sized to current DOE Tri-Lab-supported supply volumes (DOE Isotopes[6]).
- [ADC] Achieve conjugation capacity supporting 8–20 campaigns/year at 5–50 kg mAb intermediate per batch, with fill/finish throughput matched to campaign cadence.
- [Both] Achieve Class 4 (±30%) cost estimate confidence by CDR issuance, consistent with FEL-1/FEL-2 industry practice (Umbrex[59]).

CDR §2.2.2 Engineering

- Design hot cell (RLT) or OEB5 isolator (ADC) containment systems to accommodate the full half-life range (RLT) or DAR/payload potency range (ADC) represented in the current commercial product landscape (see Sections 3.1.4 and 3.2 below).
- Provide GMP area classifications and adjacencies consistent with EU Annex 1 (2022) contamination control strategy principles and ISPE Baseline Guide Volume 6 practice, even where the facility is U.S.-market-focused, to preserve optionality for global product registration (EC Annex 1[44]; ISPE BG Vol 6 TOC[61]).

CDR §2.2.3 Operations & Maintenance

- [RLT] Design for continuous (near-daily) production cadence for Lu-177 lines and campaign-based (episodic) operation for Ac-225, with maintenance windows scheduled around isotope delivery calendars.
- [ADC] Design for campaign-based multiproduct operation with full cleaning validation and containment verification (e.g., surface swab/HBEL-based carryover limits) between sponsor programs.

CDR §3.0 Design Philosophies

CDR §3.1 Product Profile

CDR §3.1.1 Product Type

[RLT] Injectable radiolabeled small-molecule or peptide-targeting-ligand conjugates administered by IV infusion; representative products include Pluvicto (Lu-177 vipivotide tetraxetan), Lutathera (Lu-177 dotatate), Azedra (I-131 iobenguane), Xofigo (Ra-223 dichloride), and Zevalin (Y-90 ibritumomab tiuxetan) (FDA Pluvicto label[2]; FDA Lutathera label[10]).

[ADC] Injectable biologic conjugates of a monoclonal antibody covalently linked to a small-molecule cytotoxic payload; representative products include Adcetris, Kadcyla, Enhertu, Trodelvy, Padcev, Polivy, Besponsa, Mylotarg, Elahere, Tivdak, and Zynlonta (FDA labels, various — see main report Section 6[17]).

CDR §3.1.2 Markets

[RLT] U.S. commercial market (primary), with facility designed to accommodate future ex-U.S. registration (EU, Japan) given the global growth of theranostic oncology.

[ADC] U.S. commercial and clinical-stage sponsor market, targeted specifically at sponsors seeking to reduce dependency on China-based conjugation CDMOs.

CDR §3.1.3 Material Characteristics

[RLT] Radioactive byproduct material subject to NRC/Agreement State licensing under 10 CFR Parts 20, 30, and 35; material characteristics defined by isotope half-life, decay mode (beta/alpha/gamma), specific activity, and daughter-product profile (relevant for Ac-225 chain: Fr-221, Bi-213, Po-213) (eCFR Part 35[39]).

[ADC] Highly potent cytotoxic material (linker-payload) classified OEB 5 (OEL <1 µg/m^3); conjugated drug substance/product classified as biologic with cytotoxic-handling precautions through fill/finish.

CDR §3.1.4 Capacity

Table 3.1.4 — Summary of Capacity Basis

Parameter	RLT Facility	ADC Facility
Annual throughput	50,000–100,000 doses/year	8–20 conjugation campaigns/year
Batch size	20–80 patient doses/run (isotope-delivery-driven)	5–50 kg mAb intermediate/batch
Campaign cadence	3–5×/week (Lu-177); 12–24×/year (Ac-225)	8–20 campaigns/year
Benchmark facility scale	65,000–80,000 sq ft (RayzeBio[4]; NorthStar[12])	55,000 sq ft (illustrative)

CDR §3.2 Process Basis

CDR §3.2.1 Scope of Operations

Table 3.2.1 — Summary of Unit Operations (RLT)

Unit Operation	Room Classification	Reference
Isotope receipt & radiation survey	Unclassified, radiologically controlled	See Block Flow Diagram, Appendix 8.1
Precursor/ligand dispensing	ISO 8 / CNC	—
Radiolabeling (conjugation)	Hot cell, ISO 7 background	—
Purification (HPLC/SPE)	Hot cell, ISO 7 background	—
Sterile filtration & bulk formulation	Grade A/B hot cell	—
Aseptic vial filling	Grade A in C/B isolator	—
QC release testing	Unclassified lab	—
Type A/B packaging & shipment	Unclassified, radiologically controlled	—

Table 3.2.1 — Summary of Unit Operations (ADC)

Unit Operation	Room Classification	Reference
mAb intermediate thaw/buffer exchange	ISO 8	See Block Flow Diagram, Appendix 8.1
Linker-payload dispensing	OEB5 isolator	—
Bioconjugation reaction	OEB5 isolator, ISO 7/8 background	—
TFF/UFDF purification	ISO 7/8	—
Bulk formulation & sterile filtration	Grade B/C	—
Bulk freeze	Controlled cold storage	—
Thaw & compounding for fill	ISO 5/Grade A	—

Unit Operation	Room Classification	Reference
Aseptic vial filling	Grade A in B, RABS/isolator	—
Lyophilization (if applicable)	Grade A in B	—
QC release testing	Unclassified lab	—

Process Flow Diagrams referenced above are provided as standalone figures in the main report (`rlt_process_flow.png`, `adc_process_flow.png`) and would be included as Appendix 8.1 drawings in an actual project CDR.

CDR §3.3 Containment & Segregation

[RLT] Containment strategy is built around hot cell primary containment (lead/tungsten-shielded, negative-pressure ventilated enclosures) with secondary containment provided by ISO 7/8 background rooms and radiologically controlled area boundaries. Segregation between isotope lines (Lu-177 vs. Ac-225) is achieved through dedicated hot cell suites to prevent cross-contamination and to allow independent scheduling given differing half-lives. ALARA principles per 10 CFR Part 20 govern shielding design and personnel access protocols (eCFR Part 20[37]).

