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Mixing Active Pharmaceutical Ingredients (APIs):

Process, Risks, Cleaning, and How PerMix Solves It

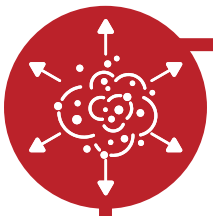
Why API Mixing Is Harder Than It "Should" Be

APIs behave like the universe's way of reminding humans that small things can be terrifying.

Most pharmaceutical blends combine:

- Micronized APIs (often cohesive, electrostatic, poorly flowing)
- Excipients (often larger, denser, free-flowing)
- Low inclusion rates (sometimes <1%, sometimes ppm-level with potent compounds)

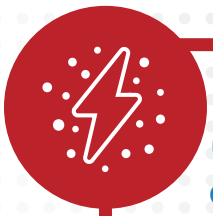
That combination triggers four classic failure mechanisms:



Segregation (the silent assassin)

Even if you achieve a great blend inside the mixer, segregation can happen:

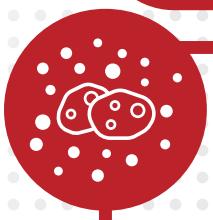
- During transfer (vacuum conveying, gravity drops)
- During discharge (funnel flow vs mass flow)
- During bin filling (particle percolation and air entrainment)
- During vibration (equipment, forklifts, packaging machines)



Electrostatics (powder cling + dose drift)

Static causes:

- API coating on walls, shafts, seals
- inconsistent discharge weights
- "hidden hold-up" that contaminates the next batch or steals yield



Agglomeration (fake uniformity)

Fine APIs can "look" blended while remaining as micro-clusters. Those clusters become content-uniformity failures when sampled.

Over-shear / under-shear (Goldilocks energy problem)

Too much energy: attrition, heat, PSD shift, possible polymorph risk for sensitive materials.

Too little energy: hot spots, agglomerates survive, CV doesn't converge.

The API Mixing Workflow (Done Properly)

Step 1

Raw Material Conditioning

Before mixing even begins, many plants:

- de-lump APIs (sieve or gentle deagglomeration)
- control humidity (static control + flow consistency)
- manage temperature (some APIs are moisture/heat sensitive)

PerMix approach: choosing mixer type and options based on whether the powder is cohesive, segregative, fragile, or abrasive—because "powder" is not one material. It's a behavior.

Step 2

Charging Strategy

How You Load Matters as Much as How You Mix

Bad charging causes immediate stratification:

- dumping API on top → it floats and smears
- adding API early into high-flow excipients → it gets buried and never disperses
- vacuum loading without controls → API fines deposit in lines and filters

Best-practice charging methods include:

- geometric dilution (API first blended into a "pre-blend" excipient fraction)
- split charging (API introduced in multiple additions)
- contained addition (isolator, glovebox interface, split butterfly valve)
- vacuum loading with dust-safe filtration and controlled inlet design

PerMix can support these strategies through inlet placement, loading accessories, and designs that reduce dead zones and deposition.

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Step

3

Mixing Phase

Particle Engagement, Not Just Bulk Circulation

This is the core truth: API uniformity requires particle-level interaction, not just moving a pile.

Why legacy mixers struggle

- **Ribbon mixers** are powerful but can create preferential flow paths and dead zones—especially with cohesive APIs.
- **Tumble blenders** are gentle but often slow and sensitive to fill level and PSD mismatch; liquid addition can be tricky.

How PerMix answers with the right mixing physics

Fluidized Zone Mixing

When the formulation tends to segregate or includes low-dose actives.

Instead of relying on gravity circulation alone, fluidized-zone designs keep the powder bed continuously reoriented. This helps:

- keep light and heavy fractions engaged
- reduce density-driven stratification
- break weak agglomerates gently
- converge CV faster and more reliably

Paddle / Plow Mixing with Intensification

When you need controlled shear + fast convergence.

For blends that need deagglomeration without overworking the entire batch, PerMix integrates:

- choppers / intensifiers positioned to target clusters
- adjustable speeds to dial energy input
- options for liquid dispersion where required

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Step 4

Liquid Addition (If Applicable)

The "Wet Spot" Trap

Some pharma processes require binders, granulation liquids, or functional coating solutions. The #1 mistake is adding liquid as a stream.

