AENOVA E-PAPER

Small Molecules: Choosing the Right Development Path

Strategic, Scalable, and De-Risked

aenova

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1 INTRODUCTION

Small and virtual pharma companies, often working with one to three early-stage drug candidates, navigate development under real-world constraints. With lean teams and a strong scientific focus, they bring agility but may not yet have deep in-house CMC expertise. Budgets are limited, API is precious, and timelines matter, not just for internal planning, but often also for investor confidence. Progressing from preclinical work to first-in-human trials requires thoughtful choices, especially when working with external partners. Balancing scientific ambition with practical execution, these teams look for ways to move forward efficiently, make the most of available resources, and build trust in a development path that fits both their molecule and their means.

This white paper offers a **structured roadmap for early CMC decision-making** tailored to such resource-constrained teams. It outlines how to integrate CMC planning from day one to avoid both over-engineering (wasting effort on overly complex solutions) and under-engineering (taking shortcuts that fail later). The following chapters demonstrate a stepwise approach: **profiling the molecule early** to understand developability risks, using a **stage-gate framework** to drive go/no-go decisions, leveraging **enabling formulation technologies** when needed, **designing scalable processes** that meet GMP standards, and proactively **mitigating risks**. By applying a science-based, fit-for-purpose mindset to each of these elements, small companies can make rapid progress with right-first-time results rather than firefighting problems down the line.

Crucially, the paper highlights that startups don't have to go it alone. A partner like **Aenova** can amplify a small company's capabilities with an end-to-end development platform. Aenova brings all three major formulation technologies in-house (**hot-melt extrusion, spray drying, and lipid-based delivery**) so the best solution for the molecule can be chosen without bias. Its development approach uses **API-sparing** techniques (miniaturized equipment and high-throughput screens) to get the most out of limited API quantities. Moreover, Aenova integrates **regulatory affairs support** from the start to ensure that even early-phase work generates the data needed for eventual approvals, averting compliance-related delays. Finally, with **all steps available from a single source**, from formulation development through clinical trial material manufacturing, packaging, and supply, Aenova provides a seamless scale-up and supply chain for its partners. In sum, this white paper equips small pharma teams with a blueprint to navigate early CMC efficiently, and shows how leveraging the right expertise and technologies can turn their constraints into a successful development strategy.

2 EARLY DEVELOPABILITY PROFILING AND ASSESSMENT

Early developability profiling is a critical first step in small-molecule oral drug development. By evaluating a candidate's key properties in the preclinical stage, teams can determine if the molecule is "developable" and plan CMC (Chemistry, Manufacturing, and Controls) strategies accordingly. This is especially important for startups and virtual pharma companies with limited API material and resources. Early profiling helps avoid wasted effort and surprises that could derail timelines. In short, it lays the foundation for informed formulation and process decisions, de-risking the development program from the outset. Skipping or rushing this step can lead to later formulation failures, costly rework, or even clinical delays due to unexpected issues.

2.1 Key Attributes to Assess

Effective developability profiling examines the **physicochemical and biopharmaceutical properties** most relevant to oral formulation. These include: **solubility** (how readily the API dissolves), **permeability** (ability to cross gastrointestinal membranes), **solid-state form** (polymorphism and crystallinity of the API), and **bulk powder properties** (e.g. particle size, flowability, hygroscopicity) [1]. Together, these factors determine how easily a drug can be made into a bioavailable oral dosage. For example, early tests might flag a compound as **"brick dust"** (extremely low solubility) or reveal multiple polymorphs – signals that special formulation approaches or salt selection may be needed. Identifying such issues upfront allows the development team to proactively design around them (for instance, planning solubility-enhancing formulations if required) rather than being caught off-guard later.

2.2 Analytical Profiling and Tools

Comprehensive analytical testing underpins early profiling by providing high-quality data on the API's behavior. A robust analytical toolkit is employed to characterize the molecule from multiple angles. Key techniques include **X-ray powder diffraction (XRPD)** and **differential scanning calorimetry (DSC)** to examine polymorphism, crystallinity, and thermal properties of the solid API, and **high-performance liquid chromatography (HPLC)** to assess purity and detect impurities. Forced degradation studies are conducted to intentionally stress the molecule (with heat, light, pH, etc.) and identify potential stability liabilities [2]. Early stability-indicating methods (e.g. HPLC assays for degradation products) and preliminary **stability studies** (accelerated and ambient conditions) help to predict shelf-life and storage requirements. These analytical

activities should be carried out in alignment with regulatory guidelines (ICH/FDA) to ensure the data is reliable. Techniques like preliminary method development and impurity profiling provide a clear picture of how the API might degrade or vary, ensuring there are no blind spots before formulation begins. Importantly, all this can be done with minimal API consumption – many CDMOs offer **API-sparing** screening programs to preserve precious material in early development [1].

