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KEY STARTING MATERIALS IN PHARMACEUTICAL MANUFACTURING: REGULATORY BOUNDARIES, IMPURITY CONTROL, AND SUPPLY-CHAIN RESILIENCE

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ABSTRACT

Key starting materials (KSMs) sit at an awkward and consequential point in drug-substance manufacturing. They are usually bought as ordinary chemical intermediates, yet they mark the place where full good manufacturing practice (GMP) begins, they carry their own impurities into the active pharmaceutical ingredient (API) process, and they often depend on a handful of upstream suppliers that the API manufacturer has never audited. This review brings these three threads together. We summarise how ICH Q7 and Q11 define and bound the starting material, and why regulators question designations made too close to the final molecule. We then discuss impurity fate and purge, with attention to mutagenic, nitrosamine, azido, elemental and solvent-related risks, and outline a proportionate analytical control strategy illustrated with methods developed in our own laboratories. The supply-chain sections examine hidden multi-tier dependency, the limits of "China-plus-one" sourcing that stops at the API stage, petrochemical and logistics exposure, and recent policy responses in India, Europe and the United States. We close with practical measures (risk-based supplier qualification, dual sourcing with real technical comparability, strategic inventory, backward integration, continuous-flow manufacturing and digital visibility) and a five-stage governance framework that treats KSM management as a shared quality, regulatory, technical and supply-chain responsibility rather than a purchasing task.

KEYWORDS: key starting materials; API starting materials; ICH Q7; ICH Q11; impurity control; genotoxic impurities; nitrosamines; supplier qualification; supply-chain resilience; backward integration; continuous-flow chemistry.

1. INTRODUCTION

When people talk about pharmaceutical quality, they usually mean the finished dosage form, and the API gets most of whatever attention is left. The material that starts the regulated synthesis is rarely discussed outside process-chemistry and regulatory-affairs circles. That is a blind spot. The KSM is where a drug substance's regulatory life begins.[1,2] It fixes the GMP boundary, shapes how much of the route a regulator expects to see described and justified, and, because impurities travel, it influences what finally reaches the patient.

A KSM is not simply the earliest convenient chemical in a synthetic route. ICH Q7 describes an API starting material as a raw material, intermediate or API that is incorporated as a significant structural fragment of the API,[1] and ICH Q11 expects its selection to be justified on scientific grounds rather than on commercial habit.[2] In daily practice the designation is a negotiated judgement. It draws on process chemistry, impurity knowledge, supplier capability and the regulatory history of similar molecules, and it is revisited for as long as the product is on the market.

The commercial context has not helped. For roughly two decades the industry rewarded low cost, offshore production, thin inventories and just-in-time buying. The result was competitive pricing, and also a chemical supply base concentrated in a few regions. The United States Food and Drug Administration's drug-shortage task force traced many shortages to economic pressures that reward the lowest price and do not reward resilient, high-quality manufacturing.[4] A later National Academies report made a similar argument and urged systematic mapping of medical-product supply chains, including their upstream tiers.[5] Pandemic lockdowns, freight disruption, energy shocks, environmental shutdowns and trade controls have shown, repeatedly, that a cheap supply chain is not the same thing as a robust one.

KSMs are especially exposed because they sit between commodity feedstocks and APIs. A problem at a petrochemical plant, a fermentation site, a port or a single intermediate manufacturer can pass through several tiers before the finished-product company notices anything. Good KSM governance therefore needs visibility well beyond the immediate

supplier. One of us has made this argument in the trade press;[3] here we develop it in more detail and connect it to the technical side of the problem.

This is a narrative review. It draws on regulatory guidance (ICH, FDA, EMA and WHO), government and parliamentary publications, selected peer-reviewed literature, and the analytical and process experience of our own laboratories, which is cited where it illustrates a point. We did not carry out a systematic literature search, and the policy sections reflect the position as we understand it in October 2026. The paper proceeds from the regulatory concept of the KSM (Section 2) to impurity and analytical control (Section 3), then to supply-chain concentration and its causes (Sections 4 and 5), supplier lifecycle management (Section 6), resilience strategies (Section 7) and an integrated governance framework (Section 8). Sections 9 and 10 contain a discussion and the conclusions.