Proper liquid addition requires:

- atomization (fine droplets)
- correct nozzle placement (into active mixing zone, not a dead pocket)
- rate control (avoid overwetting and secondary agglomeration)
- synchronization (liquid addition + mixing energy profile)

PerMix designs can incorporate spray manifolds and control-friendly systems so "liquid addition" becomes engineered—not improvised.

Step 5

Discharge and Transfer

Where Great Blends Go to Die

Even perfect in-mixer uniformity can be destroyed by discharge.

Key discharge risks:

- ratholing and funnel flow
- segregation in downspouts
- sifting segregation during vibration
- product hold-up that contaminates the next batch

PerMix design focus:

- discharge geometry that supports consistent flow
- options that reduce hold-up zones
- cleaning-aware outlet designs (because discharge is also a cleaning hotspot)

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Validation, Sampling, and Why "It Looked Fine" Isn't a Spec

API mixing performance is measured with:

- content uniformity testing
- blend uniformity sampling plans
- CV targets (especially for low-dose actives)
- sometimes PAT tools (process analytical technology) depending on plant strategy

But equipment matters because:

- dead zones create hidden failure modes
- inconsistent hold-up breaks repeatability
- poor cleanability increases cross-contamination risk and downtime

Which brings us to the part most plants feel in their bones: cleaning.

Cleaning Pharmaceutical Mixers:
Wet CIP, Dry CIP, and Hybrid Strategies

Cleaning is not "maintenance." In GMP pharma, cleaning is a validated manufacturing step with compliance implications.

PerMix supports multiple cleaning philosophies depending on:

- product toxicity/potency
- solubility characteristics
- allergen/cross-contamination requirements
- available utilities (water, steam, air, vacuum)
- turnaround time expectations

Wet CIP (Clean-in-Place):

When You Need Washdown Certainty

Wet CIP uses water (often with detergent) delivered through spray devices to remove residues.

Where wet CIP shines

- sticky residues
- water-soluble products
- products that require sanitization
- facilities standardized on wash validation methods

What makes wet CIP succeed

Wet CIP is only as good as coverage + drainability. A "CIP system" that can't hit shadow areas is just a confidence machine.

PerMix CIP engineering typically focuses on:

- spray device placement and coverage of the full internal envelope
- cleaning access to shafts, seals, outlet, and intensifier housings
- drain design to prevent pooling
- surface finishes that reduce adhesion and speed rinse

Real-world constraints

Wet CIP consumes:

- water
- effluent handling capacity
- time for drying (which becomes a microbial/validation concern in some environments)

So wet CIP is powerful—but not always the fastest path back to production.

Dry CIP:

When Downtime and Utilities Matter

Dry CIP uses directed air (and/or vacuum-assisted) systems to dislodge and evacuate powder residues without water.

Where dry CIP shines

- dry powders that are non-sticky
- rapid product changeovers
- plants trying to reduce wastewater and downtime
- products that clump or degrade with moisture
- operations where "wet cleaning" creates drying bottlenecks

PerMix dry CIP advances (the practical version):

- strategically placed air nozzles to hit typical build-up zones
- air + vacuum logic to remove loosened fines rather than just re-suspending them
- designs that avoid "dust traps" and ledges

Dry CIP isn't just a blower. The trick is to move residues out of the machine, not into the air.

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Hybrid Cleaning (Dry + Wet):

The Fastest Path to Control

This is often the best of both worlds.

A hybrid strategy typically works like:

1. **Dry CIP** first to remove bulk powder hold-up quickly (reduces what wet CIP must dissolve)
2. **Wet CIP** second for final residue removal, sanitization, and validated endpoint
3. Optional drying/air purge to return the mixer to service faster

Benefits:

- less water usage than full wet CIP alone
- faster turnaround than wet-only cleaning
- reduced effluent load
- better control over residues that are partly soluble and partly adherent

In practice, hybrid cleaning can be a major productivity lever, especially in multi-SKU operations.

PerMix Easy-Clean Mixer Options

Designed for Reality

Even the best CIP system can't compensate for a mixer full of crevices.

Easy-Clean is about removing the places residue likes to hide:

- simplified internal geometry
- reduced ledges and shadow zones
- clean-friendly shaft and seal arrangements
- faster access to internal tools (intensifiers/choppers) depending on configuration
- surfaces and weld practices aimed at cleanability and repeatability

In a pharma setting, Easy-Clean design translates to:

- less manual intervention
- shorter cleaning cycles
- more reliable verification (visual + swab)
- reduced cross-contamination risk
- higher uptime and more predictable scheduling

Putting It Together:

How PerMix Answers the Full API Mixing + Cleaning Problem

Outcome targets:

- reliable low-dose homogeneity
- controlled energy input (no overworking)
- repeatable discharge behavior
- minimized hold-up and dusting
- cleanability engineered into the geometry
- CIP strategies aligned with your plant constraints (wet, dry, hybrid)
- reduced downtime between SKUs

Because the real KPI isn't "does it mix."