2.3 Avoiding Risks and Late Surprises

The outcome of early developability profiling is a **risk-informed API profile** that guides subsequent development. Armed with this knowledge, teams know what challenges to expect (for instance, the need for solubility enhancement technology or extra care with a light-sensitive compound) and can prioritize their formulation and process efforts accordingly. A modest upfront investment in profiling pays off by preventing dead-ends, it steers the project away from unworkable formulation approaches and unforeseen stability problems. In contrast, skipping thorough profiling can be disastrous for a small company: an undetected issue (like an unstable polymorph or insoluble API) may only surface during formulation or clinical manufacturing, forcing expensive re-formulation and losing precious time and API. By conducting early profiling, even lean development teams can **de-risk** their program, avoid costly surprises, and set a solid foundation for a smooth path to first-in-human trials.

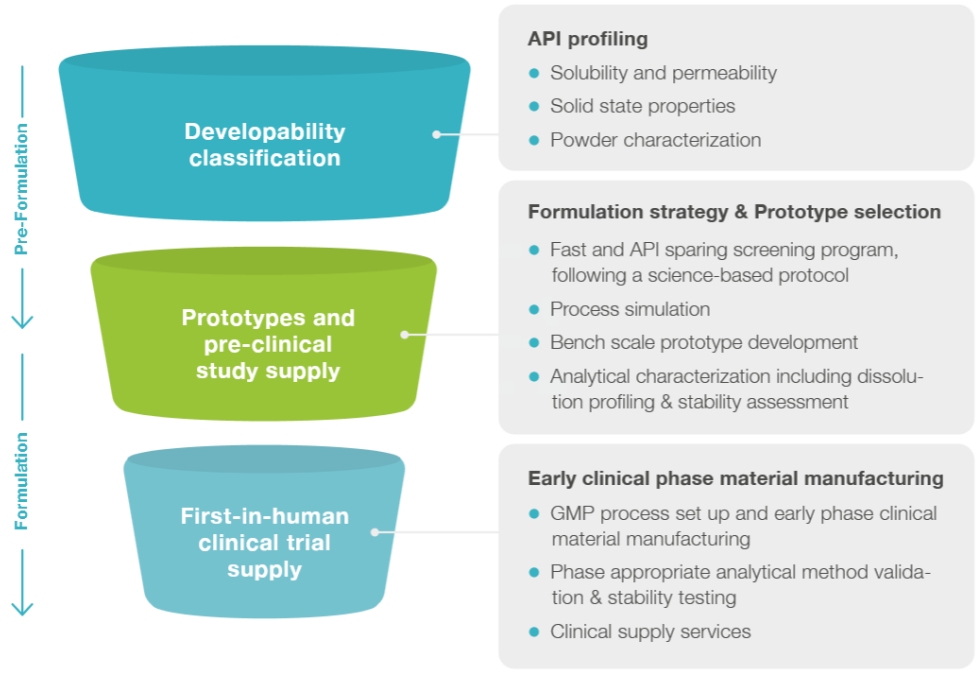


Figure 1 Aenovation ® : Aenova's Fast-Track Early-Stage Formulation Program

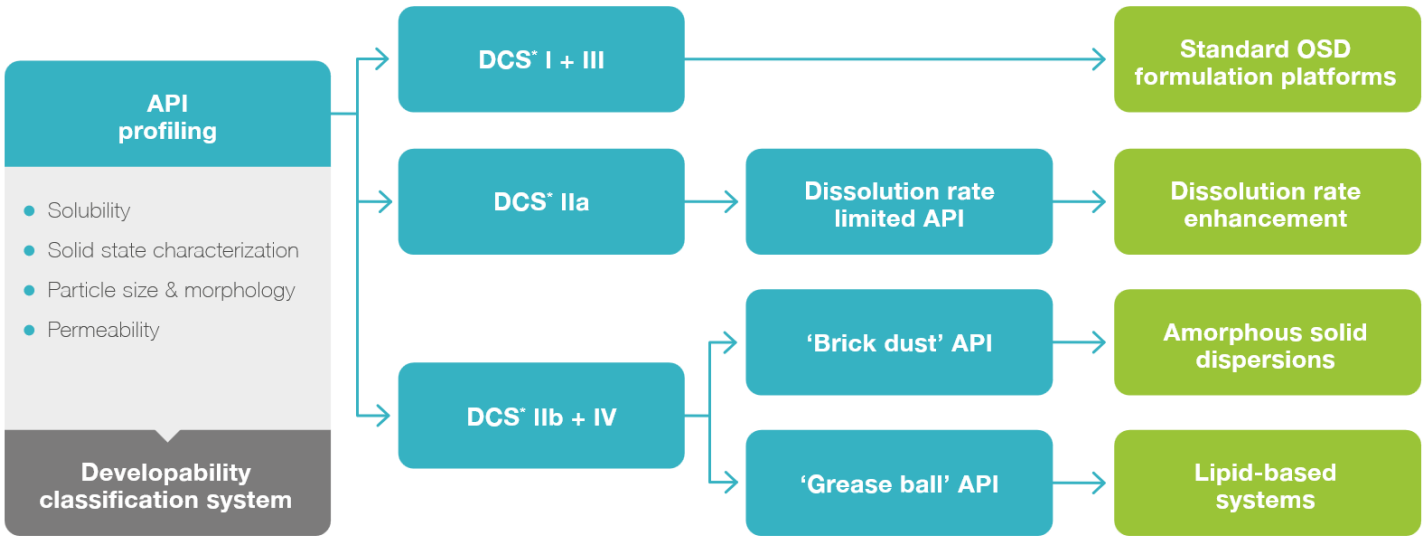
3 DECISION FRAMEWORK AND STAGE-GATE STRATEGY

Early-phase CMC development benefits greatly from a structured decision-making framework, often implemented as a **stage-gate** process. In a stage-gate model, the project is segmented into defined phases with clear **go/no-go criteria** at key milestones. For example, after **lead candidate profiling**, before **GLP toxicology studies**, and prior to **first-in-human manufacturing**, management will set specific benchmarks that must be met before advancing. These stage gates enforce discipline and ensure critical CMC questions are answered at the right time (e.g. "Do we have a stable, bioavailable formulation for first-in-human?"). This tried-and-tested approach prevents projects from rushing ahead with unresolved issues. Each development phase must satisfy predetermined CMC criteria before moving forward. By defining **go/no-go gates** early, teams avoid costly surprises and focus resources on viable candidates.

Within this framework, a **decision tree** acts as the guiding algorithm for CMC choices, especially in formulation development. Rather than a one-size-fits-all plan, the decision tree funnels each molecule into the simplest viable drug product format based on its **API characteristics**, and only escalates to more complex solutions if necessary. The goal is to avoid both **over-engineering** (unnecessary complex formulation work for an easy molecule) and **under-engineering** (an overly simplistic approach for a challenging API that later fails). For instance, if early **developability profiling** (Chapter 2) shows acceptable solubility and stability, the team might proceed with a standard oral solid dose formulation. Conversely, if a compound is a notorious "brick dust" with extremely low solubility, the framework directs the team to evaluate enabling formulation strategies right away. This priority-setting saves valuable time and API material.