2. The Regulatory Concept of a KSM

2.1 Definition and purpose

ICH Q7 defines an API starting material as a raw material, intermediate or API used in the production of an API and incorporated as a significant structural fragment into its structure. It may be bought from a supplier under a commercial agreement or made in-house, and it normally has defined chemical properties and structure.[1] ICH Q11 uses the same idea to separate starting materials from reagents, solvents, catalysts and other processing aids.[2] The accompanying Questions and Answers document goes further and explains the reasoning that should sit behind a proposal. One of its central points is intuitive once stated: the later in the synthesis a starting material enters, the more likely it is that changes to that material, or to the way it is made, will affect drug-substance quality.[6]

Two practical consequences follow. The KSM has to be chosen on process knowledge, not on convenience, and the proposed entry point into the GMP process has to be defended in writing. In other words, "KSM" is a regulatory conclusion that rests on process understanding, impurity knowledge, manufacturing history and the capacity of later steps to control what the KSM brings with it.

2.2 The GMP boundary

Q7 applies its GMP provisions from the point where the API starting material is introduced into the process, while recognising that appropriate controls should still be applied to the starting material itself.[1,7,8] People sometimes read this as saying that everything upstream of

the KSM is uncontrolled. It is not. The control strategy changes with the risk and with the regulatory status of the material, but the manufacturer must still be able to show that the KSM is fit for its intended use and consistent with the process and with the drug-substance specification.

The usual picture is a simple chain (Figure 1). The practical GMP boundary sits at the first use of the justified starting material, and its position should be supported by the synthetic route, the structural contribution of the material, the number and type of remaining transformations, impurity fate and purge, in-process controls, and the depth of process understanding.

Figure 1: Simplified manufacturing sequence and regulatory boundary.

basic chemical or biological feedstocks → chemical intermediates (outside the full API GMP framework) → **KSM (GMP boundary)** → API synthesis under ICH Q7 → drug substance.

2.3 Selection and justification

A defensible KSM proposal normally addresses the following questions together instead of one at a time:

- How much of the API structure does the material contribute, and is it isolated and well characterised?
- How many meaningful chemical transformations remain after its introduction, and can they purge impurities?
- What impurities are associated with the KSM and with the supplier's process, including mutagenic, elemental, solvent-related and route-specific species?
- Are suitable analytical methods and reference standards available?
- How capable and consistent is the proposed supplier, and would an alternative source or route change API quality?

Our own experience with intermediates illustrates why characterisation matters. Work on a metoprolol intermediate, 4-(2-methoxyethyl)phenol, showed how much a well-characterised intermediate and a validated chromatographic method contribute to later control.[9] Likewise, impurities of p-toluenesulfonylurea, a precursor in gliclazide synthesis, needed a dedicated method before their behaviour in the downstream process could be assessed.[10] In both cases, knowledge of the material came before confidence in the process.

A late KSM can look attractive because it shortens the GMP portion of the route. It can also move risk into the incoming material. If the remaining steps cannot purge a carried-over impurity, that impurity may reach the API. The latest possible KSM is therefore not automatically the most appropriate one. The principles of quality risk management in ICH Q9(R1), which now explicitly covers risks to product availability as well as to product quality, give a useful structure for weighing these trade-offs.[11]

2.4 How regulators test a designation

The European Medicines Agency's guideline on the chemistry of active substances, the WHO guidance on multisource product dossiers and the FDA's expectations all ask for a reasoned justification of the starting material, not just a declaration.[7,8,12] Reviewers commonly probe four areas: the amount of structural contribution, whether the material is a true commercial chemical or a custom intermediate made only for the API, the number of steps between the KSM and the API, and the evidence for impurity purge. Custom-synthesised materials placed only a few steps from the final molecule attract particular scrutiny.