[ADC] Containment strategy is built around OEB5 isolator primary containment for all linker-payload and conjugation operations, with single-use process paths minimizing surface contact. Segregation between sponsor programs with differing payload chemistries is achieved through dedicated single-use disposables and validated cleaning/changeover procedures with health-based exposure limit (HBEL)-derived carryover acceptance criteria, consistent with ICH Q7 and analogous ICH Q3D(R2) risk logic (ICH Q7[43]; ICH Q3D(R2)[42]).

CDR §3.4 Decontamination and Cleaning

Table 3.4 — Cleaning/Sanitization Matrix (Illustrative)

Area	Equipment Type	CIP-RIP	CIP-Full Cycle	SIP Pre-Use Sanit.	SIP Post-Use Decon	Comments
RLT — Hot cell interior	Fixed shielded enclosure	N/A	Manual wipe-down (radiological decon)	N/A	Required, survey-verified	Chemical + radiological decon; release survey required before re-entry
RLT — Fill isolator	Isolator/RABS	N/A	VHP or equivalent	Required	Required	Standard aseptic isolator decon cycle
RLT — Dose calibrator/counting equipment	Fixed instrument	N/A	Manual wipe-down	N/A	As needed	Background contamination check before/after use
ADC — Conjugation reactor (single-use)	Single-use bag/skid	N/A	N/A (disposable)	N/A	Disposal per cytotoxic waste SOP	No CIP; single-use eliminates cross-contamination risk between batches
ADC — TFF/UFDF skid	Single-use or dedicated stainless	CIP-RIP if stainless	Full CIP + validated cleaning verification	Required	Required	HBEL-based carryover acceptance criteria
ADC — Fill isolator	Isolator/RABS	N/A	VHP or equivalent	Required	Required, cytotoxic-validated	Decon must address both bioburden and residual cytotoxic payload
ADC — HPAPI dispensing isolator	Isolator	N/A	Chemical decon (oxidative/hydrolytic per payload)	Required	Required, HBEL-verified	Wipe-sample verification against HBEL before changeover

CDR §3.5 GMP Area Classifications

Consistent with EU Annex 1 (2022) and ISPE Baseline Guide practice, both facilities apply the following environmental cleanliness tiers (EC Annex 1[44]):

Classification	Description	RLT Application	ADC Application
Grade A / ISO 5	Highest-risk aseptic operations, in operation	Vial filling needle/exposed product zone	Vial filling needle/exposed product zone, lyophilizer loading
Grade B / ISO 7 (at rest)	Background to Grade A in isolator/RABS operations	Fill suite background	Fill suite background
Grade C / ISO 7 at rest, ISO 8 in operation	Less critical clean operations	Hot cell suite background	Conjugation suite background
Grade D / ISO 8 (CNC)	Controlled non-classified, dispensing/prep	Precursor dispensing, buffer prep	mAb thaw, buffer exchange, compounding
Unclassified — radiologically/HPAPI controlled	Non-GMP-classified but access-controlled for safety	Isotope receipt, decay storage, waste handling	HPAPI receipt/storage, cytotoxic waste handling

CDR §3.6 Transition & Gowning Strategy

[RLT] Personnel flow includes radiological dosimetry badge issuance at facility entry, standard GMP gowning for classified areas, and additional TLD/extremity dosimetry for hot cell operators. Material transitions into hot cell suites occur via pass-through with radiation survey checkpoints; material and personnel egress from radiologically controlled areas requires contamination survey before release to unclassified space.

[ADC] Personnel flow includes standard GMP gowning for classified areas plus additional PPE (double gloving, powered air-purifying respirators or equivalent where isolator breach risk exists) for OEB5 containment areas. Material transitions into containment suites occur via double-door pass-through with decon-capable airlocks; degowning from cytotoxic-handling areas follows a validated sequence to prevent payload transfer to unclassified space.

CDR §3.7 Process Architecture

Process architecture for both facilities follows unidirectional material and personnel flow principles, with the RLT facility prioritizing minimum transit time from isotope receipt to shipping dock (given decay economics, see main report Section 4.1) and the ADC facility prioritizing containment-boundary integrity from linker-payload receipt through bulk freeze (given cytotoxic risk, see main report Section 3.2). Process Flow Diagrams for both facilities are provided as Appendix 8.1 figures.

CDR §3.8 Utilities

[RLT] Purified water/WFI (if aqueous formulation), clean steam (if terminal sterilization used), shielded HVAC exhaust with HEPA and activated carbon filtration for volatile daughter isotopes, dedicated radioactive liquid waste decay tanks, emergency power sized for continuous hot cell ventilation and radiation monitoring, and a continuous area radiation monitoring network integrated into building automation.

[ADC] Purified water/WFI, clean steam, single-pass (non-recirculated) HEPA-filtered exhaust for HPAPI-containment areas, closed-loop isolator decontamination systems (e.g., vaporized hydrogen peroxide), segregated cytotoxic liquid/solid waste collection with validated chemical deactivation before disposal, and standard biologics cold-chain/cold-storage utilities for frozen bulk drug substance and drug product.

CDR §4.0 Concept Options

[Project-specific: 2–3 alternative concept layouts should be developed and compared here per the Front-End Loading (FEL-1/FEL-2) practice, addressing at minimum: (a) single-site vs. hub-and-spoke facility strategy, (b) dedicated vs. multiproduct suite configuration, and (c) phased vs. full-buildout capacity approach. Each option should be evaluated against the site-selection criteria in the main report Section 9.4.] — NA in this framework template; populate with sponsor-specific layout alternatives during actual CDR development.

CDR §5.0 MEP Systems

CDR §5.1 Mechanical

[RLT] HVAC systems must accommodate shielded exhaust ductwork (heavier gauge, larger footprint than standard biopharma HVAC) and HEPA/carbon filtration trains for hot cell suites; air change rates and pressure cascades follow ISO classification requirements in Section 3.5, with negative pressure maintained in hot cell primary containment relative to background.

[ADC] HVAC systems must accommodate single-pass, non-recirculated exhaust for OEB5 containment areas (no recirculation of air that has contacted HPAPI), with makeup air systems sized accordingly; standard recirculating HVAC is acceptable for non-containment classified areas.

CDR §5.2 Electrical

Both facilities require emergency/standby power sized to maintain critical containment and monitoring systems (radiation monitoring network for RLT; HVAC/exhaust and isolator integrity monitoring for ADC) through utility outages, plus standard GMP facility power quality (UPS for critical instrumentation, automation systems).

