Instituto de Salud Pública
Ministerio de Salud
Gobierno de Chile

133 años 1892 2025

From Complexity to Clarity: Chile's Regulatory Vision for Bioconjugates & Multispecifics

07/15/25

Q.F. Jorge Canales
National Medicines Agency Director
Public Health Institute of Chile

Agenda

1) The Era of Precision Medicines
2) Chile's Experience & Regulatory Landscape
3) Tackling Complexities: Regulatory, and Technical Challenges
4) Practical Evaluation Examples
5) Strategic Roadmap for Precision Medicines
6) Conclusion & Call to Action

The Era of Precision Medicines

Dawn of a New Era: Engaging Multiple Targets

Bioconjugates and multispecifics represent a new generation of therapeutics, offering unparalleled precision in targeting complex diseases. Their unique design promises revolutionary treatment approaches.

Bioconjugates

Multi-targeting

Precision Medicine

Current Landscape for Bioconjugates & Multispecifics

Antibody-Drug Conjugates (ADCs)

ADCs continue rapid growth, with new approvals and a robust pipeline targeting diverse cancers and expanding beyond oncology.

~17+
Approved
Globally (e.g., Enhertu, Kadcyla)

~530+
In Pipeline
Discovery to Clinical Stages

- **Key Trends:** Expanding beyond oncology; new payloads & conjugation tech.
- **Industry Activity:** Significant M&A (e.g., Pfizer-Seagen, AbbVie-ImmunoGen).

Multispecific Antibodies (Bispecifics)

Bispecifics show exponential growth, with numerous new approvals and diverse formats entering the clinic.

~19+
Approved
Globally (e.g., Amivantamab, Tarlatamab)

~700+
In Clinical Dev.
Clinical Trials (Phase 1-3)

- **Key Trends:** Dominance of T-cell engagers; novel formats (tri-specifics, NK-cell).
- **Clinical Focus:** Optimized dosing to manage side effects (e.g., CRS).

Bispecific ADCs (BsADCs) Pipeline

An emerging class with no current approvals, but a rapidly growing pipeline reflecting significant innovation.

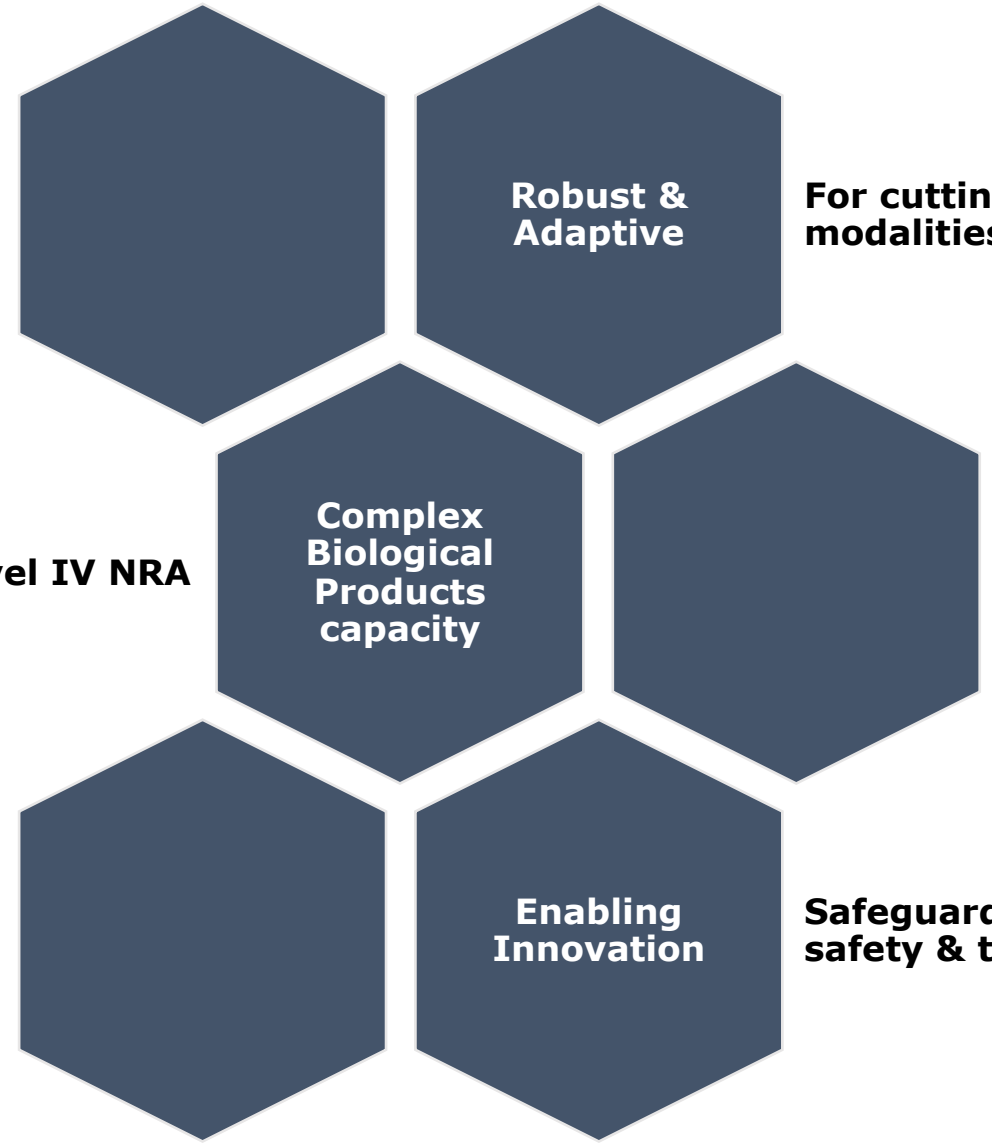
0
Approved
First approval anticipated by 2029

~60+
In Clinical Dev.
Under clinical examination worldwide

- **Key Trends:** Focus on optimizing DAR, linker chemistry, and multi-target binding.
- **Geographic Focus:** China leading in clinical trial activity for BsADCs.