A designation that fails this test is expensive. Deficiency queries, complete response letters, requests to move the starting material further upstream, additional GMP-type controls on earlier steps and delayed launches are all realistic outcomes. Early dialogue with regulators, and a justification written before the process is locked, usually costs far less than a late correction. We also find it useful to treat KSM selection as part of the whole drug-substance lifecycle, in which route design, green-chemistry choices and quality-by-design thinking are considered together.[13]

3. KSM Quality, Impurity Control and Analytical Strategy

3.1 Impurity fate and purge

Impurities in a KSM can come from its own starting substances, reagents, catalysts and solvents, from side reactions, from degradation, from inadequate isolation, and from contamination during storage and transport. Once inside the API process an impurity can be carried forward unchanged, converted into something new, or removed. Reviews of impurity profiling and characterisation, including our own, describe the analytical and mechanistic tools used to follow these pathways.[14–16] and ICH Q3A(R2) sets the reporting, identification and qualification thresholds that ultimately apply to the drug substance.[17]

A credible assessment establishes what the impurity is and where it comes from, the range expected in the KSM, how it behaves chemically under later conditions, and which unit operations (crystallisation, extraction, washing, distillation, chromatography) remove it. For mutagenic impurities, ICH M7(R2) accepts purge arguments, and semi-quantitative purge-factor approaches have become a common way to make them.[18,19] The key discipline is to base the argument on data. Low concentration alone is not evidence of removal. Spiking studies at laboratory or pilot scale, mass-balance work, orthogonal analytical methods and trend analysis across batches all strengthen a justification considerably.

3.2 Mutagenic, nitrosamine and azido impurities

KSM control matters most for impurities with mutagenic or carcinogenic potential, because the acceptable limits are so low and because errors are difficult to correct after the fact. Genotoxic impurity risk assessment has been a recurring theme in our laboratories.[20] In cetirizine, for example, we have developed methods for potential genotoxic impurities,[21] chloroacetic acids,[22] dichloroacetic acid.[23] and trace benzene,[24] and the same logic of looking upstream applies to many other molecules.

Nitrosamines changed the industry's thinking. They can arise when secondary or tertiary amines meet nitrosating agents under suitable conditions, and the amine, the nitrite source, the solvent, the catalyst or the cross-contamination route may each be traced to a KSM supplier's process or to a recovered solvent.[25–27] FDA guidance now expects a documented risk assessment, confirmatory testing where risk is identified, and control against acceptable intake limits.[26] Our methods for N-nitrosomorpholine in allopurinol.[31] N-nitrosovarenicline,[30] N-nitrosopiperazine in cetirizine.[28] and 3-amino-N-nitrosopiperidine in alogliptin.[29] show how sensitive, validated LC-MS methods can be built for these species. Azido impurities pose a related problem wherever azide reagents are used, for example in tetrazole formation, and their risk assessment depends heavily on understanding the supplier's chemistry.[32]

Other KSM- or reagent-derived impurities have been the subject of similar work: melamine in allopurinol,[33] epichlorohydrin in rivaroxaban,[34] hydroperoxide in canagliflozin,[35] an O-Boc impurity in lacosamide,[36] hexamine in febuxostat,[37] dimethyl sulfate in neostigmine methylsulfate,[38] alkyl methanesulfonates and a chloro impurity in rasagiline mesylate.[39,40] (R)-(+)-1-phenylethylamine in pregabalin.[41] and isopropylamine in metoprolol succinate.[42] A risk-based KSM programme should therefore include a documented assessment of

potentially mutagenic impurities, a review of the reagents and conditions used by the KSM supplier, control of nitrosating agents and susceptible amines where relevant, analytical methods of suitable sensitivity, a duty on the supplier to notify any process or raw-material change, and periodic reassessment as scientific and regulatory knowledge moves.

3.3 Elemental impurities and residual solvents

Catalysts, reagents and equipment can introduce elemental impurities, and ICH Q3D(R2) expects a risk assessment that covers all sources.[43] In a case study using ICP-MS we showed how such an assessment can be organised and verified.[44] Residual solvents are governed by ICH Q3C(R8),[45] and headspace gas chromatography remains the workhorse for them, as in our methods for canagliflozin and neostigmine methylsulfate.[46,47] These are classical tests, but KSMs are often recrystallised from, or washed with, solvents that differ from those in the API process, so the solvent profile of the incoming material deserves its own look.