Aenova's experience underscores the value of such a structured approach: having a rapid, **API-sparing formulation route selection** process in place allows quick identification of the optimal development path while **maximizing API resources**. Crucially, this decision-tree methodology is **customized to each molecule's needs** and every project's unique challenges are considered so that the development plan aligns with the API's properties and the sponsor's objectives [1]. In practice, this means Aenova tailors its formulation and process workflows to the molecule's profile using science based rationale, rather than forcing a standard formula, ensuring the project "remains true to your vision" [1].

Employing a stage-gated decision framework also **reduces risk** by focusing efforts on the most pressing issues. Teams concentrate on experiments that resolve key **uncertainties** at each phase gate, instead of exhaustive characterization with little added value. For example, consider two development programs: Compound A has good solubility and stability, so the decision framework green-lights a straightforward capsule formulation and minimal process optimization. Compound B, by contrast, has poor solubility and other red flags – the framework triggers an early investment in solubility-enhancing formulation and solid-form studies before proceeding. In this way, Compound A isn't over-engineered, while Compound B gets the extra engineering it needs **up front**. Each molecule receives just the right level of effort. This risk-driven selectivity prevents **analysis-paralysis** by avoiding unnecessary work, and it ensures no critical issue is ignored until too late. The end result is a lean, well-defined development strategy that accelerates progress by doing **the right work at the right time**. Such a framework keeps CMC development aligned with business objectives such as timelines, resource constraints, and product profile goals, so that early CMC decisions actively support the program's overall success. In short, a robust decision framework with stage gates helps even small teams **"get it right the first time,"** de-risking the pathway to clinic while conserving precious time and material.



*DCS = developabilty classification system, Butler, Dressman, J Pharm Sci, 2010

Figure 2 Science-Based Rationale for Selection

4 ENABLING TECHNOLOGIES AND FORMULATION STRATEGIES

When a small-molecule drug candidate has developability challenges, **enabling** formulation technologies can bridge the gap between a great molecule and a viable product. In oral drug development, poor solubility or permeability often limits absorption, an issue affecting the majority of new chemical entities. Early developability profiling (Chapter 2) flags such problems (e.g. identifying a compound as a "brick dust" with extremely low aqueous solubility or a "grease ball" with high lipophilicity), indicating that standard formulation approaches may not achieve sufficient exposure. In these cases, advanced formulation strategies are needed to improve bioavailability and ensure the molecule can reach systemic circulation in effective concentrations [3].

Rather than abandon a promising molecule, teams deploy enabling technologies in preclinical and Phase I/II development to enhance absorption and thereby de-risk the program. The decision framework from Chapter 3 guides this escalation if an API's properties show poor solubility, one quickly evaluates bioavailability-enhancing options instead of forcing a simple but inadequate formulation. Enabling technologies thus act as a toolkit for formulating "difficult" molecules into successful early-phase drug products.