CDR §5.3 Plumbing

[RLT] Radioactive liquid waste collection piping routed to dedicated decay tanks, separate from sanitary/process waste; purified water/WFI generation and distribution per standard biopharma practice if aqueous formulation requires it.

[ADC] Cytotoxic-contaminated liquid waste collection piping routed to dedicated deactivation/neutralization systems, separate from sanitary waste; standard WFI/purified water generation and distribution for aseptic fill operations.

CDR §5.4 Fire Protection

Both facilities require standard NFPA-compliant fire suppression appropriate to occupancy classification, with special consideration for: (RLT) fire suppression system design compatible with hot cell shielding structures and avoidance of water damage to radiological containment integrity; (ADC) fire suppression compatible with single-use disposable systems and containment isolators without compromising OEB5 containment boundaries.

CDR §6.0 Instrument & Control System

CDR §6.1 Scope of Work

Automation scope covers process control for hot cell/conjugation operations, environmental monitoring system (EMS) integration, and building automation system (BAS) integration for both facilities, plus radiation monitoring network integration (RLT) or containment/isolator integrity monitoring (ADC).

CDR §6.2 Level of Automation

[RLT] High degree of automation targeted for hot cell operations specifically to minimize personnel radiation exposure (ALARA), consistent with industry direction — Novartis' Indianapolis facility is described as designed for fully automated production lines, described by the sponsor as an industry first (Novartis[3]).

[ADC] High degree of automation targeted for conjugation and TFF/UFDF operations to minimize personnel HPAPI exposure and ensure batch-to-batch consistency in DAR/purity.

CDR §6.3 Supervisory Control and Data Acquisition (SCADA)

Centralized SCADA/PCS platform integrating hot cell (RLT) or conjugation/purification (ADC) process equipment, environmental monitoring, and (RLT-specific) radiation monitoring instrumentation into a unified data historian for batch record and regulatory reporting purposes.

CDR §6.4 Automation Network Architecture

Segregated automation network layers (process control network, plant floor network, business network) per standard ISA-95/GAMP 5 practice, with additional network segmentation for radiological (RLT) or containment (ADC) safety-critical instrumentation.

CDR §6.5 Process Control System (PCS)

Batch-oriented PCS architecture supporting recipe-driven, isotope-specific (RLT) or program-specific (ADC) manufacturing execution, with electronic batch records supporting real-time release testing workflows (particularly critical for RLT given decay-driven release timelines).

CDR §6.6 Packaged Equipment Controls

Skid-mounted equipment (hot cells, conjugation reactors, TFF/UFDF systems, fill lines) controls integrated to the plant-wide PCS via standard industrial protocols (e.g., OPC-UA), with vendor-supplied local HMI for equipment-level operation.

CDR §6.7 Instrumentation

[RLT] Includes dose calibrators, gamma spectroscopy systems, area radiation monitors (continuous), and standard process instrumentation (temperature, pressure, flow, pH).

[ADC] Includes in-line/at-line DAR and free-payload monitoring instrumentation where feasible, standard process instrumentation, and containment-integrity monitoring (isolator pressure differentials, particle counters).

CDR §7.0 Cost Estimate (+/-30%)

[Project-specific: A Class 4 (±30%) cost estimate should be developed here, consistent with FEL-1/FEL-2 industry practice where FEL-1 estimates typically carry ±40–50% confidence and FEL-2/CDR-stage estimates typically achieve ±25–30% confidence (Umbrex[59]; Genoil FEL[60]). Cost basis should reference disclosed benchmark investments where available — e.g., RayzeBio's Indianapolis facility represents $160M+ invested to date for a 77,000 sq ft first-of-kind end-to-end RLT site (RayzeBio[4]) — scaled to the specific facility program defined in Sections 1–3 above.]

Illustrative Cost Estimate Structure:

Cost Category	RLT Facility (Illustrative)	ADC Facility (Illustrative)
Site/civil work	[TBD — Project-Specific]	[TBD — Project-Specific]
Building shell & core	[TBD — Project-Specific]	[TBD — Project-Specific]
Process equipment (hot cells / conjugation & TFF/UFDF skids)	High — hot cells ~$500K+ each (PharmOut[14])	High — single-use conjugation/purification skids, isolators
MEP systems	High — shielded exhaust, radiation monitoring	High — single-pass HEPA exhaust, decon systems
I&C/automation	Moderate-High	Moderate-High
Commissioning/qualification	[TBD — Project-Specific]	[TBD — Project-Specific]
Contingency	30% (Class 4 estimate)	30% (Class 4 estimate)

CDR §8.0 Appendix

CDR §8.1 Process Section

Process Flow Diagrams: `rlt_process_flow.png` (RLT end-to-end flow) and `adc_process_flow.png` (ADC end-to-end flow), plus Block Flow Diagrams, Unit Operations tables (Section 3.2.1), Process Timelines (`rlt_timeline.png` — hour-by-hour; `adc_timeline.png` — day-level), and Material/Mass Balance [TBD — Project-Specific].

CDR §8.2 Architectural Section

Room list, area tabulation by classification (main report Sections 1.5 and 2.5), adjacency diagrams, and concept layout drawings [TBD — Project-Specific, developed during Section 4.0 Concept Options phase].

CDR §8.3 Mechanical Section

HVAC schematic diagrams, air change rate schedules, pressure cascade diagrams, shielded exhaust (RLT) or single-pass HEPA exhaust (ADC) routing drawings [TBD — Project-Specific].

CDR §8.4 Electrical Section

One-line electrical diagrams, emergency/standby power sizing calculations, radiation monitoring network architecture (RLT) or containment monitoring network architecture (ADC) [TBD — Project-Specific].

This framework template is intended for use as a starting structure for an actual project-specific Conceptual Design Report. All [TBD — Project-Specific] fields, Section 4.0 Concept Options, and Appendix drawings require population with sponsor, site, and process-specific data during the 15–18 week CDR development schedule detailed in the main report (Section 10).

PART IV

EPCM Shortlist & RFI/RFP Strategy

Qualified EPCM shortlist for a U.S. RLT + ADC CDMO facility program, firms considered and not recommended, capability mapping, specialty subconsultants, regional/labor and Agreement State considerations, and a weighted RFI/RFP scoring strategy.

Headings in this Part are prefixed “IV.”; the source document’s own section numbers follow the prefix.

