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Cross-Salt Extrapolation in the European Union: Regulatory, Scientific, and Strategic Considerations

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ABSTRACT

Cross-salt extrapolation—the scientific and regulatory practice of bridging non-clinical or clinical data from one salt form of an active pharmaceutical ingredient (API) to another—has gained increasing relevance within the European Union (EU) as pharmaceutical developers seek more efficient product development pathways. This approach holds particular significance in generic drug development, line extensions, and lifecycle management, where re-characterizing an API salt variant can impose substantial time and resource burdens. However, the absence of dedicated EU-level guidelines for cross-salt extrapolation has created a fragmented regulatory landscape, leading to case-by-case assessments and variable expectations across Member States.

This article critically examines the scientific rationale and regulatory landscape surrounding cross-salt extrapolation in the EU, including guidance from the European Medicines Agency (EMA), EFSA, and national competent authorities. It delves into the mechanistic and physicochemical considerations that underpin extrapolation viability -such as solubility, dissociation, exposure metrics, and target engagement – whilst also exploring how in-vitro, in-silico, and read-across methodologies are leveraged to justify extrapolation.

Furthermore, it discusses strategic considerations for pharmaceutical companies, including risk mitigation, dossier planning, and regulatory communications during procedure selection (CP, DCP, MRP). Through an integrated regulatory – scientific lens, this article proposes a structured approach for enabling cross-salt extrapolation within current EU paradigms and offers recommendations to enhance scientific consistency and regulatory predictability in this under – addressed yet increasingly relevant domain.

1. INTRODUCTION

Let's start from basic that what is salt of an active pharmaceutical ingredient (API). The specific salt of active pharmaceutical ingredient (APIs) is often formed to achieve desirable formulation properties. Although addressing poor aqueous solubility is one of the most important reasons to employ a salt formation, pharmaceutical companies also use the formation of unique salt products to commonly address other physicochemical and biological concerns such as stability, toxicity, poor absorption, and issues related to manufacturing processes. The choice of the appropriate salt form is dictated by various factors. The formation of potentially marketable salt requires concerted efforts and a thorough understanding of the physical and chemical characteristics of the API and counterions that are used. A rational decision tree approach should be followed for the selection of the best salt in the most economical way. Furthermore, all the necessary testing should be performed in the early phases of the drug development process to minimize failures. Salts can significantly alter physical/chemical properties of an API so much so that it can expedite the drug development process.

Salts can be broadly categorized into two main types based on the nature of the API:[1]

1. Salts of Weak Bases

Formed by reacting a basic drug with an acid.

- **Common acidic counterions:**
  - Hydrochloride (e.g., Metformin HCl)
  - Sulphate (e.g., Salbutamol sulphate)
  - Maleate (e.g., Chlorpheniramine maleate)
  - Tartrate (e.g., Metoprolol tartrate)
  - Citrate (e.g., Sildenafil citrate)

2. **Salts of Weak Acids:**

Formed by reacting an acidic drug with a base.

- **Common basic counterions:**
  - Sodium (e.g., Diclofenac sodium)
  - Potassium (e.g., Penicillin potassium)
  - Calcium (e.g., Pravastatin calcium)
  - Magnesium (e.g., Aspirin magnesium)
  - Tromethamine (e.g., Ketorolac tromethamine)

Each salt form can significantly affect the drug's properties. Here's why different salts are chosen:

Reason	Explanation
1. Solubility	Some salts improve water solubility (e.g., hydrochloride salts are more soluble than free base forms).
2. Stability	Certain salts protect the drug from hydrolysis, oxidation, or degradation (e.g., mesylate vs. base).
3. Bioavailability	Salts influence dissolution rate and absorption. A more soluble salt may lead to better bioavailability.
4. Manufacturability	Salts affect flow properties, compressibility, and hygroscopicity—key in tablet production.
5. Taste Masking	Bitter drugs can be made more palatable using specific salts.
6. Pharmacokinetics	Some salts offer modified release or faster onset (e.g., ibuprofen lysine is faster acting than ibuprofen base).
7. Patentability	New salt forms can be patented even if the API is off-patent (used as life-cycle management strategy).