Chile's Experience & Regulatory Landscape

The Regulatory Imperative: Ensuring Quality & Access

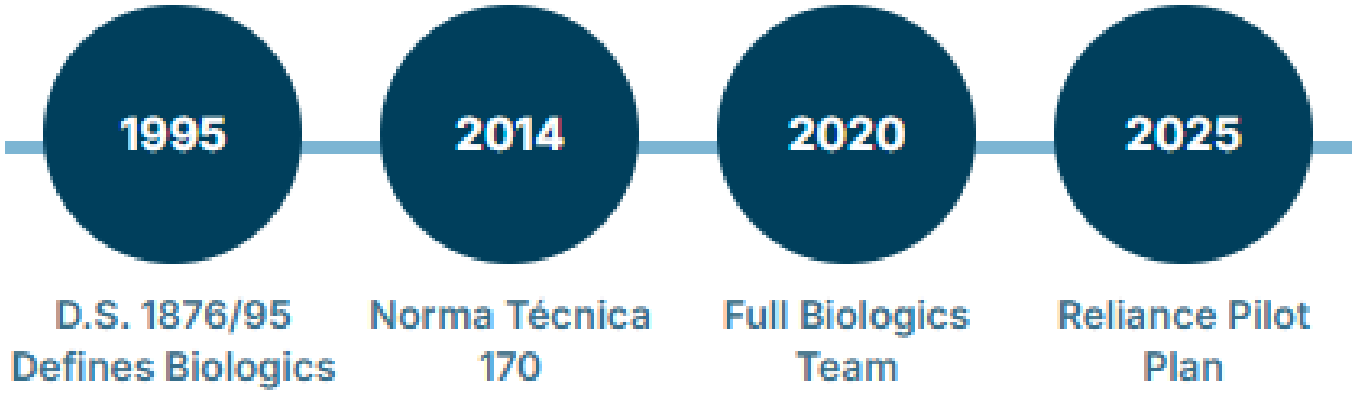


For cutting-edge modalities

PAHO Level IV NRA

Safeguarding patient safety & timely access

Chile´s Regulatory Backbone: 30 years of biologics



6

CMC Reviewers

Quality & Manufacturing

4

S&E Reviewers

Safety & Efficacy

Key challenges for the Health Authority

The increasing complexity and volume of advanced therapies, coupled with internal resource limitations, pose significant hurdles for timely review.

Key Aspects of Bioconjugate & Multispecific Evaluation

- **Diverse Formats:** From Fc-containing (KiH, CrossMab) to Fc-less (BiTEs, DARTs), each with unique properties.
- **Manufacturing Nuances:** Overcoming challenges like random chain association and ensuring reproducible production.
- **Rigorous Characterization:** Assessing dual-target binding, specific bioassays, and critical quality attributes (e.g., DAR for ADCs).
- **Stability & Control Strategy:** Ensuring long-term stability and robust control strategies for complex structures.

Global Synergy & Industry Insights

International Regulatory Evolution

Leading agencies are adapting frameworks and issuing specific guidance for novel modalities.

- **Adaptive Pathways:** Exploring flexible regulatory approaches for innovative therapies.
- **Expedited Programs:** Fast-tracking promising therapies to market (e.g., Breakthrough Therapy Designation).
- **Specific Guidance:** Issuing tailored guidelines for CMC changes, stability, and characterization.

Industry Excellence in Technology & Analytics

The pharmaceutical industry is driving innovation through advanced technologies and robust analytical methods.

- **Advanced Technologies:** Rational design, advanced conjugation techniques for ADCs, novel multispecific formats.
- **Robust Analytics:** High-resolution mass spectrometry, advanced bioassays for multi-target binding.
- **Platform & Modular Approaches:** Streamlining development through reusable platforms and modular design.

Regional Collaboration & Knowledge Exchange

Collaboration is key to harmonizing regulatory practices and sharing expertise across regions.

- **PAHO Networks:** Leveraging Pan American Health Organization networks for shared learning and best practices.
- **Harmonization Efforts:** Working towards aligned regulatory standards across Latin American NRAs.
- **Shared Experiences:** Discussing common CMC and S&E challenges and solutions among regional partners.

Tackling Complexities: Regulatory, Technical, and Training Challenges

Technical Challenges: CMC

Manufacturing Nuances

Ensuring consistent production, correct chain assembly for multispecifics, and precise drug-to-antibody ratio (DAR) for ADCs are critical and complex.

Product Heterogeneity

Characterizing and controlling the diverse variants that can arise from complex manufacturing processes is a continuous challenge.

Advanced Analytics

Requires highly sophisticated and validated analytical methods for comprehensive characterization, including multi-target binding assays and payload release kinetics.

Stability

Ensuring long-term stability of the complex molecular structure and its components throughout shelf-life is paramount and difficult.

Key Evaluation Considerations for Market Authorization

CMC Specifics Checklist

- **Manufacturing Process Control:** Component & Conjugation Characterization.
- **Product Heterogeneity:** Control & Characterize Variants (e.g., DAR, Assembly).
- **Analytical Methods:** Robust & Validated (Purity, Potency, Stability).
- **Critical Quality Attributes (CQAs):** Clear Identification & Justification.
- **Stability Program:** Comprehensive Studies Over Time.
- **Comparability:** Robust Assessments for Manufacturing Changes.
- **Developability & Scalability:** Evidence of Defined, Scalable Process.