Prepared for: Biotech Resources Group, LLC

Scope: Qualified EPCM (Engineering, Procurement, Construction Management) shortlist for a US-based CDMO facility program covering (a) radioligand therapy manufacturing — hot cells, shielded suites, Lu-177/Ac-225, NRC/Agreement State licensing — and (b) antibody-drug conjugate (ADC) manufacturing — HPAPI/OEB5 containment isolators, conjugation, TFF/UFDF, aseptic fill.

Date: August 2026

IV.1 Executive Summary

No single national-tier EPCM firm currently advertises a deep, multi-project track record spanning *both* radiopharmaceutical hot-cell/shielded manufacturing *and* ADC/HPAPI containment. The market splits into three tiers:

1. Tier 1 — Large national EPCMs with direct, named evidence in *both* domains or in one domain plus deep adjacent nuclear/GMP capability: Jacobs, IPS-Integrated Project Services, Gilbane, CRB, Genesis AEC.
2. Tier 2 — Strong general pharma/biotech EPCM or CM firms with GMP biologics/HPAPI depth but no publicly confirmed radiopharma reference project: Burns & McDonnell, AECOM, DPR Construction, Turner Construction, PM Group, Hargrove Engineers + Constructors, Salas O'Brien, SSOE Group.
3. Tier 3 — Adjacent/nuclear-pedigreed or niche/regional players worth including in a broader RFI for specific scopes (nuclear licensing know-how, isotope production infrastructure, or boutique RLT design-build track record): Fluor, Bechtel, Framatome, Amentum, SMRT/Hodess.

The most important finding for the RFP strategy: the only large, brand-name EPCM firms with a directly confirmed, named, currently active US radiopharmaceutical cGMP manufacturing building project are Gilbane (TerraPower Isotopes Ac-225 facility, Philadelphia) and IPS (BWXT Mo-99/Tc-99m facility and SOFIE Biosciences radiopharmaceutical CoE). Jacobs is the confirmed design consultant on the closest analog to your ADC/HPAPI scope (Merck's Madison, WI HPAPI/ADC facility). Given this, splitting the RFP into an RLT-lead EPCM and an ADC-lead EPCM (or a joint venture/teaming arrangement) is the lower-risk path unless a firm can demonstrate integrated capability in due diligence.

IV.2 Ranked Top-10 EPCM Shortlist

Rank	Firm	HQ / US Footprint	Size (revenue/employees)	RLT/Radiopharma Evidence	ADC/HPAPI Evidence	Self-Perform vs Pure EPCM	Typical Project Fit
1	IPS-Integrated Project Services (Berkshire Hathaway)	Blue Bell, PA; 15+ US offices	~3,000 employees globally, part of Berkshire Hathaway since 2022	Yes — BWXT ITG Canada Mo-99/Tc-99m radiopharmaceutical facility (basis of design, detailed design, CQV, BIM) IPS[62]; SOFIE Biosciences Radiopharmaceutical CMO Center of Excellence, Totowa NJ — full turnkey EPCMV, 20,000 sf, 4 cleanroom suites with isolators Manufacturing Chemist[63]	Yes — designed first commercial ADC facility (greenfield, drug substance + drug product) for a client IPS[64]; dedicated HPAPI/potent-compound lab design practice IPS[65]	Pure EPCM/EPCMV (design + CM oversight; uses CM/GC partners for self-perform trades)	Mid-to-large ($20M–$1B+); scales to full campus programs
2	Jacobs	Dallas, TX; national footprint	ENR #1 overall design firm (2024) ENR[66]; #1 in Pharmaceuticals in ENR's 2026 full market review Jacobs[67]	Partial — no confirmed radiopharma-specific manufacturing reference found; broad nuclear/DOE pedigree exists at the corporate level but not tied to a named US GMP radiopharma project	Yes — named design consultant for Merck's $69M, 70,000 sf HPAPI/ADC manufacturing facility, Madison WI (single-digit-nanogram OEL containment) Tradeline[68]; architect of record for FUJIFILM Biotechnologies' $3.2B Holly Springs CDMO campus Jacobs[69] and $1.2B expansion PharmaSource[70]; Spark Therapeutics Gene Therapy Innovation Center	Pure EPCM (design-led; partners with CM/GC for construction)	Large-to-mega ($100M–$3B+); best fit for campus-scale programs, may be oversized/overhead-heavy for a single-building RLT/ADC facility
3	Gilbane Building Company	Providence, RI; national offices	Privately held; ~$8B annual construction volume (Industrial Info Resources, 2023) Industrial Info Resources[71]	Yes — most directly relevant recent evidence in this shortlist. Selected to lead preconstruction and construction of the core and shell for TerraPower Isotopes' $450M, 250,000 sf Bellwether Laboratory (actinium-225 cGMP manufacturing), Philadelphia, groundbreaking May 2026 Gilbane[7]	No confirmed ADC/HPAPI-specific reference found; general biopharmaceutical manufacturing CM experience (e.g., Norton, MA biopharmaceutical manufacturing facility, architect Jacobs) Gilbane[72]	CM/self-perform general contractor (not a design-engineering EPCM); pair with a design engineer for full EPCM scope	Large ($100M–$500M+); strong for core-and-shell + CM on a nuclear-adjacent cGMP building
4	CRB Group	Kansas City, MO; national + international	Employee-owned; consistently ranked in ENR's top pharma design firms — #2 in 2022, up from #3 (2021), #4 (2019/2020) CRB[73]	No confirmed radiopharma reference found — flagged gap	Strong potent-compound/cell & gene therapy design-build pedigree (SlateXpace modular platform, Catalent Cell & Gene Therapy facility, CARsgen's first US cGMP facility) CRB[74], Cleanroom Technology[75]; general HPAPI capability implied via biologics/ADC-adjacent process design but no named ADC commercial reference found	Design-build / EPCM (uses self-perform CM arm on some projects)	Mid-to-large ($20M–$500M); strong biologics/cell-gene fit, radiopharma unproven
Rank	Firm	HQ / US Footprint	Size (revenue/employees)	RLT/Radiopharma Evidence	ADC/HPAPI Evidence	Self-Perform vs Pure EPCM	Typical Project Fit
5	Genesis AEC	Blue Bell, PA (Life Sciences focus)	Boutique/mid-size AEC, privately held	No confirmed radiopharma reference found	Yes — self-reported as having "helped design and build one of the very first facilities for making ADCs," including antibody production, cytotoxic payload (doxorubicin) handling, conjugation, under	Full-service AEC / design-build	Small-to-mid ($5M–$100M); best for a defined ADC suite/module rather than a full greenfield campus