3.4 An analytical control strategy proportionate to risk

Testing of a KSM should be proportionate to risk and tied to its intended use. A typical programme covers identity, assay, related substances and specified impurities, residual solvents, water content or loss on drying, and, where relevant, elemental, mutagenic and nitrosamine-related impurities, physical properties that influence process performance, and microbiological quality for susceptible materials. Table 1 summarises how the main impurity classes map onto analytical techniques, with examples from our work.

Table 1: Impurity classes relevant to KSMs, typical analytical approaches and illustrative examples from the authors' laboratories.

Impurity class	Typical origin in a KSM context	Usual technique	Examples
Alkylating agents and sulfonate esters	Reagents, solvents, acid-alcohol combinations	Headspace GC, GC-MS	Dimethyl sulphate;[38] alkyl methanesulfonates[39]
Nitrosamines	Amines with nitrosating agents; recovered solvents	LC-MS/MS, GC-MS	N-nitrosomorpholine;[31] N-nitrosopiperazine;[28] 3-amino-N-nitrosopiperidine.[29]
Azido impurities	Azide reagents in ring-forming steps	LC-MS, GC-MS, ion chromatography	Risk assessment overview[32]
Reactive or carry-over species	Starting-material residues, reagents, degradation	HPLC-UV, LC-MS, headspace GC	Melamine;[33] epichlorohydrin;[34] hydroperoxide;[35] hexamine.[37]

Residual amines and basic reagents	Reagents, resolving agents	HPLC, ion chromatography	(R)-(+)-1-Phenylethylamine;[41] isopropylamine.[42]
Elemental impurities	Catalysts, reagents, equipment	ICP-MS	Risk assessment case study[44]
Residual solvents	Process and crystallisation solvents	Headspace GC	Canagliflozin[46] neostigmine methylsulfate.[47]
Chiral identity and enantiomeric purity	Stereochemical integrity of a chiral KSM	Chiral HPLC, FTIR	Besifloxacin;[48] serine.[49]

A certificate of analysis is not a substitute for supplier qualification. The receiving site should verify that supplier results are reliable through confirmatory testing, method assessment, periodic full testing, review of analytical data and laboratory audits. Methods themselves should be built with a lifecycle view, in line with quality-by-design thinking for analytical procedures.[50] and with the current ICH Q14 and Q2(R2) guidelines on development and validation.[51,52] Where a KSM is chiral, identity and enantiomeric purity need dedicated methods, as in our work on enantiomeric impurity in besifloxacin and on FTIR identification of serine.[48,49]

4. Supply-Chain Concentration and Geopolitical Risk

4.1 The hidden dependency problem

A finished-product company may believe it has diversified because it buys an API from an Indian, European or North American manufacturer. That diversification can be an illusion if the API manufacturer relies on a single overseas supplier for its KSM or for a still earlier intermediate. The real dependency chain is longer than the commercial one: finished-product manufacturer → API manufacturer → KSM supplier → intermediate supplier → basic chemical or fermentation feedstock supplier.

Visibility that stops at the first supplier will often miss the real point of vulnerability. A serious assessment should map at least the critical upstream tiers for high-risk APIs and KSMs. Import dependence is not unacceptable in itself. The risk arises when it is concentrated in one country, one manufacturing cluster, one facility, one raw-material source or one transport route, and no contingency plan exists.

4.2 Concentration in practice: the Indian example

India is a leading supplier of generic medicines, yet its upstream chemistry depends heavily on imports. Figures given to the Indian Parliament in 2020, based on port data from the Central Drugs Standard Control Organisation, put China's share of India's imports of pharmaceutical raw materials at about 68.6% in 2017-18, 66.5% in 2018-19 and 72.4% in 2019-20 by value.[53] Individual products can be far more exposed than these averages suggest. Table 2 gives a qualitative view of the roles different regions play.

Table 2: Qualitative view of regional roles in the global KSM-to-API value chain.