Safety & Efficacy Specifics Checklist

- **Mechanism of Action (MoA):** Clear Multi-Target Engagement.
- **Pharmacokinetics/Pharmacodynamics (PK/PD):** Comprehensive Drug Disposition Data.
- **Immunogenicity:** Thorough ADA Assessment & Impact.
- **Toxicity Profile:** On-target/Off-tumor, Immune-mediated AEs.
- **Clinical Trial Design:** Appropriate Patient Selection & Endpoints.
- **Risk Management Plan:** Strategies for Monitoring & Mitigating Risks.
- **Post-Market Surveillance:** Robust Long-term Monitoring & RWE.

Unique Challenges in Design, Development & Production

Design Complexity

Engineering molecules for multiple functionalities introduces intricate design hurdles.

- **Multi-Target Specificity:** Designing simultaneous binding to 2+ targets while maintaining affinity and specificity.
- **Structural Engineering:** Ensuring correct chain assembly (e.g., KiH, CrossMab) and desired half-life for Fc-less formats (BiTEs, DARTs).
- **ADC Component Selection:** Optimizing antibody, potent payload, and stable/cleavable linker chemistry for optimal therapeutic window.

Development & Production Hurdles

Translating complex designs into consistent, scalable manufacturing processes.

- **Protein Assembly Control:** Preventing mispairing and ensuring accurate chain association during multispecific production.
- **DAR Homogeneity (ADCs):** Achieving precise and consistent drug-to-antibody ratio to control efficacy and safety.
- **Scalability & Yield:** Ensuring efficient, reproducible production with high yields at commercial scale.
- **Stability & Aggregation:** Mitigating aggregation and maintaining long-term stability of the complex molecule.

Analytical & Characterization Demands: ISP's Expectations

For Multispecifics

Confirming correct assembly, multi-target binding, and functional activity.

- **Multi-Target Binding:** Confirming simultaneous binding & affinity (e.g., SPR, BLI).
- **Molecular Assembly:** Confirming correct structure & absence of variants (e.g., MS, SEC, IEC).
- **Specific Bioassays:** Measuring potency reflecting complex MoA (e.g., T-cell redirection).

For ADCs

Precise characterization of drug conjugation, site, and component integrity.

- **DAR & Distribution:** Precisely determining drug-to-antibody ratio (e.g., HIC, MS).
- **Conjugation Site(s):** Confirming precise attachment location (e.g., Peptide Mapping, MS).
- **Component Integrity:** Assessing Antibody & Payload integrity throughout lifecycle.

Critical Quality Attributes (CQAs) & Control Strategy

For Multispecifics

- **Multi-Target Binding:** Affinity & Specificity.
- **Molecular Assembly:** Correct Structure & Purity.
- **Potency/Function:** Bioassay-Confirmed Activity.
- **Immunogenicity Risk:** Low ADA Potential.

For ADCs

- **Drug-to-Antibody Ratio (DAR):** Precise & Homogeneous.
- **Conjugation Site(s):** Confirmed Attachment Location.
- **Payload Integrity:** Active & Stable Drug.
- **Linker Stability:** Controlled Release.
- **Antibody Integrity:** Structure & Function.

Developability & Scalability Considerations

What Evaluators Look For

- **Biophysical Stability:** Evidence against aggregation/degradation.
- **Expression & Purification:** Efficient, consistent yields.
- **Formulation Robustness:** Stable at target concentrations.
- **Low Immunogenicity:** Minimized immune response risk.
- **PK Profile:** Desirable drug disposition.

Evaluation Challenges for Regulators

- **Novelty of Formats:** Adapting assessment for unique designs.
- **Limited Early Data:** Projecting from small-scale experiments.
- **Process Robustness:** Ensuring consistent quality at commercial scale.
- **Comparability:** Demonstrating consistency after scale-up changes.
- **Risk Management:** Mitigating scale-up related quality risks.

S&E Complexities

1. Mechanism-Based Toxicities

Unique risks from on-target/off-tumor effects (ADCs) and immune-mediated events (T-cell engagers).

- On-Target/Off-Tumor Effects
- Cytokine Release Syndrome (CRS)
- ICANS Neurotoxicity

2. Immunogenicity

Predicting anti-drug antibodies (ADAs) and their complex impact on safety and efficacy.

- Efficacy Reduction
- Safety Concerns
- Altered Pharmacokinetics

3. Clinical Trial Design

Designing trials for unique MoA, target populations, and severe acute toxicities.

- 🎯 Unique MoA
- 👥 Target Populations
- ⚠️ Acute Toxicity Mgmt.