Rank	Firm	HQ / US Footprint	Size (revenue/employees)	RLT/Radiopharma Evidence	ADC/HPAPI Evidence	Self-Perform vs Pure EPCM	Typical Project Fit
					cleanroom conditions Genesis AEC LinkedIn[76]; vaccine cGMP lab expansion project Genesis AEC[77]		
6	Burns & McDonnell	Kansas City, MO; national	ENR 2024 #7 overall ENR[66]; self-reported #8 in Pharmaceuticals Design (2025) Burns & McDonnell[78]	No confirmed radiopharma GMP reference found, though the firm has general nuclear/DOE engineering capability at the corporate level	No confirmed ADC/HPAPI reference found	Full-service EPC (engineer + self-perform construction under one roof — a genuine differentiator)	Mid-to-large; single-source EPC reduces interface risk but pharma-specific depth vs. CRB/Jacobs/IPS is less demonstrated
7	AECOM	Dallas, TX; national	ENR 2024 #2 overall design firm	No confirmed radiopharma reference found	Novartis B435 Clinical Cell Processing Facility renovation (6,320 sf cleanroom) AECOM[79]; general pharma/specialty chemicals practice AECOM[80]	Design + CM (AECOM Tishman for construction management)	Large; broad platform but pharma-specific/potent-compound depth thinner than CRB/IPS/Jacobs
8	DPR Construction	Redwood City, CA; national	Privately held; #1-ranked in pharmaceutical construction by ENR every year since 2017 DPR[81]	No radiopharma-specific project found	Deep cell & gene therapy CM track record: Theragent CDMO facility (LA, ENR CA Best Manufacturing Project 2022) DPR[82]; Erytech Cell Therapy Manufacturing Facility, Princeton NJ DPR[83]; OrganaBio cGMP facility, Miami BusinessWire[84]	Self-perform CM/GC (not a design engineer — pair with an engineering firm for full EPCM scope)	Mid-to-large; excellent CM partner for a cell/gene/biologics-style building; would need to team with an engineer for radiopharma-specific process design
9	Hargrove Engineers + Constructors	Mobile, AL; national life sciences practice	Employee-owned, ENR-ranked life sciences design firm	No confirmed radiopharma reference found	Explicitly lists "antibody-drug conjugates" and "potent compounds" in its life sciences service scope Hargrove[85]	Full EPC (design + construction)	Small-to-mid; good candidate for RFI inclusion given explicit ADC service claim, but needs reference-project verification during due diligence
10	PM Group	Cork, Ireland; strong US presence (NJ, NC, IN)	Global engineering firm; ranked Top 5 in Pharma by ENR PM Group[86]	No confirmed US radiopharma reference found	No confirmed ADC-specific reference found; strong cell/gene therapy design (Bayer Berkeley cell therapy facility, 100,000 sf, BSL-2, LEED Platinum) PM Group[87]	Pure EPCM (design-led)	Mid-to-large; strong global biologics pedigree, US radiopharma/ADC depth unconfirmed

Honorable mentions / Tier 2B for RFI consideration: Turner Construction (Agilent $725M biotech manufacturing expansion, Frederick CO Construction Dive[88]; Santen Pharmaceutical Manufacturing Facility Turner[89]; dedicated Pharma and Biosciences group Bio Nebraska[90]); Whiting-Turner (United Therapeutics Manufacturing Facility, Silver Spring MD, ISPE 2020 FOYA Social Impact winner Whiting-Turner[91]); Salas O'Brien (multidisciplinary pharma engineering, potent-compound fill line design on a $4.1B, 1M sf drug production facility Salas O'Brien[92], and CQV depth via its 2024 acquisition of Hughes Engineering & Consulting Salas O'Brien[93]); SSOE Group (30-year pharma design pedigree, clients include Merck, Novartis, Pfizer, Abbott, BMS, J&J SSOE[94], though no radiopharma/ADC-specific reference confirmed).

IV.3 Firms Considered but Not Recommended as Lead EPCM (with rationale)

Firm	Why considered	Why not top-10 for this RFP
Fluor	ENR 2024 #4 overall; deep DOE/nuclear pedigree (Savannah River remediation, X-energy/NuScale SMR work, Centrus Piketon EPC) ANS[95], Fluor[96]	Nuclear pedigree is DOE/nuclear-power and fuel-cycle, not GMP radiopharmaceutical manufacturing; no biotech/pharma GMP reference project identified. High risk of cultural/process mismatch with a cGMP biologics program.
Bechtel	ENR 2024 #9 overall (up from #19); Hanford vitrification, Natrium/TerraPower reactor, Vogtle 3&4, Uranium Processing Facility Bechtel[97], Bechtel[98]	Same issue as Fluor — DOE/weapons-complex/power-reactor nuclear experience, not GMP radiopharma. No pharma/biotech GMP reference found.
Amentum	Nuclear-specialty player, UK Sellafield decommissioning, "critical mission" engineering Amentum[99]	No GMP radiopharmaceutical manufacturing project identified; decommissioning/DOE focus is a poor proxy for cGMP hot-cell manufacturing design.
Framatome	Deep radioisotope production technology (Isogen JV Lu-177 at Bruce Power, Astatine-211 partnership with IBA, CERCA Tc-99m targets) Framatome/GlobeNewswire[100], ANS[101]	Framatome is an isotope-production technology/equipment provider tied to nuclear reactors, not a GMP facility EPCM. Relevant only as a potential isotope-supply technical advisor, not a shortlist EPCM candidate.
ProPharma Group	Deep CQV and cell & gene therapy consulting ProPharma[102]	Consulting-only (CQV, regulatory, quality) — not an EPCM/design-build firm. Valuable as a CQV subconsultant, not a lead EPCM.
CAI	30-year CQV/operational readiness specialist BusinessWire[103]	Same as ProPharma — CQV specialist, not EPCM. Recommend as a specialty subconsultant (see Section 5).
NNE (Novo Nordisk Engineering)	Strong global pharma engineering pedigree, $2.6B Novo Nordisk Kalundborg expansion Cleanroom Technology[104]	Limited/no confirmed independent US project track record outside Novo Nordisk's own network; unclear US market presence for third-party CDMO work.
Stantec	ENR Top 10 design firm in Manufacturing/Pharmaceuticals (2022); particle-therapy (cancer radiation) center experience	Particle-therapy centers are radiation-adjacent but not radiopharmaceutical manufacturing; no ADC/HPAPI reference found.
Skanska	Built Seagen's $215M, 269,097 sf biomanufacturing facility (ADC-pipeline biologics), Everett, WA Skanska[105]	Directly relevant ADC-adjacent CM experience, but flagged as a cautionary case study: post-Seagen acquisition, Pfizer abandoned/wound down the site after sinking an estimated $350–400M BioProcess Insider[106] — an M&A/ownership risk, not an execution failure by Skanska. Worth a conversation but not top-10 given the unclear reference outcome.
Clark Construction, Barton Malow, Zachry, Black & Veatch, Arcadis, Cordi Construction	Requested for review	No confirmed pharma/biotech GMP or radiopharma/ADC reference project was found for these firms in this research pass. They should not be excluded outright — regional offices or specific business units may have relevant experience not visible in public web sources — but they cannot be placed on a verified top-10 list without direct reference checks. Recommend a basic capability questionnaire only if the shortlist needs to be widened.
SMRT Inc. + Hodess Cleanroom Construction (regional/boutique)	Actual builder of RayzeBio's Indianapolis radiopharmaceutical manufacturing facility (63,000 sf, $160M, opened July 2025) — site selection, programming, detailed design, and construction oversight converting a warehouse into an ISO 7 cleanroom R&D/manufacturing facility SMRT[107]	Not a national top-10 EPCM by scale, but this is arguably the single most directly relevant named US RLT facility precedent in this entire research effort. Recommend including in the RFI as a regional specialist / potential JV partner rather than excluding it for lack of brand recognition.