2. WHAT IS CROSS-SALT EXTRAPOLATION IN THE EU

In the European Union, cross-salt extrapolation refers to the use of scientific and regulatory data from one salt form of an active substance to support the authorization of an different salt form of the same active moiety – within a centralized, decentralized, mutual recognition, or national marketing authorisation procedure.

Why Cross-Salt Extrapolation Becomes Relevant in the EU

When the reference product (RP) is available in a different salt form and in context with the Directive 2001/83/EC, generic application (Article 10(1)) require the same active substance as the RP but the RP in the EU may be available in a salt form that the applicant does not wish to use (or cannot use due to patent/exclusivity).

Let's take an example of this, the EU RP is Ramipril hydrochloride, and the applicant wants to file Ramipril mesylate. So here the cross-salt extrapolation allows bridging data from the available RP salt to the applicant's salt by demonstrating the sameness of the active moiety and bioequivalence.

Now another approach can be filing a Hybrid Application also known as (Article 10(3)) when there are differences in the salt, route, strength, dosage form, or indication from the EU authorised reference product. It becomes relevant because cross-salt extrapolation allows partial reliance on RP data while supporting changes with additional studies and outcome of this

application will be reduced clinical burden with tailored supportive data.

Let's take another scenario where there is no EU reference product available in the desired salt where the innovator product in the EU is approved in Salt A, but the applicant wants to develop a generic in Salt B (which may be used in other countries like US, UK etc.). When the EU RP in the desired salt is not authorized or marketed, extrapolation becomes scientifically necessary to justify comparability of the two salts and rely on existing RP data.

Meanwhile, switching from Non-EU to EU RP for generic submission can also be one of the approaches, where applicant developed data using the US RP (e.g., citrate salt), but for EU submission, the RP is hydrochloride salt. Here, agency needs strong scientific justification for which the applicant must bridge the US salt form with the EU-approved form via *in-vitro* dissolution testing, comparative pK studies, literature evidence, salt dissociation and pharmacokinetic equivalence justification. Patent or regulatory exclusivity also needs to be avoided because EU regulations recognize patents and market exclusivity (8+2+1 years rules) and if the RP is protected the sponsors may choose an alternative salt form of the same API and cross-salt extrapolation enable hybrid or full applications using alternate salt without infringing IP.

Now if we look from orphan drug consideration point of view then Directive 141/2000/EC defines that "similar medicinal product" as having the same active substance, which clearly indicates that changing salt form may support arguments of dissimilarity for bypassing orphan drug exclusivity (only if clinical superiority is not proven by the sponsor of the first product, so applicants needs to be careful because CHMP and COMP may examine salt differences cas-by-case.

3. SCIENTIFIC RATIONALE FOR CROSS-SALT EXTRAPOLATION

The main scientific rationale for cross-salt extrapolation is that active moiety should be same. Despite from differences in salt form, the therapeutic activity arises from the same active moiety (parent compound) for e.g., metformin hydrochloride where metformin will be parent compound and its dissociation from the salt *in vivo*. So once administered, salts dissociate into the free base or acid, meaning pharmacological activity is independent of the salt form. Now, bioequivalence focuses on systemic exposure meaning that regulatory guidelines from stringent regulatory authorities like EMA and FDA emphasize that bioequivalence studies evaluate systemic exposure (AUC, C_{max}) to the active moiety and if the rate and extent of absorption of the active moiety are comparable, the clinical performance is assumed to be equivalent – regardless of its salt form.

Cross-Salt Extrapolation can be justified when the salt form of the active pharmaceutical ingredient has minimal influence on the pharmacodynamics. Most of the salts are selected for physicochemical advantages (e.g., solubility, stability, manufacturability) and do not alter receptor binding, potency, or efficacy, so it can be said that pharmacodynamics of the molecule is governed by the free form and not its salt form.