Practical Evaluation Examples

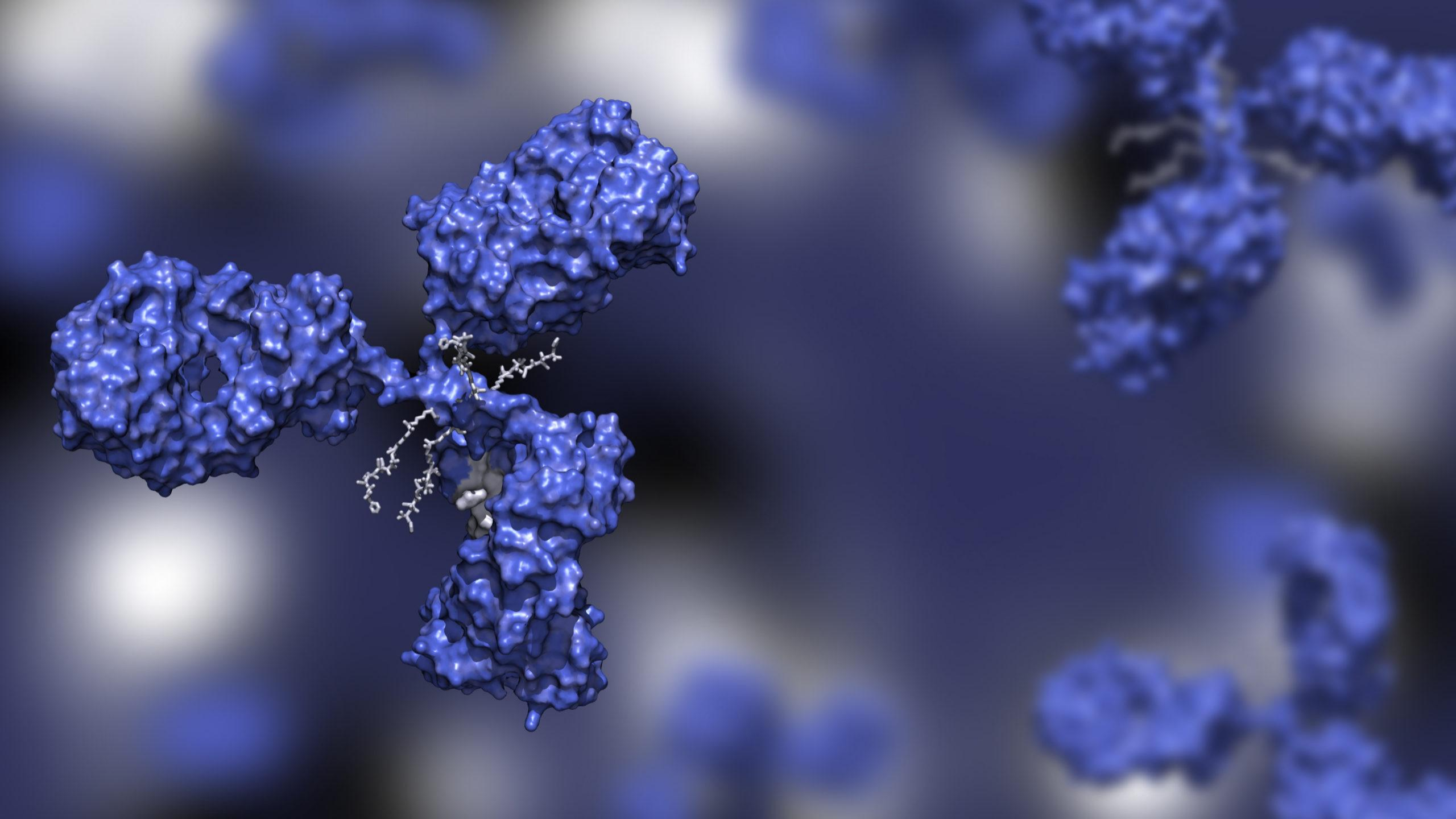
Bioconjugates & Multispecifics Submitted to ISP (YTD)

ADC´s

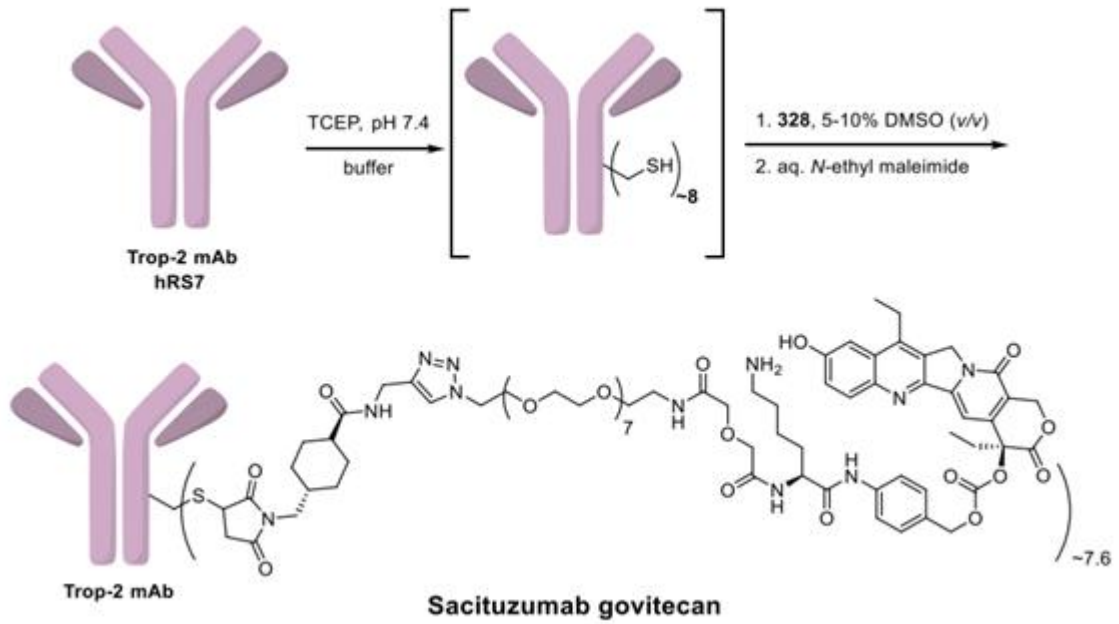
Product	API
Adcetris	Brentuximab vedotina
Padcev	Enfortumab vedotina
Trodelvy	Sacituzumab govitecan
Enhertu	Trastuzumab deruxtecan
Blenrep	Belantamab mafodotina
Elahere	Mirvetuximab soravtansina