4.1 Hot-Melt Extrusion (HME): Amorphous Dispersion for "Brick Dust" APIs

Hot-melt extrusion is a proven **technology for bioavailability enhancement** that is especially suited for solid APIs with very low water solubility due to strong crystal lattice. In HME, the API is blended with a polymer matrix and melted under heat and shear, then rapidly cooled to form an **amorphous solid dispersion (ASD)**. This process disrupts the drug's crystalline structure, yielding an amorphous form with higher apparent solubility and faster dissolution [4]. By **transforming a poorly soluble crystalline API into a dispersed amorphous state**, HME can significantly increase the dissolution rate and concentration of drug in the gut/ gastrointestinal fluid. The result is improved absorption of compounds that would otherwise dissolve too slowly to be viable. Importantly, HME has **tremendous value in early development**. It requires relatively small API quantities for formulation screening (Aenova even uses lab-scale simulation with minimal API to prototype HME formulations [3]) and produces solid dispersions that can be directly filled into capsules or compressed into tablets for early phase studies (first in animals). Modern HME platforms are scalable from bench to GMP production.

For example, Aenova's new twin-screw extruder can seamlessly scale up amorphous dispersion formulations from laboratory batches to full GMP manufacturing. This means a successful Phase I formulation can be directly scaled for later phases without changing the core process [3].

In short, HME is an ideal strategy when an API has adequate permeability ("grease ball" APIs can also benefit) but is limited by **crystallinity and solubility** – the technology enables a stable, fast-dissolving amorphous form early, accelerating the path to proof-of-concept.

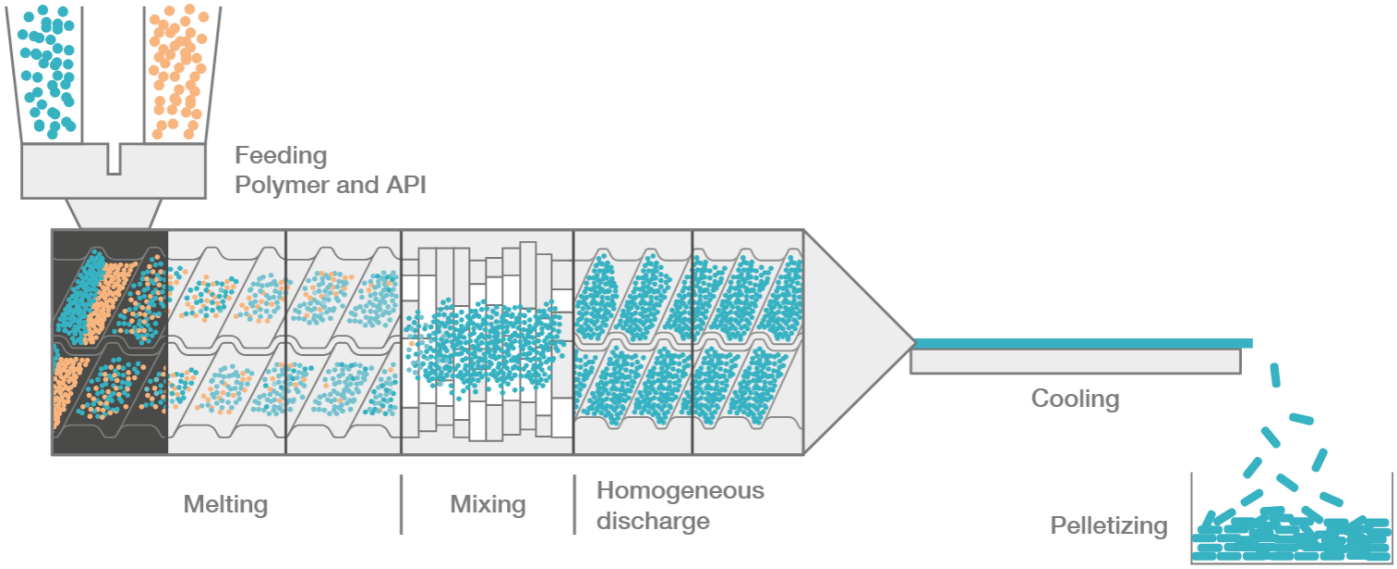


Figure 3 HME – Amorphous dispersion for Brick dust APIs

4.2 Spray Drying: Rapid Solvent-Based Dispersion for Poorly Soluble APIs

Spray drying is another core **ASD technology** used to tackle poor solubility, often for the same class of challenging compounds as HME (brick dust APIs and other BCS Class II drugs). In a spray drying process, the API is dissolved in a solvent together with polymers or surfactants, then sprayed into a chamber with hot gas to evaporate the solvent rapidly. The drug dries as fine particles embedded in a polymer matrix, essentially forming an amorphous solid dispersion similar to HME, but via a solution route. Spray drying can **dramatically improve dissolution**: the high surface-area particles and amorphous drug form lead to much faster and

more complete dissolution in gastrointestinal fluids, boosting absorption [3]. A key advantage in early development is speed and flexibility: spray-dried dispersions can be prepared and adjusted quickly by tweaking solvent or excipient ratios, allowing rapid iteration on formulation recipes. It is also relatively API-sparing: small lab spray-dryers can produce sufficient amorphous material with only grams of API for initial studies.