When precedent and scientific consensus i.e., literature and past regulatory decisions support the notion that the salts of the same active moiety can be scientifically bridged, if there will be no clinically significant differences in terms of:

- Solubility or permeability which would affect absorption
- Toxicity profile or excipient interactions
- PK parameters that would impact safety/efficacy

Speaking in the words of ICH and EMA, EMA's Bioequivalence Guideline (2010) and Article 10(1) of Directive 2001/83/EC has supported applications based on essential similarity even with different salts, provided justification and supporting data (e.g., BE study vs free base) are given.

When the scientific justification for the cross-salt extrapolation is sufficient enough to satisfy the regulatory agency, it can avoid duplicative clinical trials, aligning with 3Rs (Replace, Reduce, Refine) in principles in research ethics. Provided that when there is enough analytical justification i.e., *in vitro* studies (e.g., dissolution profiles) which often show equivalence between salt forms when normalized to free base, reinforming the case for extrapolation.[2]

Given are the possible conditions under which cross-salt extrapolation can be justified:

1. Same route of administration
2. Same dosage form type i.e., both are modified release tablets
3. Comparable *in vitro* dissolution
4. Bioequivalence established to the RMP (even if salt differs)
5. No safety or efficacy concerns specific to the salt.

4. REGULATORY LANDSCAPE FOR CROSS-SALT EXTRAPOLATION IN THE EU

In European Union, cross-salt extrapolation applications are examined under the below legal frameworks:

- Directive 2001/83/EC, particularly Article 10(1) (generics), 10(3) (hybrid), and 10a (well-established use).
- Guideline on the Investigation of Bioequivalence

Ideally the choice of regulatory pathways depends on the level of similarity/difference between the salt forms and whether bioequivalence with the reference product can be adequately demonstrated.

If we look from EMA's point of view, it does permit use of a different salt form if the active moiety is the same and bioequivalence is demonstrated, and it should be proved that there are significant differences in terms of safety and efficacy and no new clinical / safety data will be required if the pharmacokinetics are comparable.

CMDh has also confirmed that cross-salt extrapolation is acceptable in principle under Article 10(1) or 10(3) depending on:

- Whether the therapeutic moiety is released immediately and identically.
- There is absence of any impact on absorption, distribution, metabolism, or excretion i.e., ADME.
- Pharmaceutical comparability and justification of safety profile.

A live example from CMDh is "When a different salt is used, the applicant must demonstrate that the different form does not change the safety/efficacy profile of the product."

Now let's focus on the key requirements for the acceptance of justification of cross-salt extrapolation:

Requirement	**Details**
Same therapeutic moiety	Must be released unchanged *in vivo*
Bioequivalence study	Must compare the test salt with the reference product (RP).
Justification for change in salt	Non-clinical and clinical rationale showing no new safety concerns.
Impurity profile and manufacturing	Must not introduce toxicologically relevant impurities.
BCS classification (if applicable)	BCS-based biowaivers may be possible for class I or III drugs
Bridging data	Sometimes required to demonstrate equivalence across

Common regulatory routes in the EU which can be used during the cross-salt extrapolation application are **Article 10(1) Generic, Article 10(3) Hybrid and Article 10(a) Well-Established Use or WEU application.**

Now if we focus on where the real-world application, challenges are faced then the first point of discussion will be the lack of RP in same salt form across EU which may lead to providing additional justification in DCP/MEP procedures. Sometimes divergent national decisions can arise if one RMS/Member state questions comparability. One of the major challenges faced during the cross-salt extrapolation is the SmPC harmonization because there are issues between the salt forms which may lead to objections and patent and data exclusivity on one salt form can affect the submission timing. If we look for scientific advice and go for best practice than it is better to seek scientific advice from the national authorities or EMA when planning such submissions. Ideally the authority may also help in:

- Salt selection
- Bioequivalence design
- In vivo performance
- Safety comparability

Ideally, there are chances that cross-salt extrapolation can be accepted in the EU if scientific justification is robust, and bioequivalence is demonstrated. However, it demands careful attention to PK comparability, regulatory strategy, and early engagement with regulators to avoid approval delays or referrals.[3]

5. REGULATORY EXPECTATIONS

In European Union, cross-salt extrapolation is where bioequivalence, safety, and efficacy data of one salt of an active substance is used to support the approval of a different salt form and these applications are evaluated under a rigorous regulatory framework.

