Accelerating complex generic drug development through advanced deformulation

Applying Q1/Q2/Q3 assessment and advanced analytical capabilities to reverse engineer reference products

As regulatory expectations for complex generics increase, deformulation, or reverse engineering, plays an important role in successful Abbreviated New Drug Applications (ANDAs). FDA expectations increasingly emphasise excipient identity (Q1), quantitative matching (Q2) and, where applicable, microstructural equivalence (Q3) to demonstrate pharmaceutical equivalence and bioequivalence with the Reference Listed Drug (RLD).

This white paper explores the evolving regulatory landscape, including 21 CFR 314.94, Product-Specific Guidances (PSGs), USP standards and ICH quality frameworks, and how these requirements can be translated into a practical deformulation and analytical strategy.

We also demonstrate our analytical expertise, advanced instrumentation and experience in complex excipient characterisation for precise, data-driven Q1/Q2/Q3 assessment, and how these capabilities can support more efficient complex generic development, from reverse engineering and formulation decisions through to bioequivalence readiness and filing.

UNDERSTANDING DEFORMULATION IN THE ANDA CONTEXT

Deformulation is the structured analytical process of:

- **Q1 sameness:** Identifying all excipients and their functional grades.
- **Q2 sameness:** Quantifying excipients within FDA-acceptable ranges (typically ±5%).
- **Q3 sameness:** Matching critical microstructural attributes (viscosity, particle size, rheology, release kinetics).

For parenteral, ophthalmic/otic and many topical products, Q1/Q2 sameness is the most efficient and highest confidence pathway for regulatory acceptance. For complex dosage forms such as modified release formulations, emulsions, suspensions and long acting injectables, oscillatory rheology, particle characterisation, IVRT/IVPT and dissolution provide vital Q3 performance insights.

INDUSTRY IMPERATIVE: STRATEGIC IMPORTANCE OF DEFORMULATION

In today's generic drug development landscape, deformulation has become a strategic capability rather than a supporting laboratory activity. Escalating formulation complexity, compressed timelines and reduced regulatory transparency, particularly around Q1/Q2/Q3 expectations, have elevated deformulation to a primary driver of development speed, cost control and approval success.

Accelerating time to market

Advanced deformulation enables rapid convergence on a high confidence target formulation, significantly reducing development uncertainty. By replacing iterative trial and error with data driven formulation insight, companies can:

- Shorten R&D timelines through faster prototype optimisation.
- Achieve earlier bioequivalence readiness.
- Reduce submission cycles and regulatory deficiencies.
- Enhance predictability during scale-up and commercialisation.

Collectively, these advantages support faster ANDA filing and improved first cycle approval performance.

Enhancing cost efficiency and risk management

Early stage understanding of innovator composition and structure directly translates into economic and operational benefits. Deformulation reduces late stage failures and informs smarter formulation and process decisions, resulting in:

- Lower analytical and formulation development costs.
- Identification of cost effective, regulatorily acceptable excipients.
- Optimised manufacturing processes.
- Reduced risk of reformulation and stability failures.
- Stronger, more targeted quality control strategies.

As a result, deformulation serves as a powerful risk mitigation lever across the product lifecycle.

REGULATORY CONTEXT: Q1/Q2/Q3 AS A STRATEGIC REQUIREMENT

Regulatory expectations for qualitative (Q1), quantitative (Q2), and microstructural (Q3) sameness are central to approval of complex generics. Since FDA's 2015 policy change, applicants are no longer informed which formulation components deviate from Q1/Q2 requirements, only that a deviation exists. This shift has transferred the full diagnostic burden to the applicant, making high precision deformulation essential for regulatory compliance.

Key regulatory drivers

- 21 CFR 314.94 establishes mandatory Q1/Q2 sameness for select dosage forms.
- 21 CFR 320.22 enables biowaivers when equivalence can be demonstrated without clinical studies.
- FDA Product specific guidances increasingly emphasise *in vitro* testing, Q3 characterisation, and non clinical bioequivalence pathways.
- ICH Q8/Q9/Q10 frameworks align deformulation with Quality-by-Design, risk based development, and lifecycle control strategies.

Supporting regulatory databases, including the Orange Book and the Inactive Ingredient Database, further position deformulation as a foundational input to formulation strategy and regulatory justification.

RECIPHARM' S DEFORMULATION STRATEGY: Q1/Q2/Q3 ROADMAP

Recipharm employs a deeply integrated analytical workflow to achieve regulatory-compliant deformulation, supported by an advanced instrumentation suite and specialised extraction and sample-preparation techniques.