Like HME, spray drying is readily scalable. Aenova, for instance, offers **state-of-the-art spray drying setups from lab units up to full GMP production equipment** [3]. This ensures continuity from early feasibility batches through larger clinical trial material, all on the same technology platform. By implementing spray drying technology at early stages, companies can create **enhanced-release formulations** of insoluble compounds that achieve blood levels needed for efficacy, while preserving the ability to scale that process as the project advances. Spray drying is particularly useful for compounds that are heat-sensitive/thermolabile (since it's a lower-temperature process than HME) or those requiring high drug loads in the dispersions. Overall, it is a versatile early-phase tool to rapidly **turn a poorly soluble API into an absorbable form**, de-risking molecules that would fail in a crystalline form.

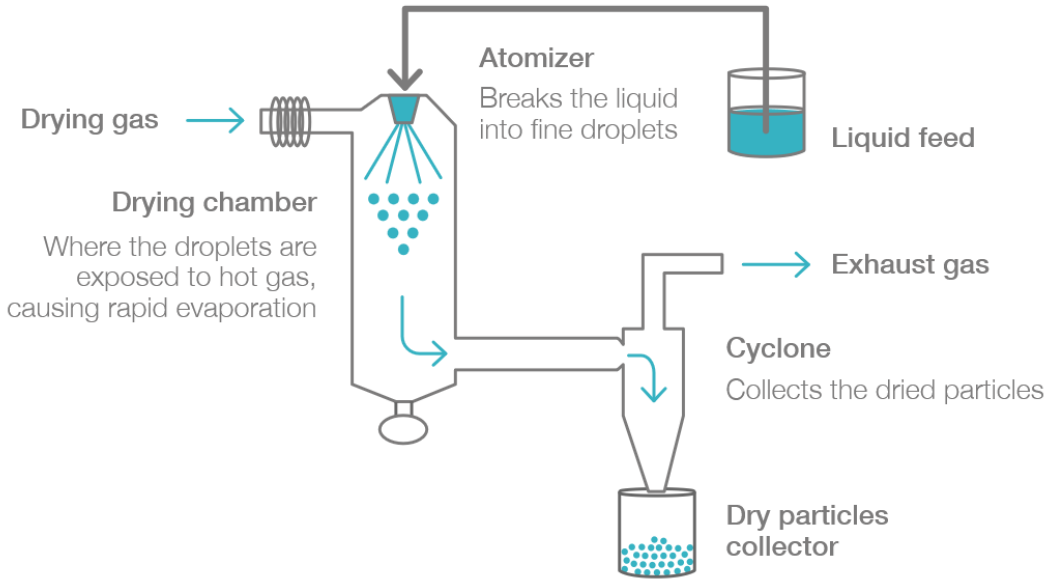


Figure 4 Spray Drying – Rapid Solvent-Based Dispersion

4.3 Lipid-Based Systems: Solubilizing "Grease Ball" Molecules in Formulation

Lipid-based formulation (LBF) approaches are the third pillar of enabling technologies, offering a solution especially well-matched to "grease ball" APIs, i.e. molecules that are **highly lipophilic** (high Log P) and **practically insoluble in water**. These compounds often dissolve readily in fats, oils, or surfactants, which lipid formulations leverage to keep the drug in a solubilized state. Common LBF strategies include self-emulsifying drug delivery systems (SEDDS/SMEDDS), microemulsions, and lipid solutions or suspensions encapsulated in softgel capsules.

The principle is that **the drug is pre-dissolved in an oily or surfactant medium**; upon ingestion, the formulation forms fine emulsified droplets in the gastrointestinal tract, preventing precipitation and improving contact with the absorptive membranes. This bypasses the slow dissolution step that limits bioavailability for crystalline drugs. Lipid systems can greatly increase the absorption of molecules with decent permeability but extremely low aqueous solubility, often achieving higher bioavailability than solid dispersions for very hydrophobic APIs. In addition, with adequate formulation, lipid-based formulations can also increase bioavailability of poorly permeable molecules and limit hepatic first pass by promoting lymphatic delivery. In early development, lipid-based formulations are attractive because they are fast to prototype (e.g. simply mixing API into various lipid vehicles to screen solubility and stability) and require minimal API for feasibility testing. A candidate that is not orally absorbable in a powder form might achieve excellent exposure when delivered in a lipid capsule, enabling **early proof-of-concept** in animal models or Phase I trials. LBF is also **highly flexible** in scaling: small bench-top mixers can prepare liquid-filled capsules for Phase I, and the same formulation can later be scaled to larger batch production or transitioned to fill-finish manufacturing with relatively straightforward process development.