If we look from scientific justification front then the applicants must provide a robust scientific rationale explaining that why a different salt is being developed whether it is giving improved stability, solubility, manufacturability then that of its reference product. Also needs to be justified whether there is any lack of therapeutic difference between the proposed and reference salt forms and whether the change in salt form affects the pharmacokinetics, pharmacodynamics, or clinical performance.

Ideally, bioequivalence studies are conducted between the new salt form and the reference product even if the reference product contains a different salt and if the salt of test product dissociates completely *in vivo* into the same active moiety as that of reference product, then waiver of additional studies may be considered which leads to subject of full justification.

Speaking in terms of regulatory pathway impact then generic application i.e., Article 10(1) can be used if the salt is shown to be therapeutically equivalent and fully dissociative. A hybrid application i.e., Article 10(3) may be required if the salt change leads to different therapeutic claims, route of administration, or non-bioequivalent profile. A Well-Established Use or Full Dossier may be needed if significant differences in performance are found. The WEU application under Article 10a of Directive 2001/83/EC is based on literature data i.e., no requirement to submit proprietary clinical / non-clinical data). A WEU application is ideally utilized when the active substance has been in well-established medicinal use for at least 10 years within the EU, with recognized efficacy and an acceptable level of safety.

While applying for a WEU-based marketing authorization, the literature may refer to a different salt of the active substance than the one being proposed in the new application and in such cases, cross-salt extrapolation becomes necessary to justify that the different salt form does not impact efficacy, safety, or pharmacokinetics. If we take example of this case then if published literature supports amlodipine maleate and you wish to file a WEU application for amlodipine besylate then the applicant must demonstrate that the active moiety is the same and provided scientific justification (e.g., BCS class, dissolution studies, PK bridging studies, or in vitro data) to show that the difference in salt form is not clinically significant.

EMA has accepted cross-salt extrapolation in several WEU application provided robust justification is presented but sometimes extrapolation may be rejected if the salt alters pharmacokinetics or safety profile and when incomplete justification is provided regarding dissolution, absorption, or salt-specific toxicity.

So exactly when a cross-salt extrapolation via WEU is acceptable in EU?

- Activity moiety must be the same
- Salt-specific clinical data – not required if equivalence is scientifically justified
- When pharmacokinetic impact is minimal or well explained
- Route of administration is same
- Use history is of 10+ years of well-established use of any salt form[4]

6. CHALLENGES AND CONTROVERSIES IN CROSS-SALT EXTRAPOLATION IN THE EU

As discussed previously that cross-salt extrapolation is the regulatory acceptance of data from one salt form of an active substance to support approval of another salt and pharmaceutical companies has gained increasing interest in the EU due to evolving generic drug strategies and limitations in the availability of reference medicinal products (RMPs). However, its regulatory acceptance remains complex, with several scientific, legal, and strategic challenges.

The major scientific challenge is the bioequivalence concern because cross-salt products must demonstrate bioequivalence to the reference product, often via in vivo studies and changes in solubility, permeability, or pKa due to different salt forms can alter absorption profiles, complicating bioequivalence demonstration.

Even when the active moiety remains the same, sometimes rate and extent of absorption may differ and regulators may questions whether observed PK differences are attributable to salt differences or formulation variables. For BCS class I and III substances, *in vitro* bioequivalence waivers (biowaivers) are possible – but salt forms must dissolve rapidly and similarly. Different salts may not meet the same BCS criteria, disqualifying them from biowaivers.