Recipharm' s deformulation excellence is anchored in:

- Decades of complex-generics expertise.
- Advanced analytical platforms.
- Extraction methodologies.
- Expert chemists experienced across dosage forms.
- Proven track record of meeting timelines and regulatory expectations.

Our integrated approach reduces project uncertainty, compresses development timelines, and increases the probability of first-cycle ANDA approval.

Q1 Sameness: Qualitative excipient identification
Our goal in Q1 sameness is to identify the complete excipient list (names and grades) in the RLD. This can be achieved by Multi technique screening, GC MS/LC MS for volatiles/semi volatiles, elemental (ICP MS), and targeted wet chemistry to confirm identities and functional roles. Advanced microscopy, DSC/TGA for form and thermal behaviour. Capabilities allow identification of excipients across polymers, surfactants, sugars, volatile agents, inorganic buffers, and mineral components.

Q2 Sameness: Quantitative excipient profiling
Recipharm goal in Q2 sameness is to quantify each excipient to within ±5% of RLD levels (FDA's commonly accepted tolerance for most routes when Q1/Q2 is pursued).

This can be achieved by using a calibration quality quantitative assays (HPLC/UPLC with universal or specific detectors, GC FID/MS, coulometric Karl Fischer, ICP for salts), combined with mass balance and stoichiometric models for salts/buffers. For water content or volatile systems, applying headspace GC and thermogravimetry tests.

Q3 Sameness: Microstructure & performance equivalence
Q3 sameness becomes critical in case of Topicals, ophthalmic, emulsions, suspensions, long acting depots, where microstructure dictates local bioavailability. Q3 sameness can be achieved at Recipharm through evaluation of:

- **Physical structure:** PSD (laser diffraction), microscopy, DSC/TGA for transitions, Rheometry for flow/viscoelasticity.
- **Performance:** USP <1724> IVRT (e.g., Franz diffusion), discriminating dissolution/dispersion methods for suspensions/emulsions, *in vitro* permeation tests.
- **Comparative release:** *In vitro* release profiling (and IVIVC where feasible) to support equivalence and set clinically relevant specifications.

RECIPHARM INSTRUMENTATION MATRIX

EXCIPIENT CLASS	TYPICAL ANALYTE/MARKER(S)	BEST DETECTOR(S)	RATIONALE
Sugars & polyols	Native sugars/polyols; monosaccharide profile (hydrolysis for lactose)	RI, ELSD, CAD	Non UV chromophores; RI/ELSD/CAD give universal/non-volatile response
Starches/dextrins/maltodextrin	Glucose after hydrolysis	RI, ELSD, CAD	Converts polymers to measurable monomers
Cellulose & derivatives	Degree of substitution (DS), ash, sodium (CMC), methoxy/hydroxypropyl content	UV/PDA (derivatised), RI/CAD, ICP OES/MS	Derivatisation gives UV response; ICP quantifies inorganic substituents
Fats & oils	FAME profile; total triglycerides; peroxide/anisidine values	GC FID, UV/PDA, CAD/ELSD	FID highly sensitive & linear for hydrocarbons; HPLC for non volatile TGs
Surfactants (nonionic/ionic) (polysorbates, SDS)	Homologues, total content, residuals	CAD/ELSD, UV/PDA (chromophore), IC Conductivity	CAD/ELSD universal for non volatile surfactants; IC for anionic/cationic
Amino acids & small organics	Individual amino acids, buffering species	UV/PDA or FLD (OPA/FMOC, DNFB derives), IC Conductivity	Derivatisation yields strong UV/FLD; IC separates inorganic/organic ions
Inorganic salts	Cations/anions; elemental content	IC Conductivity, ICP OES/MS	Gold standard for ions/elements; low LOD/LOQ
Organic acids/bases	Identity & assay; counter ion balance	UV/PDA, IC Conductivity	Good resolution and quantitative robustness
Preservatives and parabens	Individual preservative assay & profile	UV/PDA	Strong UV chromophores; simple, selective
Antioxidants (BHT, BHA)	Individual antioxidant assay	UV/PDA, GC FID	UV active; some volatile → GC FID works well
Silicates/talc (mineral excipients)	Si, Mg, Al, trace metals	ICP OES/MS	Multi element quantitation & traceability
Polyethylene glycols (PEGs)	Average MW, homologue distribution	RI, CAD/ELSD	No UV; mass dependent separation
Cyclodextrins	Degree of substitution; purity	CAD/ELSD, RI, UV	Non volatile, weak UV
Residual solvents (excipients or blends)	ICH Class 1–3 solvents	GC FID (quant), GC MS (ID)	Compendial, sensitive, selective
Semi-solids	Microstructure sameness	Rheometer/Viscometer	Flow property helps in product sameness and IVRT
Semi-solid/ophthalmic	Release equivalence	IVRT	*In vitro* correlation with reference
Semi-solid/ophthalmic	Dermal permeation equivalence	IVPT	*In vivo* correlation with reference
Oral products	Performance and equivalence	Dissolution	*In vitro* correlation with reference