BsAbs

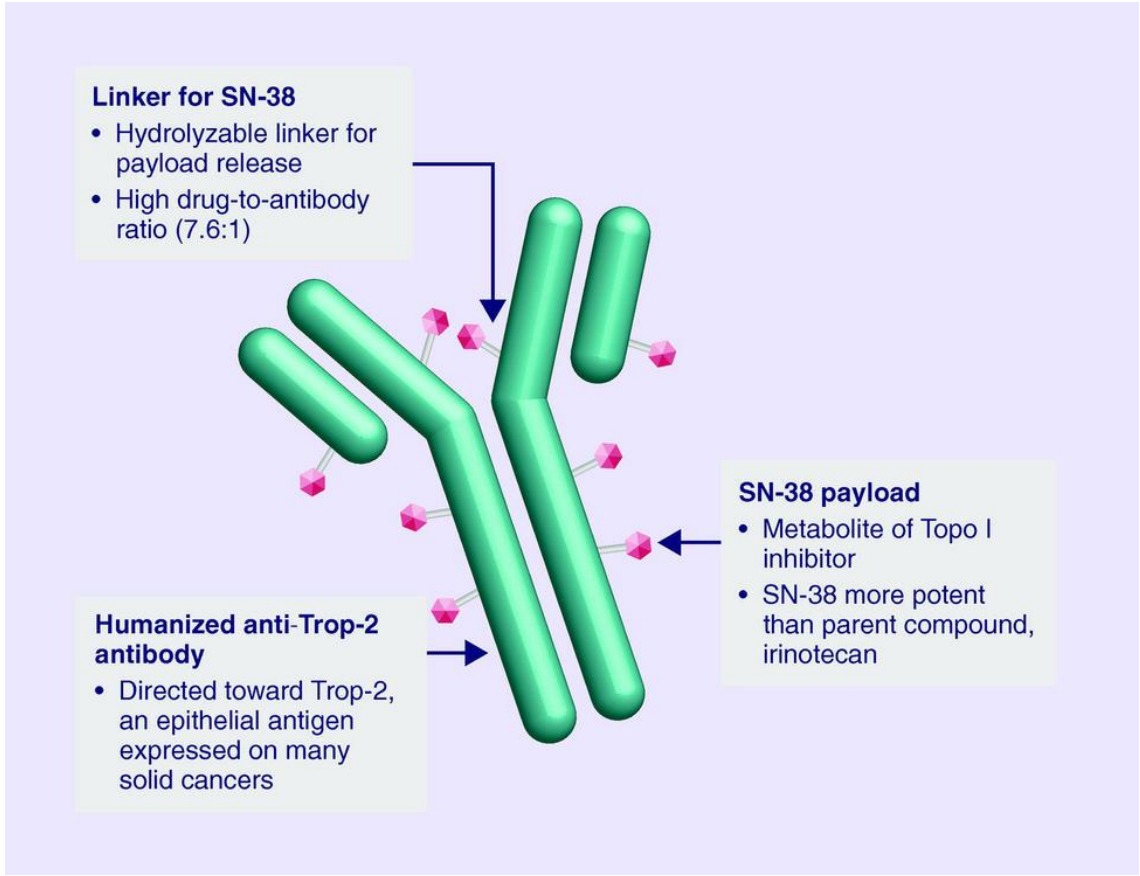
Product	API
Blyncito	Blinatumomab
Talvey	Talquetamab
Elrexfio	Elranatamab
Lunsumio	Mosunetuzumab
Columvi	Glofitamab
Epkinly	Epcoritamab
Rybrevant	Amivantamab
Vabysmo	faricimab



Trodelvy´s CMC Considerations (ADC)



https://www.chemicalbook.com/article/how-is-sacituzumab-govitecan-synthesised.html



Structure of Sacituzumab govitecan, source: Gilead Sciences, Inc.

Trodelvy´s CMC Main Concerns (ADC)

Aspect	Details of Concern	Impact on Product
ADA Assay Validation	Insufficient data to demonstrate the assay's fitness for purpose (e.g., sensitivity, specificity, robustness).	Risk of inaccurate detection or quantification of anti-drug antibodies (ADAs).
Immunogenicity Assessment	Compromised reliability of immunogenicity data from clinical samples.	Potential misinterpretation of drug's pharmacokinetics, pharmacodynamics, safety profile (e.g., hypersensitivity), and clinical efficacy.
Regulatory Compliance	Failure to meet regulatory expectations for analytical method validation for biological products.	Contributed to the issuance of a Complete Response Letter (CRL), delaying approval.
Resolution	Extensive additional validation studies and data submission were required.	Ensured reliability of immunogenicity data, critical for product safety and efficacy assessment.

Trodelvy´s CMC Considerations (ADC)

Initial Concerns & CRL (Jan 2019)

GMP Deficiencies

The initial review found poor manufacturing practices and a non-compliant quality management system.

Assay Suitability

There was insufficient data to support the suitability of the assay for detecting anti-drug antibodies (ADA).

Resolution & Approval (March 2020)

Extensive Improvements

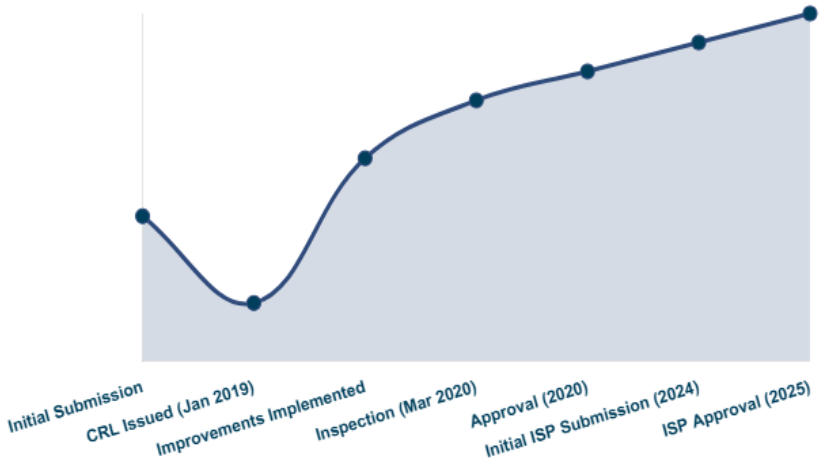
Immunomedics implemented comprehensive upgrades to quality management, controls, and manufacturing processes.