IV.4 RLT vs. ADC vs. Both — Capability Mapping

Firm	RLT/Radiopharma Strength	ADC/HPAPI Strength	Recommendation
IPS	Strong (BWXT, SOFIE)	Strong (named ADC commercial facility, HPAPI labs)	Best candidate for a single integrated EPCM if scope and price are competitive
Gilbane	Strong (TerraPower Isotopes Ac-225, current/active)	Unconfirmed	Best CM partner for the RLT/hot-cell building shell; pair with a process engineer
Jacobs	Unconfirmed (general nuclear pedigree only)	Strong (Merck HPAPI/ADC design consultant)	Best fit for the ADC/HPAPI process design scope, especially at campus scale
CRB	Unconfirmed	Moderate (potent-compound/cell-gene adjacent, no named ADC project)	Consider for ADC/biologics scope only after reference verification
Genesis AEC	Unconfirmed	Strong (self-reported ADC facility design-build)	Consider for a defined ADC module/suite, not a full campus
SMRT/Hodess	Strong (RayzeBio, direct RLT precedent)	Unconfirmed	Regional specialist for the RLT building specifically
DPR / Turner / Whiting-Turner	Unconfirmed	Moderate-strong (cell/gene therapy CM track record)	CM-side partners; pair with a design engineer for either scope

Strategic implication: Given that no single Tier-1 firm has strong, named, verifiable evidence in *both* domains, the lowest-risk approach is either (a) a split-scope RFP — one EPCM leading RLT/hot-cell design (IPS or Gilbane-led team) and one leading ADC/HPAPI design (Jacobs, CRB, or Genesis AEC-led team) under a single construction manager, or (b) require bidders to name their radiopharma and/or ADC subconsultant/JV partner explicitly in their RFI response if bidding as an integrated single EPCM.

IV.5 Specialty Subconsultants/Vendors to Name in the RFI (Non-EPCM)

These firms should be named in the RFI as required or optional named subconsultants/vendors, since the EPCM's success depends heavily on their integration even though they are not EPCM firms themselves.

Hot Cell OEMs (RLT shielded manufacturing cells)

- Von Gahlen (Zevenaar, Netherlands) — hot cell/shielded cell manufacturer used in BWXT and SHINE Technologies "Supercell" (10-hot-cell system) projects SHINE[108]; Von Gahlen[109]
- Comecer (Castel Bolognese, Italy; part of ATS Life Sciences Group; US office in Rolling Meadows, IL) — hot cells and PAPI/HPAPI isolators (OEB5) Comecer[110]

Isolator OEMs (HPAPI/OEB5/ADC containment)

- Extract Technology (UK/US) — 60+ years, OEB5 containment isolators for dispensing, sampling, charging, and pack-off operations; partnered with Fitzpatrick Company on HPAPI roll compaction Extract Technology[111]

- SKAN AG (Switzerland/US) — aseptic isolators and the Cellana isolator platform for ATMP/cell-gene GMP manufacturing SKAN[112]; BioPharm International[113]
- Howorth Air Technology (UK) — delivered a turnkey 6-suite ADC containment expansion at OEL of 1 ng/m^3 (task-based) for a CDMO, including preparation isolators, kilo booths, RotoVap isolators, and lyophilizer process isolators Howorth[114]

Health Physics / Radiation Safety Consultants (shielding design, NRC/Agreement State licensing)

No single national "brand name" dominates this space the way Jacobs or CRB dominate pharma EPCM; health physics is typically delivered by specialized boutique consultancies. Representative firms with shielding-design and radioactive materials licensing practices identified in this research:

- Astarita Associates — shielding design, radiation protection program development, radioactive material license application support Astarita Associates[115]
- Benchmark Health Physics, LLC (MA/NH, national) — RSO support, NRC and Agreement State licensing, shielding evaluations, ALARA planning Benchmark Health Physics[116]
- Nevada Technical Associates (NTA) — radioactive materials license applications (NRC and state), radiation safety program development, shielding design NTA[117]
- QALTEK — NRC/Agreement State license applications and amendments, shielding design, dose assessment, ALARA program implementation QALTEK[118]
- ATOM SPEC — sealed source/device registration, shielding design, licensing and amendments ATOM SPEC[119]

Recommendation: Run a short, separate RFI/RFQ specifically for health physics/radiation safety consulting in parallel with the EPCM RFP, since this scope is typically subcontracted by the EPCM but the owner should pre-vet and potentially direct-select this consultant given how licensing-critical it is to the RLT timeline.