STRUCTURED DEFORMULATION METHODOLOGY

A stepwise deformulation strategy is typically implemented to systematically establish qualitative, quantitative, and microstructural equivalence with the reference product, thereby supporting regulatory compliance and efficient development. The first phase focuses on qualitative excipient identification (Q1), where the formulation components are classified and confirmed using complementary analytical techniques. Organic excipients are identified through chromatographic and spectral methods such as HPLC and GC–MS, volatile components are characterised using GC FID or GC–MS, and inorganic constituents are determined through elemental and ionic analyses using ICP and ion chromatography.

Once the excipient framework is defined, the process advances to quantitative composition analysis (Q2). In this stage, precise excipient levels are established to closely match the reference listed drug. Organic excipients are quantified using validated chromatographic methods, buffer systems and mineral content are measured through IC and ICP techniques, and moisture or residual volatile levels are assessed using Karl Fischer titration and headspace gas chromatography. This quantitative clarity reduces formulation uncertainty and limits the risk of regulatory deficiencies.

The final phase addresses microstructural and performance characterisation (Q3) to confirm functional equivalence beyond composition alone. Rheological profiling is performed to compare structural and flow behavior, while *in vitro* release and permeation testing (IVRT/IVPT) assess drug product performance. Dissolution characteristics and release kinetics are also evaluated to ensure consistency with the reference product's behavior. Together, these sequential steps form a cohesive, data driven deformulation approach that aligns with FDA expectations and accelerates regulatory dossier readiness.

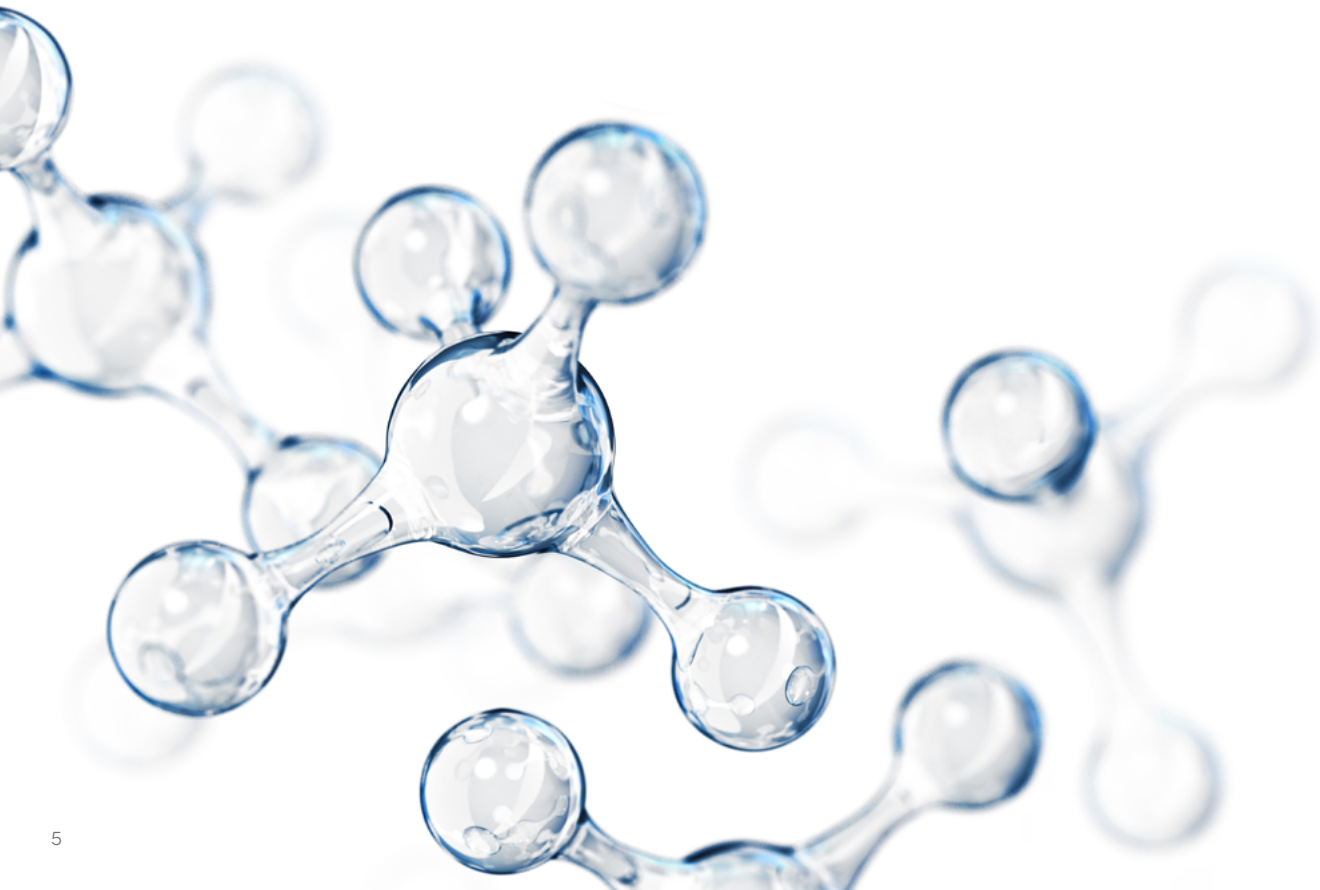
Complex generics were de-formulated in a quick and minimal turnaround time. These complex generics are of different dosage forms like solid oral dosage forms, liquid dosage forms, topicals, and Aerosols. Q1/Q2 Deformulation has helped the customer to save the reasonable amount of time in developing a product and dossier approval.