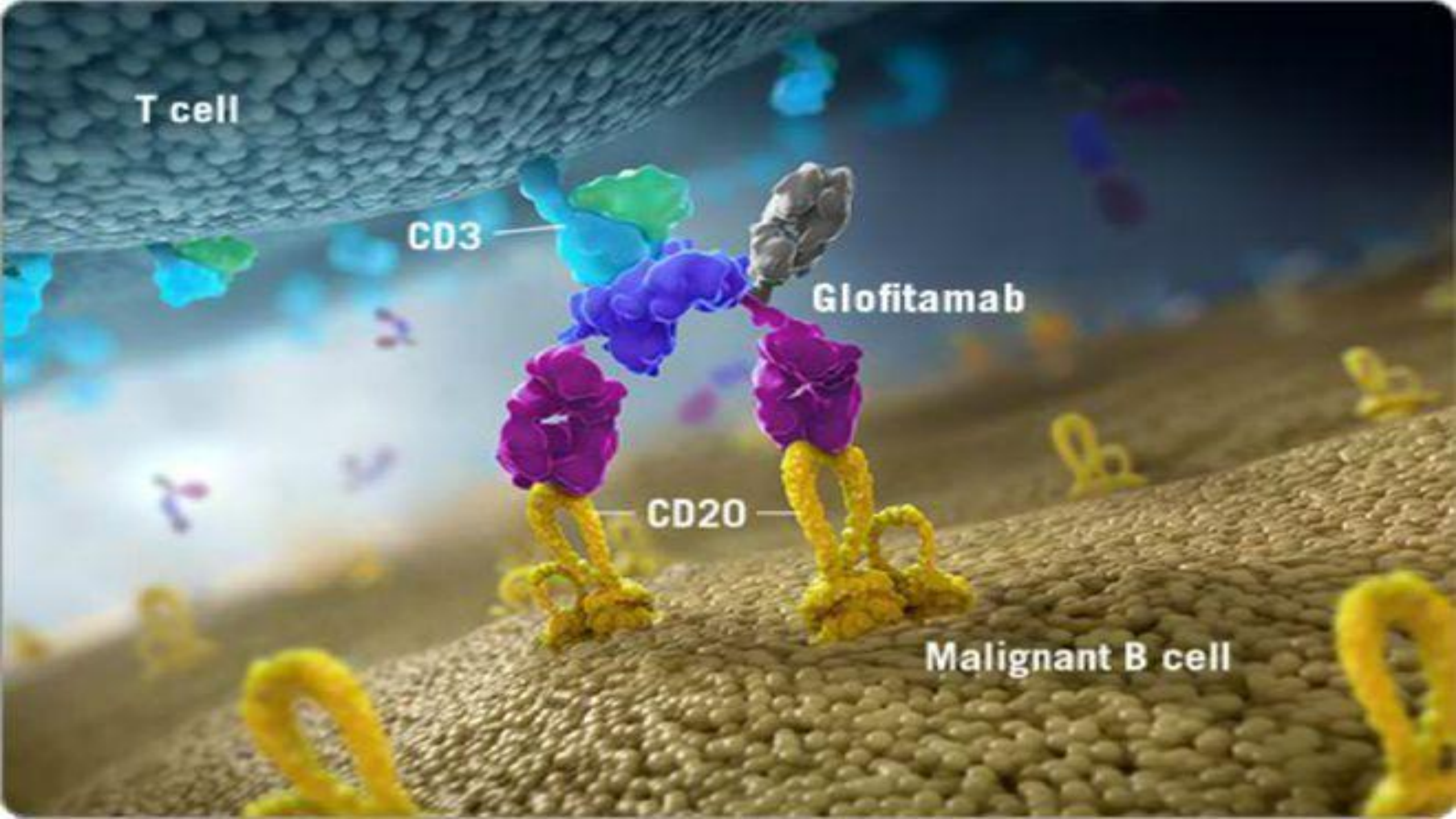
Inspection Confirmed

A pre-license inspection verified that all deficiencies were adequately addressed, leading to approval.

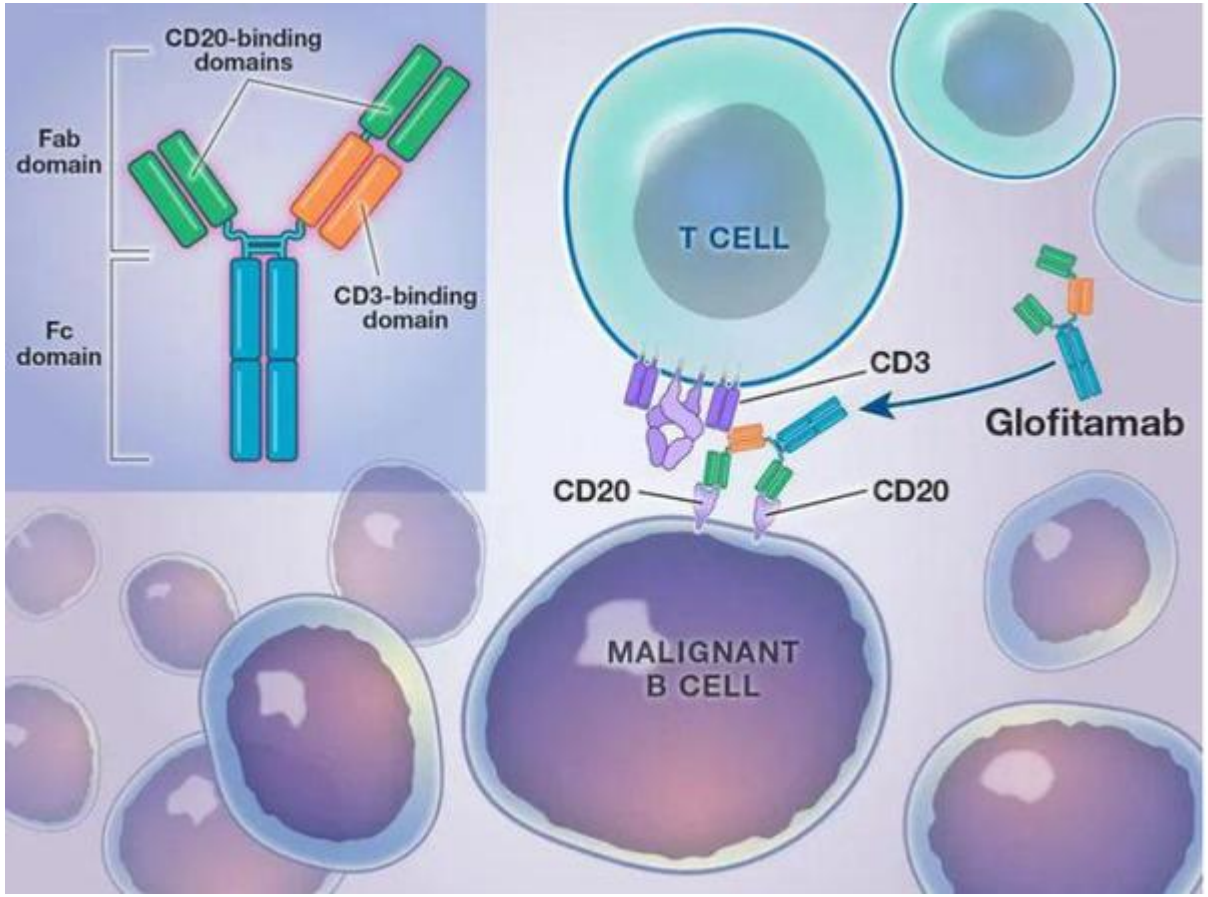
From Challenge to Compliance: An Evolving Journey