Speaking in terms of regulatory challenges then there is lack of harmonized EU guidance because there is no dedicated EMA guideline which specifically addresses cross-salt extrapolation and assessment in the cross-salt extrapolation application is case-by-case, leading to inconsistent decisions between member states and RMS or CMS in DCP / MRP procedures.

Sometimes, cross-salt extrapolation often cannot be done via Article 10(1) Generic Application due to strict sameness criteria and sponsors may opt out for article 10a WEU or 10(3) hybrid pathways – but these require additional data, increasing

complexity and cost. Sometimes the interpretation of Reference Member State in extrapolation is pivotal in DCP and if other CMSs disagree, it may trigger CMDh arbitration, causing delays or refusals.

If the RMP is still under data exclusivity, cross-salt products cannot rely on it unless under a different legal basis and sometimes, reference products of the desired salt are unavailable or withdrawn which leads to applicants to refer to EU-authorised alternatives and it raises questions about legal access and bridging data. There are many commercial controversies where critics argue that cross-salt extrapolation can be used to circumvent data exclusivity or gain faster market entry using minimal data and sponsors face regulatory unpredictability, especially when planning multi-country submissions and some times member states may request additional bridging studies or non-clinical data, even when RMS finds them unnecessary.

Labeling and SmPC adaptations is also considered as one of the most rigorous challenges faced during cross-salt extrapolation because differences in salt form may require adaptations in the summary of product characteristics (SmPC), particularly in sections related to composition, pharmacokinetics, and pharmacodynamics and divergences in SmPC between salt forms may raise concerns during CMDh review or national implementation. If we take example of the divergent opinions than case examples show that even when RMS accepts extrapolation, some CMS reject application due to lack of identical salt in the RMP and concerns about therapeutic equivalence or interchangeability.

So, cross-salt extrapolation in the EU continues to evolve in a regulatory grey zone. While scientifically feasible in many cases, its success depends on strong justification, robust bioequivalence data, and strategic regulatory planning. Until harmonized EU guidance is developed, stakeholders must navigate challenges carefully to avoid delays or refusals in marketing authorization.

7. STRATEGIC CONSIDERATIONS FOR APPLICANTS DURING CROSS-SALT EXTRAPOLATIONS IN THE EUROPEAN UNION

Further given strategic considerations and recommendations are based on our real-world experiences. In the European Union, cross-salt extrapolation presents a nuanced regulatory challenge that demands a strategically well-structured approach. Applicants seeking to gain marketing authorization for a drug product which contains a salt form different from that of the reference medicinal product (RMP) must align their development and submission strategy with both scientific robustness and legal acceptability under the EU pharmaceutical legislation.

A primary consideration involves the scientific justification for extrapolating clinical and non-clinical data between two different salts of the same active pharmaceutical ingredient. It is imperative that sponsors present thorough evidence demonstrating that the salts, despite their different counter-ions, dissociate in vivo to release the same active entity and exhibit comparable physicochemical and biopharmaceutical properties. Key parameters, such as solubility, dissociation constant (pKa), stability, and particle size, should be evaluated and presented to support the assertion that the therapeutic performance of the two salt forms is clinically not different. If bioequivalence studies are not feasible or ethically justified, the submission should instead rely on a scientifically sound bridging strategy, supported by literature data or in vitro comparability, to establish therapeutic equivalence.

From regulatory pathway standpoint, applicants must carefully assess the legal basis of the application. In cases where no RMP exists for the specific salt intended for development, the generic application pathway under Article 10(1) may not be appropriate. Instead, applicants may opt for hybrid applications under Article 10(3) of Directive 2001/83/EC, allowing for partial reliance on published literature while justifying the difference with additional data. Where the salt has a well-documented safety and efficacy profile in the public domain, bibliographic applications under Article 10a WEU may also be viable.

To reduce regulatory uncertainty and align expectations early in the development process, proactive engagement with national competent authorities or the European Medicine Agency (EMA) through Scientific Advice procedures is highly recommended. This allows applicants to seek preliminary feedback on the acceptability of their extrapolation strategy, the appropriateness of the selected legal basis, and any anticipated data requirements. Such engagement is particularly crucial when pursuing decentralized or mutual recognition procedures, where harmonizing among concerned member states is essential for a successful outcome.