Challenges encountered

- **Complexity of the excipient matrix:** Excipients are not always simple, pure compounds. They may include binders, fillers, lubricants, and coatings that can interact with the API, making it difficult to isolate individual components.
- **Difficulty in separation and quantification:** Identifying the exact quantity (Q2) of excipients in a tablet matrix is challenging due to interference from other components. Separation often requires advanced, multi-step techniques such as differential solubility, filtration, HPLC, and GC.
- **Quantification limitations:** Detecting and quantifying excipients present in very low concentrations is technically challenging.

Technical approach & solutions

At Recipharm, we have built numerous case studies with deep knowledge of each excipient's behaviors and right quantification technique, which will ensure Q1/Q2 approach is accomplished.



CASE STUDIES

QUANTIFICATION OF POLYMERS IN DOSAGE FORMS:

Polymers such as Hydroxyethyl cellulose (HEC), and Hydroxypropyl cellulose (HPC) are added to pharmaceuticals primarily as inactive excipients to improve stability, control drug release, and modify viscosity.

Quantification of these polymers is highly complex because they are high-molecular-weight polymers, often cross-linked or blended, and lack strong, specific chromophores for easy detection (like UV absorption).

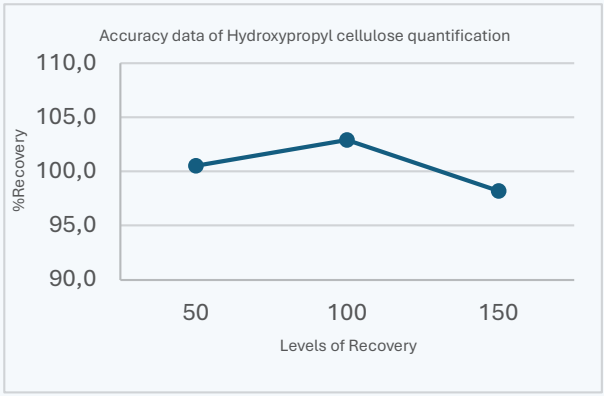
- **Lack of specific detection methods:** Neither material has a strong UV-active group, requiring methods like refractive index detection (in HPLC), charged aerosol detection (CAD), or chemical derivatisation/colorimetric assays (e.g., phenol-sulphuric acid).
- **High viscosity and gelation:** Polymers form complex, high-viscosity gels that are difficult to process or dissolve for analytical techniques.
- **Interpolymer Complexes:** They are often used together to form matrices where interactions with each other and the API (active pharmaceutical ingredient) make isolation or selective quantification challenging.
- **Grade Variability:** Both materials come in varying viscosity grades, molecular weights, and substitution levels (for HPC), which can influence the detection signal, necessitating accurate calibration with the same material grade.