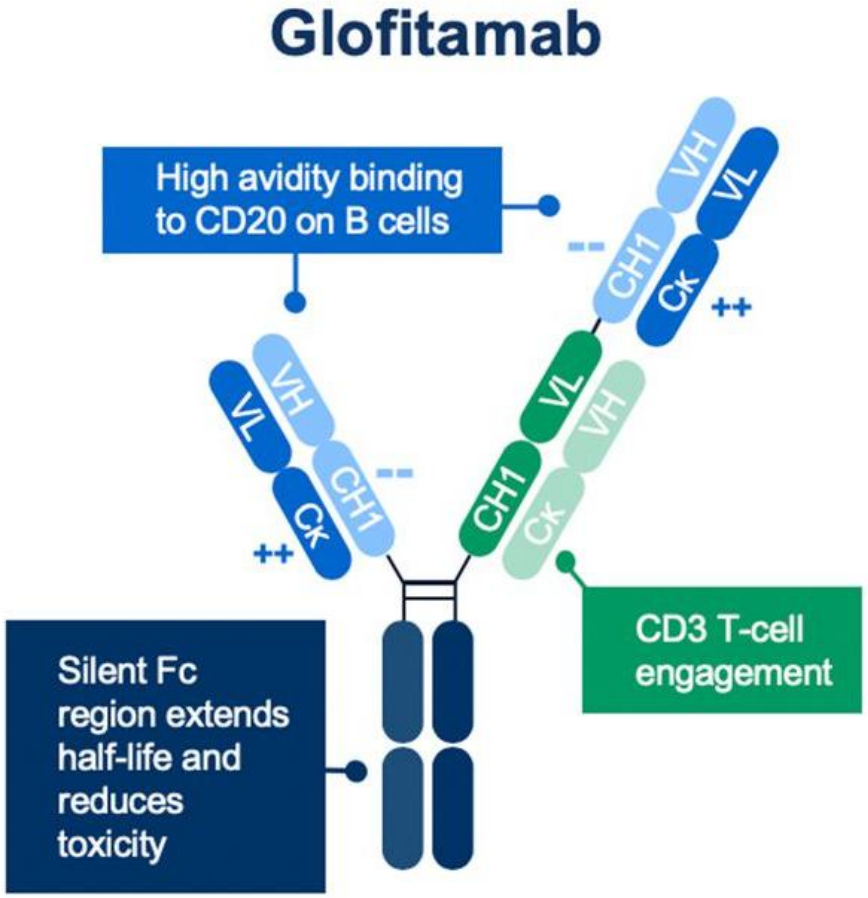
This chart illustrates the significant turnaround in quality assurance and the ongoing commitment to regulatory excellence.




T cell
CD3
Glofitamab
CD20
Malignant B cell

Columvi´s CMC Considerations





Dickinson, M. J., Carlo-Stella, C., Morschhauser, F., Bachy, E., Corradini, P., Iacoboni, G., Khan, C., Wróbel, T., Offner, F., Trněný, M., Wu, S.-J., Cartron, G., Hertzberg, M., Sureda, A., Perez-Callejo, D., Lundberg, L., Relf, J., Dixon, M., Clark, E., Humphrey, K., & Hutchings, M. (2022). Glofitamab for relapsed or refractory diffuse large B-cell lymphoma. The New England Journal of Medicine, 387(24), 2220-2231 . https://doi.org/10.1056/NEJMoa2206913

Columvi´s CMC Key Evaluation Checks

Bispecific Antibody
Engineered to bind CD20 (B-cells) & CD3 (T-cells).

Fc Modification
"PG LALA" mutation prevents unwanted immune activation.

CHO Cell Production
Drug substance produced using genetically engineered cells.

Multi-Step Purification
Chromatography & filtration ensure high purity.

Aseptic Filling
Sterile filling of vials to prevent contamination.

Rigorous Testing
Ensures identity, purity, and potency of the drug.

Lot Release Program
Mandatory ISP review before sale.

24-Month Shelf Life
Supported by extensive stability studies.