Furthermore, applicants should develop a strong narrative around the risk-benefit profile of the product, explicitly addressing the irrelevance of the salt form in altering therapeutic outcomes. The clinical overview and summary modules of the dossier should incorporate a clear and evidence-backed explanation of the extrapolation rationale. The overall emphasis must be on establishing that the difference in salt does not translate into a difference in efficacy, safety, or quality that would warrant additional clinical data.

Another strategic advantage lies in referencing relevant regulatory precedents. Citing previous EU decisions or assessment reports where cross-salt extrapolation was deemed acceptable under similar scientific and regulatory contexts can strengthen the justification and demonstrate alignment with current regulatory thinking. Where applicable, CMDh or CHMP assessment reports, or national public assessment reports (PARs), should be included to illustrate regulatory consistency.

It is also important to ensure that the Common Technical Document (CTD) modules are tailored to reflect these scientific and regulatory requirements. In addition to the clinical modules, the quality module (Module 3) should address any formulation or manufacturing differences arising from the use of a different salt and confirm that such differences do not impact the performance or stability of the final product.

Applicants must also be prepared to respond to potential regulatory queries that may arise during the validation and assessment phases of the procedures. Common concerns include the justification for the selected salt, potential differences in impurity profiles or interactions with excipients, and the absence of comparative in vivo data. A comprehensive response strategy should be in place to address these concerns effectively and efficiently.

For applications involving paediatric indications or those seeking orphan designation, special attention must be paid to ensure compliance with paediatric investigation plan (PIP) requirements and to justify similarity in terms of orphan status, as regulatory may treat different salts as distinct active substances unless sufficient evidence is provided.

Lastly, applicants should continuously monitor regulatory trends, guidance updates, and position papers issues by EMA, CMDh, and national agencies. As regulatory expectations evolve, particularly in the context of increasing reliance on non-clinical and in vitro data, maintaining up-to-date knowledge is essential for timely and successful product development.

In conclusion, successful cross-salt extrapolation in the EU hinges on the integration of scientific rigor, strategic regulatory pathway selection, proactive authority engagement, and thorough documentation. By anticipating challenges and addressing them primitively within the dossier, applicants can significantly improve the likelihood of regulatory approval.

8. CONCLUSION

Cross-salt extrapolation within the EU regulatory framework remains a scientifically grounded but procedurally stringent strategy, necessitating rigorous justification to bridge difference between salt forms of the same active moiety. While the underlying assumption – that therapeutic equivalence can be inferred between different alts of the same active substance – may be pharmacologically valid, EU regulators require robust evidence to mitigate any uncertainty arising from physicochemical or biopharmaceutical variability.

In the absence of a dedicated EMA guidance on cross-salt extrapolation, the assessment is inherently case-dependent and relies heavily on demonstrating bioequivalence, comparable dissolution behaviour, and the absence of clinically relevant differences in exposure, efficacy, and safety. Bridging approaches must be scientifically substantiated, typically involving pharmacokinetic studies under steady-state or single-dose conditions, complemented by in vitro comparability of dissolution profiles across the pH range and BCS classification support where applicable.

Furthermore, strategic positioning of the extrapolation—whether under a full dossier, hybrid application, or well-established use (WEU)—has significant implications for the depth of non-clinical and clinical data required. The lack of a reference medicinal product in the same salt form often necessitates reliance on bibliographic data and prior regulatory precedents, yet these alone are insufficient without mechanistic justification and comprehensive CMC characterization.

In conclusion, cross-salt extrapolation in the EU can be a viable regulatory pathway, if applicants adopt a data-driven, scientifically rigorous approach, supported by proactive engagement with regulatory authorities. The evolving regulatory science landscape underscores the need for greater harmonization and guidance to enhance predictability and facilitate efficient market access without compromising public health safeguards.

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