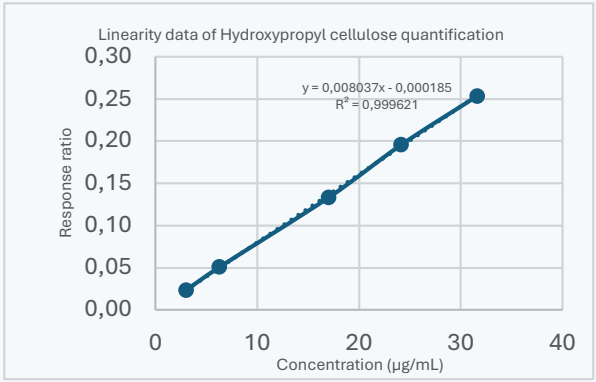
Results & achievements

Quantification of these excipients from solid dosage forms and topicals were developed and optimised for by HPLC-RI detector for Hydroxyethyl cellulose (HEC) and Gas chromatography for Hydroxypropyl cellulose (HPC) with the principle of size Exclusion Chromatography in HPLC-RI Detector and by converting the hydroxypropyl groups of HPC into volatile compounds, typically 2-iodopropane for Hydroxypropyl cellulose (HPC) quantification.

Methods are found specific in presence of other cellulose materials and starch derivatives with perfect Linear correlation and accuracy of ±5%.

Linearity and accuracy data:





QUANTIFICATION OF MAGNESIUM STEARATE IN DOSAGE FORMS:

Quantifying magnesium stearate (MgSt) in pharmaceutical formulations is considered a moderately to highly complex analytical task, primarily due to its nature as a mixture of salts, its low concentration in finished products (typically 0.5–1.0% w/w), and its insolubility in conventional solvents.

The complexity stems from the need to separate and measure MgSt, an inactive excipient with no UV chromophore.from an active pharmaceutical ingredient (API) and other excipients, often requiring specific extraction or derivatisation techniques.

- **Low concentration & distribution:** MgSt is typically added at very low levels (~1%), and the phenomenon of interest is often its surface distribution rather than total content.
- **Variability in composition:** Commercial MgSt is not a pure compound; it is a complex mixture of magnesium stearate, magnesium palmitate, and magnesium oleate. This causes variability between suppliers and affects analytical consistency.
- **Insolubility:** MgSt is practically insoluble in water, ethanol, and ether, making sample preparation tedious and often requiring harsh reagents like nitric acid to break down the compound.
- **Matrix interference:** The API or other excipients (like talc or magnesium carbonate) can contain magnesium, interfering with methods that measure total magnesium content.

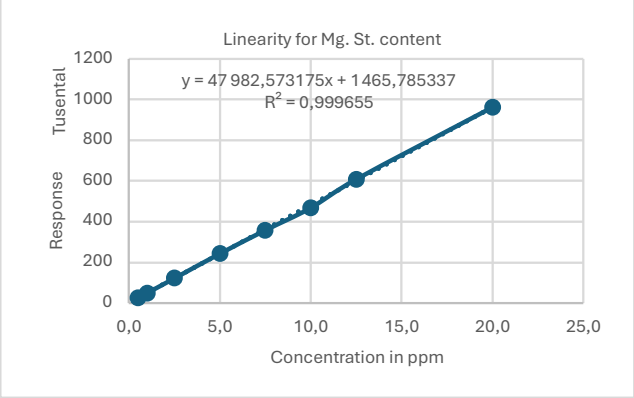
Results & achievements

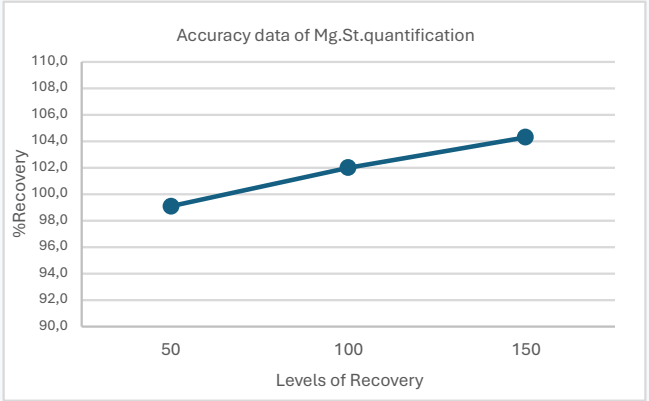
ICP-AES/OES method for MgSt quantification in presence of other excipients such as sodium starch glycolates, BCS class IV molecules was developed with high accuracy and mass balance.