The main considerations are ensuring the lipid excipients are safe and compatible, and that the drug remains dissolved under physiological conditions. When used appropriately, lipid-based technologies offer a powerful means to rescue compounds that would otherwise be undeliverable by conventional oral dosage forms.

4.4 Choosing the Right Technology Based on API Properties

Critically, the choice of enabling formulation should be guided by the API's characteristics, **not by whichever platform a development partner happens to prefer or have on hand**. Each technology has its sweet spot: for example, a very polar but poorly soluble "brick dust" might lean toward polymer-based amorphous dispersion (HME or spray dry), whereas an extremely lipophilic "grease ball" might be better served by a lipid-based matrix. Experienced teams use the API's solubility profile, permeability, dose, and solid-state behavior to decide the optimal route. This scientific selection is where an end-to-end CDMO like Aenova adds value. **Unlike niche providers limited to one technology, Aenova offers all three major bioavailability platforms in-house** (hot-melt extrusion, spray drying, and lipid formulation) and can therefore choose the best approach for the molecule rather than forcing a one-size-fits-all solution [5]. This breadth of capability, combined with an integrated development approach, means formulation scientists can remain **platform-agnostic** and focus on what will maximize the drug's performance.

Notably, all these technologies at Aenova are available from lab scale to clinical supply scale, with equipment trains designed for seamless scale-up. A molecule can be developed on the right technology from the start and later scaled up without disruptive tech transfers or process changes, avoiding delays and **de-risking the path to GMP manufacturing** [3]. Finally, efficient API-sparing prototyping methods support early decision-making: Aenova's teams can simulate and screen formulation options with minimal API (through mini-scale extruders, small spray dryers, solubility screenings, etc.), so that companies can rapidly assess feasibility of each approach before committing resources [5]. In summary, enabling technologies and formulation strategies should be viewed as a flexible toolkit guided by science – one that, when applied adeptly, allows even challenging drug candidates to advance into the clinic with an optimized chance of success.

5 PROCESS DEVELOPMENT AND GMP READINESS

Moving from a laboratory concept to a therapy for patients requires **early attention** to process development and Good Manufacturing Practice (GMP) readiness. Even during lead optimization or preclinical stages, teams must ask: **Can we make this compound consistently at larger scale if our trials succeed?** A phase-appropriate, scalable process is the backbone for reliable clinical trial material. By designing with the **end in mind**, small companies can avoid costly surprises later. In fact, deferring process planning is a common pitfall as late-stage scale-up problems or quality lapses can derail timelines. This chapter emphasizes building robust processes early and embedding GMP principles from day one to ensure a smooth path through clinical phases.

5.1 Plan for Scalability from Day One

Early process development is necessary for small or virtual pharma to prevent costly tech-transfer headaches later. Even in preclinical stages, teams must ask: **Can this candidate be made consistently at a larger scale if it succeeds?** A phase-appropriate process should be designed upfront that reliably produces clinical trial material and can expand 100-fold or more. This means establishing a robust API synthesis and solid form early, and developing the drug product process (e.g. mixing, granulation, encapsulation) with the end goal in mind. Aenova's early development approach explicitly builds **GMP process setup for initial clinical material** [1], ensuring that even first-in-human batches are made using reproducible methods. By investing in **bench-scale prototypes within GMP-compliant pilot facilities** [6], companies lay the groundwork for smooth scale-up as the program advances.

5.2 Use Scalable Platforms to Avoid Rework

A key strategy in early process development is choosing technologies and equipment that scale linearly from lab to commercial production. This avoids the common pitfall of having to reinvent or transfer the process mid-development. For example, Aenova offers state-of-the-art spray drying with **equipment from laboratory scale to full GMP production**, meaning a solubility-enhancing formulation developed on a lab spray dryer can be directly scaled up on analogous GMP equipment. Similarly, their hot-melt extrusion platform enables **seamless scalability from early formulation screening to GMP batches** [3]. By leveraging such continuity, small companies can develop processes on

day one that are already compatible with later phase manufacturing. This platform continuity **minimizes tech-transfer risks** and keeps critical know-how in one place as batch sizes grow [7]. The takeaway is clear: design your process with the Phase III vision even while in Phase I, using tools that won't force a change of course as demand increases.

5.3 Build GMP Readiness into Documentation and Quality

Process design alone is not enough – early investment in **documentation, analytical methods, and QA** is equally important for GMP readiness. Even early clinical materials are expected to meet GMP standards for consistency and quality. Therefore, teams should implement **phase-appropriate analytical method development, validation, and stability studies** during early development [1]. By generating data that aligns with regulatory expectations from the start, you avoid gaps that could trigger IND/IMPD delays. Aenova's regulatory and quality experts engage at the outset to **focus development on complete, relevant data sets required for approval**, preventing delays from missing information [8]. In practice, this means initial analytical methods are developed with eventual validation in mind and critical process parameters are documented thoroughly even at bench scale. Not only does this satisfy current Phase I needs, but it also smooths the path for later phases: there is less need to backtrack and "retro-fit" quality compliance because it was built in early. As Aenova's approach shows, involving QA and regulatory teams early **ensures all activities align with future submission requirements** [7], so that by the time you reach pivotal trials, your CMC package is on solid footing.