IV.6 US Regional / Labor Market and Agreement State Considerations

NRC Agreement State status (as of March 2025, 39 Agreement States) NRC[5]

Agreement States issue and administer their own radioactive materials licenses (under authority delegated by the NRC per Section 274 of the Atomic Energy Act) rather than routing applications through the NRC directly. As of March 2025, there are 39 Agreement States NRC Backgrounder[120]; Connecticut, Indiana, and West Virginia have filed letters of intent to become Agreement States but had not yet completed the process as of that date ECOS[121].

Key implication for site selection: Indiana — the current center of gravity for US RLT manufacturing (Novartis, Curium, Orano Med, POINT Biopharma/Lilly, SpectronRx, RayzeBio) — is a Non-Agreement State, meaning radioactive materials licenses there are issued directly by the NRC (Region III office) rather than by the Indiana state government TeleRadiation[122]. This has practical implications:

- Licensing timeline and process will run through NRC headquarters/regional review rather than a state health department, which some practitioners find slower but more standardized nationally.
- If the client is instead considering an Agreement State (e.g., Texas, California, New Jersey, Maryland, North Carolina, Massachusetts — all Agreement States NRC list[5]), the state radiological health agency (e.g., Texas Department of State Health Services, California Department of Public Health Radiologic Health

Branch) becomes the licensing authority, and EPCM/health-physics teams need State-specific experience, not just NRC experience.

- Novartis's own US RLT network illustrates this split: Millburn, NJ and Carlsbad, CA are in Agreement States; Indianapolis, IN and the newly announced Denton, TX site span both categories (TX is an Agreement State; IN is not) Novartis[123].
- EPCM/health-physics selection should explicitly verify direct experience with the specific licensing jurisdiction (NRC region or named state agency) of the chosen site — this is not a generic "radiation experience" checkbox.

Regional biotech/radiopharma manufacturing hubs and labor market notes

- Indianapolis, IN / Purdue Research Park: Now the densest US cluster of RLT manufacturing (Novartis/AAA, Curium Noblesville, Orano Med Brownsburg, POINT Biopharma/Lilly, SpectronRx Bunker Hill) Novartis[124], Curium[125], Orano Med[126], BioSpace[127]. Indiana offers strong state economic-development incentives (e.g., the $6.5M/10-year tax abatement for AAA/Novartis's original facility FiercePharma[128]) and a growing specialized cGMP/radiopharma skilled-trades and technician labor pool, but is a Non-Agreement State (NRC-direct licensing).
- North Carolina (Holly Springs / Research Triangle): Major biologics/CDMO cluster (FUJIFILM Biotechnologies $3.2B+ campus with Jacobs as EPCM Jacobs[69]); NC is an Agreement State; deep unionized and open-shop skilled trades base for large biomanufacturing construction.
- New Jersey (Millburn / greater NJ pharma corridor): Novartis's first US RLT site Novartis[129] and IPS's home turf (Blue Bell, PA is adjacent); NJ is an Agreement State; historically strong pharma-experienced trades labor but higher labor cost and union density than Sun Belt sites.
- Philadelphia, PA (Bellwether District): Emerging radiopharma/isotope hub — TerraPower Isotopes' $450M Ac-225 facility with Gilbane as CM Gilbane[7]; PA is an Agreement State.
- Texas (Denton): Novartis's newest RLT site, groundbreaking 2026 Novartis[123]; TX is an Agreement State (Texas DSHS); generally open-shop labor market with lower construction labor costs than coastal hubs, but less deep GMP-specialized trades pool than NJ/NC/Indianapolis — plan for import of specialized cleanroom/hot-cell trades crews.
- California (Carlsbad): Novartis's West Coast RLT site BioProcess International[130]; CA is an Agreement State (CDPH Radiologic Health Branch); highest labor costs and union density of the hubs listed, but deep biotech-experienced trades base (San Diego biotech cluster).
- Wisconsin (Madison/St. Louis MO axis for ADC/HPAPI): MilliporeSigma's Verona, WI HPAPI/ADC campus (Jacobs-designed) and St. Louis BioConjugation Center of Excellence represent the most mature US ADC manufacturing cluster Pharmaceutical Technology[131], BusinessWire[132]; useful as a comparable labor-market/EPCM reference region if HPAPI-experienced trades availability is a site-selection factor.

General labor-market considerations to flag in the RFI

- Ask each bidder to state whether their proposed self-perform or subcontracted trades workforce is union, open-shop, or mixed, and their specific experience recruiting/retaining trades crews certified for cleanroom, hot-cell, and potent-compound containment work (this is a scarcer skill set than general commercial construction).
- Ask bidders to disclose their current backlog and workforce commitments in the target region — the Indianapolis/NC/NJ radiopharma and biologics boom means top-tier trades crews and CQV specialists are in high demand and can create schedule risk regardless of EPCM firm quality.

IV.7 RFI/RFP Strategy

IV.7.1 Recommended number of firms to invite

- Invite 6–8 firms to the RFI stage, narrowing to 3 firms for full RFP/technical proposal, and ideally 2 finalists for best-and-final negotiation.
- Suggested RFI invite list based on this research: IPS, Jacobs, Gilbane, CRB, Genesis AEC, Burns & McDonnell, DPR (paired with an engineering partner), and SMRT/Hodess (as the regional RLT specialist wildcard). If pursuing a split-scope strategy, invite IPS and Gilbane specifically for RLT-lead proposals and Jacobs/CRB/Genesis AEC for ADC-lead proposals.

IV.7.2 Prequalification criteria (minimum bar to advance past RFI)

1. Demonstrated completion of at least one cGMP biologics or sterile injectable manufacturing facility in the last 7 years (named, verifiable, with client reference).
2. Demonstrated experience with potent compound/HPAPI containment (OEB4 or higher) OR radioactive materials handling/NRC-Agreement State licensed facility — ideally both, but at minimum one, with the other addressed via a named subconsultant/JV partner.
3. Bonding capacity and financial strength sufficient for the anticipated project value (request current bonding capacity letter).
4. No unresolved OSHA willful/repeat citations or debarment in the past 3 years; TRIR at or below the ENR/BLS construction industry benchmark (industry average TRIR ≈ 2.2–2.3 per 100 FTE per 2024 BLS data) HCSS[133], with TRIR below 1.0 and EMR below 0.7 considered "world-class" per industry benchmarking Vertikal RMS[134]. (For reference, DPR reports a combined incident rate under 2.0 per 100 employees and a 0.33 EMR DPR[135]; Jacobs reported a TRIR near 0.04 on its Holly Springs project team as of 2024 LinkedIn/Jacobs[136].)
5. Willingness to name specific radiopharma/ADC subject-matter-expert personnel (not just company-level case studies) who will be assigned to the project.