Region	Principal role	Upstream KSM and intermediate exposure
China	Large-scale producer of basic chemicals, intermediates and KSMs, often in vertically integrated clusters	Low for its own supply; strong influence over global prices and availability
India	Major exporter of APIs and finished formulations	Substantial reliance on imported KSMs, intermediates and some APIs; two-thirds or more of raw-material imports by value came from China in 2017-20.[53]
United States and Europe	Major consumption markets with growing policy interest in domestic and allied supply	Material exposure to offshore upstream supply; limited domestic upstream capacity.[4,5]

4.3 The limits of "China-plus-one"

A "China-plus-one" strategy can lower direct reliance on a single country, but it does not deliver resilience if the second supplier draws on the same Chinese upstream network. Sourcing an API from another country does little if that manufacturer still buys its KSM or key intermediate from one Chinese source. Without backward integration to the early precursors, regional diversification stays shallow.

A meaningful diversification assessment therefore looks at country and regional concentration, common ownership or shared infrastructure, shared upstream raw materials, common ports and logistics providers, supplier capacity and headroom, lead times and minimum order quantities, the regulatory approvals needed for a second source, and the time to qualify and scale an alternative. In some cases backward integration into key intermediates is necessary. In others, regional stockholding, process flexibility or a qualified alternative route is more practical.

4.4 Policy responses

Governments have started to act. India's Production Linked Incentive scheme for critical KSMs, drug intermediates and APIs, approved in 2020, offers sales-linked incentives for a defined list of products, and it is complemented by a scheme for bulk-drug parks that supports shared infrastructure.[53,54] In Europe, the Commission proposed the Critical Medicines Act in 2025, and in May 2026 the European Parliament and Council reached a provisional political agreement. The agreement is aimed at diversified sourcing in public procurement, strategic projects for the manufacture of critical medicines and their active substances in the EU, and partnerships with like-minded countries; it still needs formal approval.[55] In the United States, the shortage and supply-chain reports cited above have shaped continuing federal discussion about resilience.[4,5] Such policies create opportunities for domestic and regional manufacturers, but they will only work if they address the whole chain, from feedstock and utilities to analytical capability and skilled people, rather than the API stage alone.

5. Upstream Feedstocks, Energy and Logistics

5.1 Petrochemical dependence

Many synthetic KSMs trace back, a few steps up the chain, to petrochemical feedstocks. Crude-oil cracking and aromatic processing supply benzene, toluene and xylenes, and the commodity chemicals built from them (phenol, aniline, acetic acid and its anhydride, and many alcohols, acids and amines) end up as raw materials for KSM manufacture. A pharmaceutical intermediate may look like a specialty product, but its price and availability are often tied to the same forces that move bulk chemicals:

- crude-oil and natural-gas prices;
- refinery operating rates and petrochemical plant outages;
- energy and environmental regulation;
- extreme weather;
- geopolitical conflict, sanctions, export controls and trade restrictions;
- port congestion and shipping disruption.

Because the pharmaceutical volume in any one of these chemicals is small compared with the volume sold to other industries, a pharmaceutical buyer is rarely in a position to command priority during a shortage. This is one reason why upstream mapping matters. It is also why

KSM planning should include feedstock exposure and not only the name of the immediate vendor.

5.2 Logistics and stability

Transport conditions deserve attention for a quality reason as well as a delivery reason. Some KSMs and intermediates are hygroscopic, oxidation-sensitive, volatile, reactive, temperature-sensitive or unstable on extended storage. A longer route, a rerouted vessel or a delay at a port can therefore turn into a quality event as well as a late delivery. We have seen in our own work how moisture can alter the behaviour of a drug substance: moisture uptake in neostigmine methylsulfate was followed by FTIR,[56] and the interaction of rasagiline mesylate with moisture was studied by FTIR, XRD and TGA.[57] These were final drug substances (API,s), but the lesson carries upstream. When a material is moisture- or heat-sensitive, specification, packaging, transport mode and storage should be agreed with the supplier, and incoming testing should be able to detect degradation that occurred in transit.

Power fluctuations, scheduled industrial curtailments and tighter regional environmental controls at major chemical sites can also interrupt the supply of raw starting materials with little warning. These risks are often not visible to a finished-product company unless it has asked about them.