6 INTEGRATING PROCESS DESIGN AND QUALITY: THE AENOVA MODEL

The synergy of early process development with GMP readiness is exemplified in Aenova's integrated development model. Aenova deploys **dedicated early-phase project teams** (experienced formulation scientists, process engineers, analysts, and project managers) that shepherd a molecule from preclinical formulation through clinical manufacturing [1]. This "one team" approach ensures that knowledge is carried forward and that phase-appropriate documentation and workflows are in place at every step. In practice, Aenova tailors its ways of working to each project's needs, adjusting the level of documentation and formality to suit the development stage while still meeting compliance requirements. Crucially, the

continuity of equipment from lab to GMP scale in Aenova's facilities means that a process can be developed on bench-scale apparatus and then directly scaled up on analogous pilot-scale equipment with minimal modifications. This eliminates the friction of tech transfer between different platforms and reduces the risk of having to reinvent the process mid-development. It also supports a seamless transition to **clinical trial supply**, since the same infrastructure used for prototypes can manufacture clinical batches under GMP, and packaging/labeling is handled within the same organization [1]. By integrating development and GMP manufacturing under one roof, Aenova can rapidly advance programs: indeed, its coordinated approach enables support of multiple new products launches each year (on the order of ten) without compromising quality or timelines.

For a small or virtual pharma company, leveraging such an integrated model can be a game-changer. It means that from the earliest API and formulation work, the process is being "built for purpose", not only to solve a technical challenge, but to do so in a way that remains viable as the project grows. Late-stage scale-up failures, reformulations, or ad-hoc technology transfers between vendors are largely **avoided by design**. Instead, the focus can be on optimizing the process and product, confident that what works in the lab will be translated to the clinic. Moreover, as clinical phases progress, the documentation and quality systems are already maturing in parallel, smoothing interactions with regulators. The payoff for this rigorous early planning is a high probability of supplying **Phase I/II trials on schedule and with consistent product quality**, which in turn sets the stage for Phase III and commercialization with far fewer hurdles. In summary, investing in process development and GMP readiness early is an insurance policy for the molecule's future: it builds a scalable, quality-centric foundation that keeps the path to the clinic clear of avoidable obstacles and ensures the right development path leads all the way to successful outcomes.

7 RISK MITIGATION AND STRATEGIC PLANNING

No drug development program is without risk. The key is how proactively those risks are identified and managed. For resource-constrained startups and virtual pharma teams, **early risk assessment** is essential. We recommend conducting a CMC risk review at project outset to pinpoint potential pitfalls. Common early-stage CMC risks include:

Formulation failure or under-characterized formulations: the drug can't be made bioavailable, or the dosage form's performance is not well understood.

Stability issues: short shelf-life or degradation under normal conditions.

Scale-up difficulties: processes that work at bench scale may falter in larger batches.

Regulatory documentation gaps: missing or inadequate CMC data leading to delays or clinical holds.

Clinical supply disruptions: supply chain problems (such as reliance on a single API/excipient source) causing material shortages.

Each identified risk should have a corresponding mitigation plan. For example, if **API stability** is uncertain, initiate accelerated stability studies on prototype formulations early, discovering any show-stopping degradation well before first-in-human trials. Aenova's fast-track development program builds in **phase-appropriate analytical method validation and stability testing**, ensuring shelf-life issues are caught at the earliest phase [1]. If supply chain fragility is a concern (e.g. a single-source ingredient), a prudent strategy is to qualify multiple suppliers and establish **backup supply plans** so that clinical material isn't delayed by shortages. In short, early planning means thinking through "what could go wrong?" and taking steps up front to prevent it.

Beyond lab-based risks, **regulatory strategy** plays a critical role in mitigation. Many early-stage setbacks (including FDA clinical hold letters) stem from CMC documentation gaps or quality issues. Engaging regulatory experts early helps align the CMC plan with guidelines and avoid surprises. For instance, ensuring your stability studies and other data meet ICH requirements means the IND/IMPD package will be complete and acceptable [8]. By building quality into the process from day one (a **Quality by Design mindset**) and keeping meticulous

records, teams can avoid costly do-overs. It's wise to maintain a "living" CMC dossier even in early development, continuously compiling analytical results, formulations, and process information so that nothing important is lost. This phase-appropriate approach to quality and data integrity lays a solid foundation for later regulatory filings.