The KPI is validated batches per week, with minimal deviation risk, and fast, documented changeovers.

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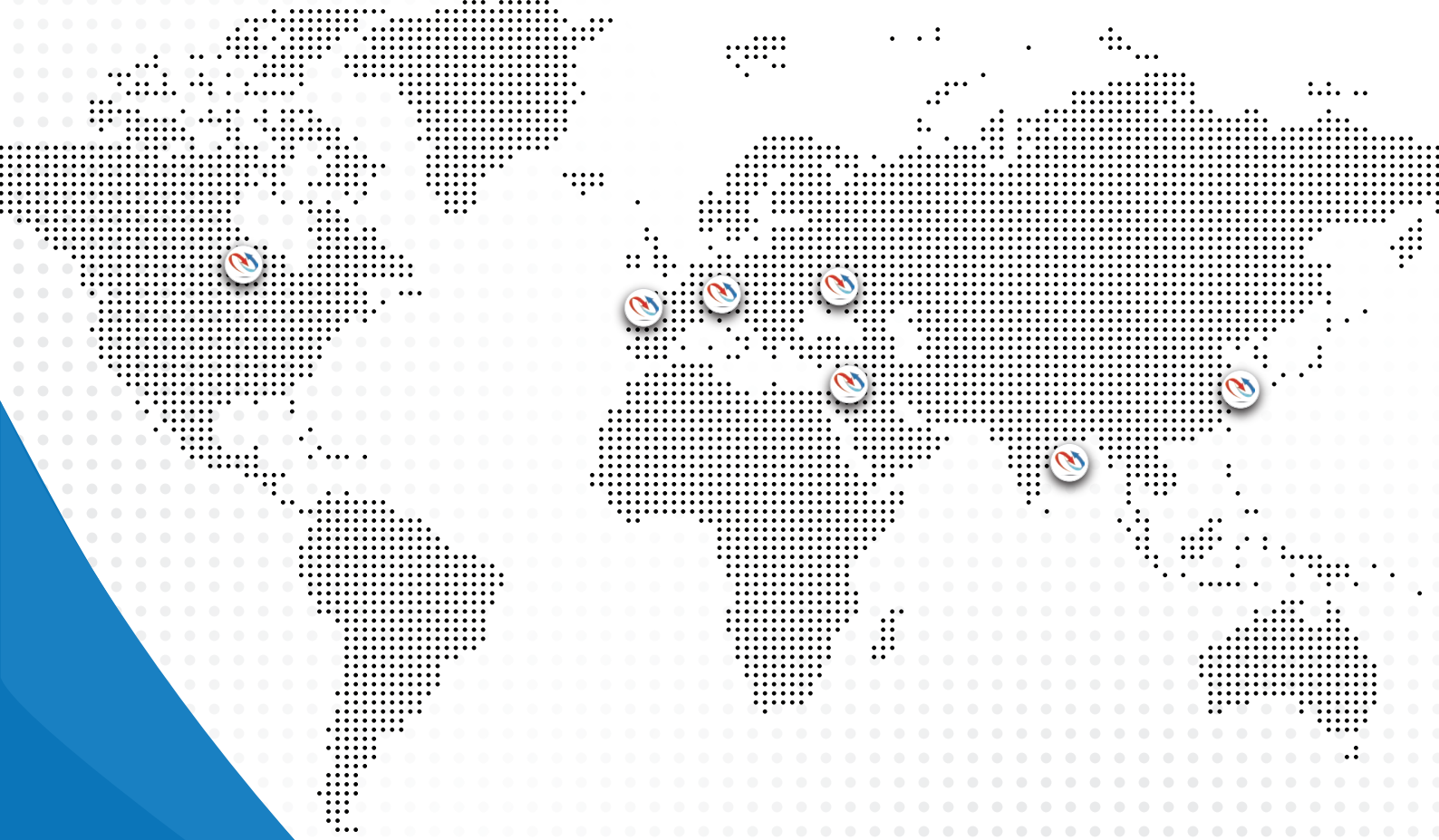

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