6. Supplier Qualification and Lifecycle Management

6.1 Risk-based qualification

Qualifying a KSM supplier means looking at technical, quality, regulatory, commercial and supply-chain factors together. A reasonable programme reviews the supplier's process and process controls, its quality-management system, its analytical methods and laboratory controls, and its deviation, change-control, complaint and recall systems. It includes an audit of manufacturing and testing facilities, verification of regulatory and inspection history, a look at environmental, health, safety and waste-management practice, confirmation of capacity and business continuity, an assessment of the supplier's own upstream sources, and a check on data integrity and electronic-record controls. The framework of ICH Q10 is a helpful reference for how the pharmaceutical quality system should extend to outsourced activities and purchased materials.[58]

Qualification should be risk-based. A supplier of a structurally simple, stable, low-risk material does not need the same level of oversight as a supplier of a complex KSM with

potential mutagenic impurities and little downstream purge capacity. Over-auditing the first case wastes scarce audit resources, and under-auditing the second is where problems start.

6.2 Quality agreements and change control

A written quality agreement turns expectations into obligations.[59] It should say who is responsible for specifications and test methods, sampling and release, deviation and investigation reporting, out-of-specification and out-of-trend results, change notification, reprocessing and rework, storage and transport, retest or expiry periods, complaint handling, regulatory support, audit rights, and data retention.

Change control is the clause that matters most. Changes to the KSM's process, site, raw materials, solvents, catalysts, equipment, scale, analytical methods, specifications or packaging may all affect API quality. The API manufacturer needs enough information to carry out an impact assessment before accepting the change, and enough regulatory flexibility, in the sense of ICH Q12's lifecycle-management concepts, to manage the consequences in the dossier.[60]

6.3 Continuing oversight

Qualification is not a one-off event. Ongoing oversight includes periodic audits, review of batch trends and analytical variability, evaluation of deviations and complaints, monitoring of delivery performance, verification testing, attention to regulatory and inspection news, reassessment of business continuity, and awareness of changes in upstream manufacturing. A supplier who always meets specification but whose deliveries are slipping, whose analytical results drift unexplained, or who communicates changes poorly may be an emerging risk, and the pattern often becomes visible well before a failed batch does.

6.4 CULTURE AND COMMUNICATION

Systems depend on people who will report bad news. A buyer who suspects that a supplier has changed a raw material, or a chemist who notices an odd trend in a KSM, has to feel able to say so. We have argued elsewhere that psychologically safe working environments are a practical quality and resilience factor in pharmaceutical manufacturing, not a soft extra.[61,62] Applied to KSMs, the point is simple: early signals from the bench, the warehouse and the purchasing desk are among the cheapest risk-detection tools a company has.

7. Strategies for KSM Supply-Chain Resilience

7.1 Dual sourcing with technical equivalence

Dual sourcing reduces the impact of a single-site failure, but naming a second supplier is not the same as having one. The alternative KSM must be characterised and its effect on the API process evaluated. A comparability exercise should cover chemical identity and structure, impurity profile, physical properties, residual solvents and elemental impurities, stability and storage behaviour, process performance, API impurity profile, yield and crystallisation behaviour, and final API quality and stability.

Different suppliers frequently use different synthetic routes. Even when two KSMs meet the same specification, route-specific impurities can influence the downstream process, so a risk-based bridging strategy is often needed before the second source goes into routine use. Orthogonal analytical fingerprinting is particularly helpful here. High-resolution LC-MS/MS and GC-MS can reveal differences in impurity profiles that a compendial-style specification would miss, and ICP-MS can confirm the elemental picture.

7.2 Multi-source regulatory dossiers

The time needed to approve a new source can be the real bottleneck, not the time needed to find one. Dossiers that name primary and alternate KSM suppliers from the start, supported by comparability protocols, demonstrated purge capability and standardised validation data, allow a company to switch with a notification or a limited variation, instead of starting a full regulatory submission from zero. The same logic applies to filings in several regions, where a source approved in one market may not yet be in another.

7.3 From just-in-time to just-in-case

Strategic inventory is the simplest resilience measure and also the most expensive in working capital. The right level depends on supplier lead time, demand variability, shelf life or retest period, storage requirements, availability of alternative sources, time needed for regulatory approval, the clinical criticality of the associated API and the consequence of interruption. We think it is a mistake to apply a single number of months across all materials. Stock should follow risk and recovery time. A chemically stable KSM with a long qualification timeline and no practical alternative may justify a large buffer, while a readily available material with several approved sources may justify almost none.