Viral Safety
Validated viral clearance steps in manufacturing.

GMP Facilities
Production sites compliant with Good Manufacturing Practices.

Columvi´s CMC Main Concerns

Conditional Approval

Requires further follow-up to confirm clinical benefit.

Ongoing Monitoring

Continuous safety surveillance is crucial.

Phase III Study

Commitment to further trials to confirm long-term benefit.

Efficacy Limitations

Insufficient data for high-grade B-cell lymphoma.

Cytokine Release Syndrome (CRS)

Most important adverse event; requires careful management.

Other Serious Risks

Neurologic events, tumor lysis, serious infections.

Strategic Roadmap for Precision Medicines

ISP's Precision Medicine Strategy

⚙️ Regulatory Adaptation

- ✨ Differentiated Review Pathways
- 📜 Targeted Technical Guidance
- 📊 Enhanced Post-Market Surveillance
- 🧪 Proactive Scientific Advice/Sandboxes

🤝 Ecosystem Nurturing

- 📑 Policy Integration for Access
- 📈 Incentives for Local Development
- 📣 Targeted Communication & Training
- 🌎 Regional & Global Collaboration

Conclusion & Call to Action

Key Takeaways

CMC Challenges & ISP Actions

Complex Manufacturing:

Navigating intricate production processes to ensure consistent, high-quality product batches.

ISP Action: Implementing flexible regulatory pathways for novel manufacturing techniques and providing early scientific advice to developers.

Advanced Characterization:

Developing and validating robust analytical methods for these highly complex molecules.

ISP Action: Leveraging cutting-edge analytical capabilities for rigorous assessment and actively participating in international collaborations to align with and adopt standardized characterization methods.

Product Stability:

Establishing appropriate storage conditions and shelf-life parameters to guarantee therapeutic integrity.

ISP Action: Establishing and applying specific guidelines for stability studies during product evaluation, tailored to the unique properties of bioconjugates and multispecifics.

Safety & Efficacy Hurdles & ISP Actions

Target Specificity:

Ensuring precise action on intended biological targets while minimizing off-target effects.

ISP Action: Requiring comprehensive in vitro and in vivo studies to confirm target engagement and assess potential off-target interactions during the evaluation process.

Immunogenicity Risk:

Proactively assessing and managing the potential for unwanted immune responses in patients.

ISP Action: Mandating robust immunogenicity testing strategies and post-market surveillance plans to monitor patient responses, ensuring long-term safety.

Dose Optimization:

Determining optimal dosing strategies to maximize therapeutic benefit and ensure patient safety.

ISP Action: Encouraging adaptive trial designs and requiring detailed pharmacokinetic/pharmacodynamic data to inform optimal dosing regimens during regulatory review.

The Path Ahead for ISP Chile

References

- ISP Team & Challenges: WCBP 2025 ISP Chile Presentation Jose Crisostomo (Jan 2025).
- Bioconjugate/Multispecifics Formats & Challenges: Jose Crisostomo & David E. Thurston, "Advances in the Use of Bispecific Antibodies for Cancer Therapy and Other Diseases" (Oct 2019).
- Global ADC Approvals (2024): BOC Sciences, "Review of FDA-Approved ADC Drugs up to 2025"; Biopharma PEG, "Global Sales of Antibody-drug Conjugates (ADCs) in 2024".
- Global ADC Pipeline (2024): Alira Health, "The 2024 Global Antibody-Drug Conjugates Report"; GlobeNewswire, "Antibody Drug Conjugate (ADC) Market Research 2024-2035".
- Global Multispecific/Bispecific Approvals (2024): Biopharma PEG, "Bispecific Antibodies: Approved Therapies & Emerging Pipeline Drugs"; evitria, "FDA approved bispecific antibodies".
- Global Multispecific/Bispecific Pipeline (2024): ResearchAndMarkets.com, "Global Multispecific Antibodies Market, Drug Sales, Dosage, Price & Clinical Trials Report" (June 2025); FierceBiotech, "Speed, Scale, and Success – The Rise of Bispecific Antibodies in Targeted Therapies" (March 2025).
- Bispecific ADCs Pipeline (2024): ResearchAndMarkets.com, "Bispecific Antibody Drug Conjugates Outlook 2024-2029".
- International Regulatory Guidelines: EMA (2016 Guideline on Monoclonal Antibodies and Related Products), FDA (2019 Draft Guideline for Bispecific Antibody Development Programs).
- CMC & S&E Checklist: Synthesized from provided documents and general regulatory principles for advanced biologics.
- Dickinson, M. J., Carlo-Stella, C., Morschhauser, F., Bachy, E., Corradini, P., Iacoboni, G., Khan, C., Wróbel, T., Offner, F., Trněný, M., Wu, S.-J., Cartron, G., Hertzberg, M., Sureda, A., Perez-Callejo, D., Lundberg, L., Relf, J., Dixon, M., Clark, E., Humphrey, K., & Hutchings, M. (2022, December 11). Glofitamab for Relapsed or Refractory Diffuse Large B-Cell Lymphoma. The New England Journal of Medicine, 387, 2220–2231. https://doi.org/10.1056/NEJMoa2206913 European Medicines Agency. (2016, July 21).
- Guideline on development, production, characterisation and specification for monoclonal antibodies and related products (EMA/CHMP/BWP/532517/2008). European Medicines Agency. (n.d.).
- Columvi 2.5 mg concentrate for solution for infusion: Summary of product characteristics. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, & Center for Biologics Evaluation and Research. (2021, May).
- Bispecific Antibody Development Programs: Guidance for Industry. U.S. Food & Drug Administration, Center for Drug Evaluation and Research, Office of Biotechnology Products. (2023, May 5).
- BLA Executive Summary: Product Quality Review(S) (Application No. 761309Orig1s000).

Chile *tiene* al ISP

Thanks!