IV.7.3 Weighted scoring matrix (100 points total — adjust weights to your priorities)

Criterion	Weight	Scoring guidance
Technical capability (GMP biologics/pharma design-build depth)	20	Named reference projects, scale/complexity match, in-house process engineering depth
Radiopharma/nuclear experience (hot cells, shielding, NRC/Agreement State licensing)	20	Direct named project evidence weighted highest; adjacent DOE/nuclear-power experience weighted lowest
HPAPI/ADC containment experience	15	Named OEB4/OEB5 containment project evidence; isolator/conjugation suite design experience
Regulatory/CQV integration capability	15	In-house CQV team vs. reliance on subconsultant; FDA/EMA GMP audit track record
Schedule certainty	10	Track record of on-time delivery on comparably complex projects; proposed project schedule realism
Cost transparency	10	Open-book/GMP contracting willingness, cost estimating methodology, contingency management approach
Local labor market fit	5	Trades workforce availability/plan for the chosen site, union/open-shop strategy
Safety record	5	TRIR, EMR, OSHA citation history

IV.7.4 Sample RFI question set

RLT/Hot Cell-Specific:

1. Describe your firm's direct design and/or construction experience with shielded hot cell suites for radiopharmaceutical (Lu-177, Ac-225, or comparable alpha/beta emitter) manufacturing. Name the project, client (if disclosure permits), scope of your role, and completion date.
2. What is your firm's experience navigating NRC direct licensing (Non-Agreement State) versus state Agreement-State radioactive materials licensing? Which specific states/regions have you obtained licenses in?
3. Describe your approach to shielding design coordination — do you have in-house health physics expertise, or do you subcontract this scope? Name your typical health physics/radiation safety subconsultant(s).
4. What hot cell OEM(s) have you integrated into past projects (e.g., Von Gahlen, Comecer, or others), and what was your role in that integration (specification, procurement management, installation oversight)?
5. Describe your experience with short-half-life isotope process timelines and how facility/utility design accommodates rapid, continuous production and same-day/next-day distribution logistics.

ADC/HPAPI-Specific:

6. Describe your direct experience designing and/or constructing OEB4/OEB5 containment suites for HPAPI or ADC conjugation. Name the project, occupational exposure limit (OEL) target achieved, and client reference.
7. What isolator OEM(s) have you worked with (e.g., Extract Technology, SKAN, Comecer, Howorth), and describe your role in isolator specification, integration, and containment performance verification (e.g., SMEPAC testing).
8. Describe your experience integrating TFF/UFDF (tangential flow filtration/ultrafiltration-diafiltration) skids and downstream purification suites with upstream conjugation processes in a single facility.
9. How does your firm approach aseptic fill-finish design for cytotoxic/high-potency drug products, including personnel and environmental protection strategy?

General/Integration:

10. If proposing as a single integrated EPCM for both RLT and ADC scopes, name your internal team members or named subconsultant/JV partners who bring direct radiopharma and direct ADC/HPAPI experience respectively.
11. Describe your CQV (commissioning, qualification, validation) capability — in-house or subcontracted — and your track record with FDA pre-approval inspections for comparable facilities.
12. Provide your current TRIR, EMR, and bonding capacity, and disclose any OSHA citations or debarments in the past 3 years.
13. Describe your current backlog and workforce plan for the proposed project region, including union/open-shop strategy and availability of cleanroom/hot-cell-experienced trades crews.

IV.8 Key Gaps and Recommendations for Direct Follow-Up

1. No large national EPCM was found with a directly confirmed reference project combining both RLT hot-cell and ADC/HPAPI scopes in one building. Treat any firm's claim of "integrated capability" with healthy skepticism during due diligence — ask for named projects, not capability-page language.

2. The identity of the EPCM/general contractor for Novartis's Indianapolis, Carlsbad, and Denton RLT facilities was not confirmed in this research pass — despite extensive searching, Novartis's press materials do not name their EPCM/GC. This is worth a direct outreach or FOIA-style inquiry (e.g., Indiana Economic Development Corp filings, local building permit records) if you want to benchmark against the largest RLT buildout in the US.
3. SMRT/Hodess's role as builder of RayzeBio's Indianapolis facility is the single most concrete "apples-to-apples" US RLT building precedent found — recommend a direct reference call with RayzeBio (now part of BMS) facilities leadership if possible, regardless of whether SMRT is shortlisted.
4. Health physics/radiation shielding design consultancy is a fragmented boutique market — no dominant national brand was identified. Plan a separate, parallel RFQ for this scope rather than assuming your EPCM's named subconsultant is automatically the best available option.
5. Given IPS's unique dual-domain evidence (BWXT/SOFIE for RLT, named ADC commercial facility for ADC) and its backing by Berkshire Hathaway (financial stability for a multi-year, multi-hundred-million-dollar program), IPS merits the most rigorous due diligence and reference-checking of any firm on this list, since it is the closest fit to a true single-source integrated EPCM.

Sources

All findings above are cited inline with direct URLs. Primary source categories used: firm websites/project pages (Jacobs, IPS, CRB, Gilbane, Genesis AEC, DPR, Turner, Whiting-Turner, AECOM, Bechtel, Fluor, Burns & McDonnell, Hargrove, PM Group, Salas O'Brien, SSOE, Skanska, SMRT, Framatome, Extract Technology, SKAN, Howorth, Comecer, Von Gahlen); regulatory sources (NRC.gov agreement state pages); trade press (FiercePharma, BioProcess International, Cleanroom Technology, Pharmaceutical Technology, Manufacturing Chemist, Construction Dive, Tradeline); and industry rankings (ENR Top 500 Design Firms 2024, ENR digital archive pharmaceutical sector rankings).

APPENDIX

Source List

Consolidated, deduplicated list of every source cited in this compendium. Superscript numbers in the body text correspond to the entries below; all URLs are clickable.

A.1 Figures

A.2 Numbered Sources

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