7.4 Backward integration

Backward integration can take several forms: internal manufacture of the KSM, investment in an intermediate supplier, long-term supply agreements, joint ventures, local production of critical feedstocks, development of alternative synthetic routes and regional manufacturing clusters. It can improve supply assurance and deepen process knowledge. It also brings capital, environmental, operational and regulatory responsibility, and so it needs a business case that considers total cost, capacity utilisation, technical complexity, environmental compliance and long-term demand. For a mid-sized API manufacturer, a selective approach (integrating only the few KSMs where the exposure is greatest) is usually more realistic than trying to own the whole chain.

7.5 Continuous-flow and greener manufacturing

Continuous-flow chemistry is well suited to hazardous, strongly exothermic, highly energetic or hard-to-scale reactions, and a considerable body of work describes its use in API manufacture.[63,64] Benefits include better heat and mass transfer, smaller reaction volumes, tighter control of conditions, smaller inventories of hazardous intermediates, improved worker and environmental safety, more consistent quality and, in principle, modular or distributed production. ICH Q13 now gives a regulatory framework for continuous manufacturing of drug substances and drug products.[65] Flow is not a universal fix. It requires suitable equipment, process-development expertise, control systems, analytical integration, maintenance capability and a regulatory strategy. For selected high-volume or hazardous KSMs, however, it may make regional or onshore production economically viable and reduce dependence on large, centralised plants.

Green-chemistry approaches complement this. Ionic liquids and other alternative media have been explored as reaction media in drug synthesis.[66,67] and polyethylene glycol has been used as a medium for the efficient synthesis of a heterocyclic series.[68] Such methods are not KSM-specific, but cleaner routes with fewer hazardous reagents lower both the impurity burden and the environmental cost of domestic production.

7.6 Digital supply-chain visibility

Digital tools can join quality, procurement, manufacturing, regulatory and supplier data. Useful functions include multi-tier supplier mapping, risk dashboards, batch and analytical trend monitoring, automated change-notification workflows, inventory and lead-time alerts, scenario analysis, supplier performance scoring, and integration with enterprise-resource-

planning, laboratory-information-management and quality-management systems. The limiting factor is data quality. A sophisticated dashboard built on incomplete or out-of-date supplier information can give false confidence, and the most valuable first step is often the unglamorous one of getting suppliers to tell you who their suppliers are.

8. An Integrated KSM Governance Framework

KSM management works best when it is owned by a cross-functional team and not left to procurement alone. We suggest five stages, summarised in Table 3. They are not a strict sequence: findings at one stage routinely send the team back to an earlier one, and the lifecycle review in Stage 5 feeds straight into the criticality assessment in Stage 1.

Table 3: Five-stage governance model for key starting materials.

Stage	Core questions	Typical outputs
1. Criticality assessment	How important is the API therapeutically? Are there alternative suppliers? How concentrated is production geographically? How complex is manufacture? What are the impurity and patient-safety risks, the lead time and shelf life, and the regulatory cost of change? What happens if supply stops?	Risk ranking of KSMs; list of high-criticality materials
2. Technical and regulatory assessment	Is the synthetic route understood? Does the KSM contribute a significant structural fragment? Is the GMP boundary justified? What is the impurity fate and purge evidence? Is the analytical strategy adequate? Is the process capable? What filing commitments exist?	KSM justification file; impurity purge assessment; control strategy
3. Supplier and supply-chain assessment	Who are the direct and upstream suppliers? Where are they located? What are their capacity and utilisation, raw-material dependencies and logistics routes? What business-continuity and environmental or regulatory risks apply?	Multi-tier supplier map; audit plan; supplier risk profile
4. Mitigation planning	Which measures fit the risk: dual sourcing, strategic inventory, alternative route, backward integration, long-term contracts, regional manufacture, enhanced incoming testing, more frequent audits?	Approved mitigation plan with owners, timelines and costs
5. Lifecycle review	Has anything changed: supplier or site, process or raw material, a regulatory observation, a new impurity concern, a disruption, demand, or the API process or specification?	Updated risk ranking; change-control actions; dossier updates

The first stage is deliberately broad. It is tempting to concentrate on the KSMs with the highest spend, but spend and criticality are different things. A low-cost KSM that is the only route to a life-saving API deserves more attention than a high-cost one with five qualified sources. The second and third stages bring in the technical and supply-chain views that, in

many organisations, sit in separate departments and speak to each other only after something has gone wrong. The fourth stage is about choosing proportionate tools, and the fifth recognises that none of the earlier assessments stays valid for long.