Challenging part in this quantification is the extraction of MgSt from other excipients and achieving mass balance for quantification Which could be achieved by strong folds of development experience in handling such complex molecules.

Specificity, linearity and accuracy of ±5% was achieved by developing a method which uses strong acids and neat solution using a rigorous extraction process based on the knowledge and assessment of product.

Linearity and accuracy data:





QUANTIFICATION OF SODIUM STARCH GLYCOLATE (SSG) IN DOSAGE FORMS:

Sodium Starch Glycolate is used as disintegrating agent in solid oral dosage forms. Typically, present at 2-8%. Being a non-chromophore component, quantification of Sodium Starch Glycolate is a challenging process. This involves separation of SSG from other excipients and getting the right accuracy. Presence of Starch and other sodium containing molecules is likelihood due to the large number of fillers in solid dosage form will make this extraction of quantification process still more complicated.

Results & achievements

Robust analytical method with right separation technique which will enable to quantify can separate the unique characteristic of Sodium Starch Glycolate (SSG) into solid oral dosage form and can be able to quantify the right quantity of it in presence of other components.

Accuracy of this method is ±5%, which makes it suitable for the quantified amount.

CONCLUSION

Deformulation has become an increasingly important capability in complex generic drug development, driven by growing formulation complexity and evolving regulatory expectations. As regulatory transparency around Q1 and Q2 sameness has reduced, the ability to independently and accurately characterise reference products has become increasingly important. A systematic, science-led deformulation approach can establish clear qualitative, quantitative and microstructural benchmarks, providing the understanding needed to reduce development uncertainty and guide formulation decisions.

By accelerating formulation development, improving cost efficiency and reducing the risk of late-stage development or regulatory issues, deformulation can support faster market entry and improved approval outcomes. When aligned with FDA guidance and ICH Quality by Design principles, it can also support regulatory compliance, product robustness and lifecycle management.

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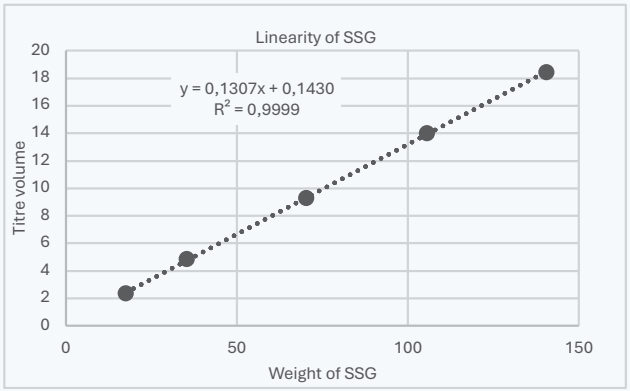

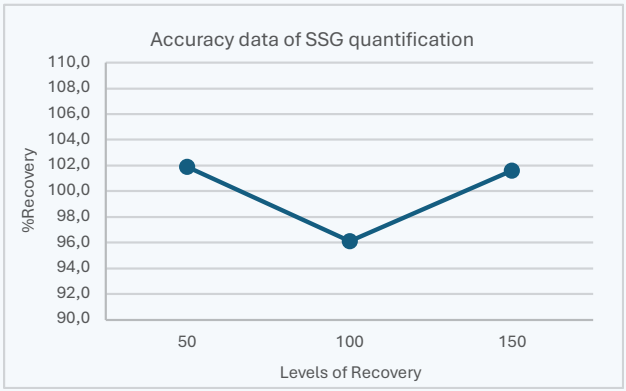

About Recipharm

Recipharm is a leading contract development and manufacturing organisation (CDMO). We operate development and manufacturing facilities in France, Germany, India, Italy, Portugal, Spain, Sweden and the US and are continuing to grow and expand our offering for our customers. We are supporting pharmaceutical companies with our full service offering, taking products from early development through to commercial production. For over 30 years, we have partnered with our clients throughout the entire product lifecycle, providing pharmaceutical expertise and managing complexity, time and time again. We conduct our business as we always have and continue to deliver value for money with each customer's needs firmly at the heart of all that we do.

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