Another major challenge for small companies is the **knowledge gap and operational complexity** of CMC tasks outside the core expertise of a lean team. This is where the **right development partner** can dramatically reduce risk. Partnering with an integrated CDMO (Contract Development and Manufacturing Organization) offloads many technical and logistical risks to specialists. An end-to-end partner can manage formulation development, analytical testing, scale-up, clinical trial material manufacturing, and even regulatory filings as a one-stop solution. This minimizes hand-offs between different vendors as each tech transfer or communication gap is a risk in itself. For example, Aenova provides a **fast, API-sparing formulation screening program** alongside in-house process development, so scarce API material is used efficiently. All key formulation technologies are available under one roof, from lab scale through pilot plant, enabling scale-up on the same equipment and avoiding disruptive transfers [1]. Moreover, Aenova assigns a dedicated project team (scientists, analysts, project managers) to each program, ensuring real-time communication across disciplines and proactive issue resolution. This integrated "one team" approach means that activities like packaging and stability testing are coordinated, for instance, ensuring that clinical trial labels and expiry dates are backed by actual stability data. Critically, a full-service CDMO also brings **QA/RA** support and scenario planning: their regulatory affairs experts and quality assurance systems help navigate compliance, while their experience allows them to anticipate scale-up needs or supply bottlenecks in advance. The result is a de-risked development pathway where **logistics, quality, and timelines** are all managed in a holistic way. As Aenova notes, its end-to-end expertise in logistics, compliance, and GMP quality helps streamline the supply chain, reduce complexity, and keep trials on schedule [9]. In short, choosing the right partner is an effective risk mitigation strategy for startups: it provides access to breadth of expertise and infrastructure that would be hard to build alone, and it ensures nothing falls through the cracks.

Finally, effective risk management requires **continuous re-assessment and strategic planning** at each stage of development. Early CMC planning is not a one-and-done exercise, but an ongoing practice of updating the risk profile as new data emerges. Teams should formally revisit and update their risk mitigation plan at each major milestone or stage-gate. For example, after first-in-human Phase I studies, the CMC risks for Phase II (such as larger scale synthesis or longer stability requirements) should be re-evaluated and the mitigation

strategies adjusted accordingly. This structured reassessment ensures that new information, perhaps a stability trend observed, or a slight change in formulation performance, is fed back into the plan. It also reinforces contingency planning: if a new risk surface (say, an impurity appears during scale-up), the team already has a mindset of proactively addressing it rather than reacting in crisis mode. **Reliable data** is the compass for these decisions.

By basing strategy adjustments on solid analytical and manufacturing data, companies can make informed choices rather than guesses. In practice, this might mean expanding stability studies when unexpected degradants are seen or performing additional formulation optimization if bioavailability in Phase I was lower than predicted. The overarching message is one of flexibility and vigilance. By consciously managing risks and building contingency measures early, small companies can avoid common pitfalls that derail development, like having to repeat a study due to a CMC failure or running out of GMP material at a critical time.

In summary, a proactive risk-mitigation mindset paired with strategic planning is invaluable for emerging pharma teams. It allows even lean startups to **move confidently through development with fewer surprises**, knowing that they have anticipated challenges and put strong backup plans in place. With careful early planning, expert partnerships, and continuous risk-focused thinking, a small company can keep its molecule on the right development path and on schedule to reach patients, all while conserving precious time and resources. By treating risk management as a core discipline, just as important as the science itself,startup CMC leaders can greatly increase their odds of success in the journey from bench to clinic.

8 CONCLUSION

A strong early CMC strategy can make the difference between a molecule's swift advancement or its stagnation. This paper has illustrated what **"good" early CMC practice** looks like: it is **science-driven**, focusing on the critical attributes and experiments that truly matter for the molecule, and **fit-for-purpose**, meaning no more and no less than what is needed to achieve the next milestone. Robust early CMC work is also inherently **scalable and documented** and all development steps are well-documented to meet regulatory expectations. The end result of this disciplined approach is a program that is largely **de-risked** by first-in-human: with solid formulation performance, a reproducible process, and a CMC data package that can withstand investor or agency scrutiny. In short, early CMC done right is **lean but comprehensive** and every piece of work has a purpose and bolsters the path forward.

Another key theme is the power of **structured decision-making and integrated partnerships** in leveling the playing field for small companies. By implementing stage gates and clear go/no-go criteria, even a tiny team can ensure it "gets it right the first time" and doesn't waste precious time or material on missteps. Likewise, engaging in an end-to-end development partner (like Aenova) can give a virtual pharma access to capabilities it could never build alone. As an all-in-one CDMO, Aenova can take a program from early formulation through GMP manufacturing and clinical supply under one roof. This kind of partnership **streamlines handovers and retains knowledge** throughout development, translating to fewer delays and surprises. With a trusted, integrated team driving CMC, small companies dramatically improve their odds of meeting each milestone on time and on budget.

Conversely, neglecting the early CMC fundamentals often leads to painful consequences – reformulating or reworking processes mid-development, timeline slips, and sometimes even clinical holds or missed investor goals. The message is clear: **Now is the time to implement a structured CMC approach**, think beyond just Phase I, and choose partners who enable and not complicate your development path. By doing so, even the leanest biotech can confidently navigate from bench to clinic, turning a promising small molecule into a successful therapy.

9 MORE INFORMATION

[1] https://www.aenova-group.com/content/AENOVA_Aenovation-EarlyPhaseDev_One-Pager_2025.pdf

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