9. DISCUSSION

KSM management sits where pharmaceutical science, regulatory policy, industrial economics and national health security meet. The central question is not whether a KSM is made at home or abroad. It is whether the manufacturing process is understood, whether quality is consistently controlled, whether impurities can be managed, whether the chain is visible enough to anticipate trouble, and whether a recovery plan exists and has been tested.

The point of designation deserves a frank comment. The KSM designation should not be used mainly to reduce the number of GMP steps. A designation that is too late may lower immediate compliance costs while raising impurity, supplier and regulatory risk. An unnecessarily early one may add controls that bring little benefit to product quality. The right place lies between these, and it is found by balancing process understanding, risk control, purge capability and regulatory expectation, preferably with regulators involved early. The impurity-focused work summarised in Section 3 shows that the most troublesome contaminants (alkylating agents, nitrosamines, azides, reactive carry-over species) are often traceable to chemistry that happens before or around the KSM boundary, which is the strongest practical argument against minimising the boundary.

For Indian manufacturers, domestic-production initiatives are an opportunity to strengthen the upstream chemical ecosystem. Resilience, however, needs more than plant capacity. It needs reliable utilities, environmental compliance, process-development talent, analytical infrastructure, effluent and waste-management capability, a mature quality culture and predictable regulatory implementation. Without these, incentives may produce capacity that is expensive, under-used or hard to keep in compliance. The same caution applies to the European and North American policy efforts discussed earlier.

A resilient KSM strategy also has to be economically sustainable. Regional manufacture will often carry a higher direct cost than concentrated offshore sourcing. The comparison should therefore include avoided disruption, lower regulatory exposure, better supply assurance, fewer emergency purchases and protection of patient access. These benefits are real but

diffuse, and they are rarely visible in a purchase-price comparison. Purchasers, regulators and payers all have a part in making them count.

This review has limitations. It is narrative and was not based on a systematic search, so the selection of literature reflects the authors' judgement. Several of the illustrative methods cited come from our own laboratories, and they are used here as examples of what is feasible and not as a benchmark against other work. Policy developments, particularly in Europe and the United States, are moving quickly, and the status of schemes described here should be checked at the time of reading. Finally, the governance framework in Section 8 is a synthesis of regulatory expectations and industrial experience. It has not been validated prospectively, and we would welcome comparative case studies of its use.

Several gaps invite further work. Shared, quantitative multi-tier supply-chain mapping for a defined set of critical KSMs would make risk far easier to compare across companies. Publicly accessible purge-factor data for common KSM-related impurities would reduce duplicated experimental effort. Regulatory expectations on starting-material justification differ in detail between regions, and clearer convergence would help companies that file in several markets. Finally, case studies of KSMs moved from imported to regionally produced, including flow-based examples with full cost and quality data, would help the industry judge where backward integration actually pays.

10. CONCLUSIONS

KSMs are foundational to pharmaceutical manufacturing and should be handled as critical quality and supply assets. Their selection sets the practical GMP boundary, influences impurity control, affects the regulatory acceptability of the drug-substance process and can decide whether API production continues in a disruption.

A sound KSM strategy has several parts: a scientifically justified designation, a data-based assessment of impurity fate and purge, risk-proportionate analytical control, qualified and monitored suppliers, visibility of the upstream tiers, effective change control and credible contingency measures. Dual sourcing with proven comparability, strategic inventory, selective backward integration, continuous-flow chemistry, regional production and digital monitoring can each strengthen resilience when matched to the risk of the specific material.

The industry needs to move beyond a narrow cost-per-kilogram view. A KSM should be judged by what it contributes to patient safety, regulatory compliance, operational continuity and public-health security. Companies that bring process chemistry, analytical science, quality assurance, regulatory affairs, procurement and supply-chain planning into one conversation will be better placed to keep medicines flowing in an unsettled world.

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