3 Technical Manual for Sulfolane Extraction in Pharmaceutical API Production Target Users

Global API manufacturers, fermentation antibiotic pharmaceutical factories, fine pharmaceutical intermediate workshops, pharmaceutical chemical procurement teams, FDA/EMA supplier auditors

Regulatory Basis

ICH Q3C (R9), China GMP 2010 Appendix 2, FDA 21CFR, EMA solvent recovery guidelines; 2026 mass production pharmaceutical grade standards

Core Chapters

1. Quality Control Baseline of Pharmaceutical Grade Sulfolane (ICH Q3C Compliance)
2. Core Extraction Separation Mechanism of Sulfolane for Heterocyclic & Antibiotic Molecules
3. Special Extraction Process for Heterocyclic Pharmaceutical Intermediates
4. Industrial Extraction Solution for Cephalosporin & Macrolide Fermentation Broth
5. Closed-Circuit Purification System for Pharmaceutical Solvent Recovery
6. Graded Resource Recovery & Harmless Treatment of Sulfolane Pharmaceutical Wastewater
7. Full GMP Standard for Storage, Transfer & Cleaning in Clean Workshops
8. Impurity Risk Analysis Linked to API Quality
9. API Factory Procurement Selection, Inventory & Annual Consumption Calculation Guide
10. Full Compliance Document List for Global Pharmaceutical Factory Audit

1 Quality Control Baseline of Pharmaceutical Grade Sulfolane
Sulfolane CAS:126-33-0, categorized as Class 2 solvent under ICH Q3C, PDE=1.6 mg/day, maximum residual limit in API finished product ≤160 ppm (0.016%).
Three Grade Classification for Procurement

Test Item	Industrial General Grade (Forbidden for API)	High-Purity Intermediate Grade	Antibiotic Extraction Special Grade	Test Method
Sulfolane Purity (GC)	≥99.50%	≥99.90%	≥99.95%	GC-FID
Water Content	≤50 ppm	≤20 ppm	≤10 ppm	Coulometric Karl Fischer
Color (APHA)	≤10	≤5	≤3	Platinum-Cobalt Colorimetry
Free Acidity (H_2SO_4)	≤0.001%	≤0.0005%	≤0.0002%	Acid-Base Titration
Single Metal Ion (Na/Fe/Ca/Cu)	≤10 ppb	≤5 ppb	≤1 ppb	High-Resolution ICP-MS
Total Heavy Metal	≤30 ppb	≤12 ppb	≤5 ppb	ICP-MS
Low-Boiling Mercaptan/Butadiene Impurity	≤100 ppm	≤30 ppm	≤5 ppm	GC-MS
High-Boiling Polymer Tar	≤50 ppm	≤15 ppm	≤3 ppm	Residue Test
Peroxide	≤10 ppm	≤3 ppm	≤0.5 ppm	Iodometric Titration
Chloride Ion (Cl^-)	≤5 ppm	≤1 ppm	≤0.1 ppm	Ion Chromatography
Microbial Limit	No Control	≤10 CFU/g	≤5 CFU/g	Membrane Filtration

Test Item	Industrial General Grade (Forbidden for API)	High-Purity Intermediate Grade	Antibiotic Extraction Special Grade	Test Method
Particles (≥0.2μm)	No Control	≤50 pcs/mL	≤10 pcs/mL	Liquid Particle Counter

Mandatory Procurement Red Line

Industrial grade sulfolane is strictly prohibited for API and antibiotic extraction. Excessive metal and acidic impurities generate unknown API impurities and trigger direct process non-compliance during FDA/EMA inspection.

2 Core Extraction Separation Mechanism of Sulfolane in Pharmaceutical Applications

Sulfolane dielectric constant: 43.3, strong polar aprotic solvent with exclusive solubility for heterocyclic and antibiotic molecules containing N/S/O heteroatoms. Four major advantages over ethyl acetate and dichloromethane:

1. High selectivity for heterocycles & antibiotics: Prioritizes dissolution of pyridine, thiophene, cephalosporin nucleus and macrolide lactone ring, barely dissolves sugar, protein and inorganic salt; emulsion entrainment ratio <0.05%, minimizing API yield loss
2. Wide thermal stability window for low-temperature pharmaceutical separation: Stable below 230°C; solvent desorption under vacuum at ≤170°C avoids thermal degradation of heat-sensitive antibiotics such as erythromycin and cephalosporin C
3. Controllable water miscibility, simple back-extraction: Salting-out via NaCl/$(NH_4)_2SO_4$ achieves fast phase separation; single-stage distribution coefficient K>12, cutting single solvent dosage by 40% and extraction stages
4. Low volatility, GMP & explosion-proof friendly workshop: Far lower VOC emission than halogenated solvents, non-hazardous cargo without dedicated explosion-proof warehouse to reduce workshop renovation cost

Applicable Pharmaceutical Molecules

1. Heterocyclic intermediates: Pyridine, thiophene, pyrrole, imidazole, triazole, indole, quinoline, pyrimidine
2. Fermentation antibiotics: Cephalosporin C, 7-ACA, erythromycin, azithromycin, clarithromycin, tetracyclines

3. High-polar synthetic APIs: Sulfonamides, sartans, pyrrole hypoglycemic drugs, antifungal heterocyclic APIs

3 Special Continuous Countercurrent Centrifugal Extraction Process for Heterocyclic Intermediates

Applicable to separation of heterocyclic products from alkanes and low-carbon alcohols in synthetic mother liquor, four units: pre-treatment → multi-stage countercurrent extraction → water washing desalination → vacuum solvent removal.

3.1 Pre-Treatment Unit

0.5μm PTFE precision filtration of synthetic mother liquor to remove catalyst solid and polymer residue; saturated ammonium sulfate salting-out solution added to reduce sulfolane-water miscibility and improve phase separation; full nitrogen blanketing to avoid solvent oxidation and acid generation.

3.2 Three-Stage Countercurrent Centrifugal Extraction (LXC Centrifugal Extractor)

1. Operating parameters: 40–55°C, organic/aqueous phase ratio 1:3~1:5, residence time 90–120 s
2. Material flow: Aqueous mother liquor fed to stage 1, fresh pharmaceutical grade sulfolane fed countercurrently to stage 3
3. Two outlet streams
    - Aqueous raffinate: Inorganic salt & low-carbon alcohol, sent to wastewater treatment system
    - Rich solvent phase: Sulfolane + high-purity heterocycle, sent to water washing desalination unit
4. Separation performance: Heterocycle extraction yield ≥98.5%, alkane removal rate 99%, eliminating repeated recrystallization pre-purification

3.3 Water Washing Desalination Unit

Two-stage countercurrent pure water washing to remove entrained Na^+, Ca^{2+} and Cl^- from rich solvent; all washing water collected for centralized solvent recovery.

3.4 Vacuum Solvent Removal Unit

Rich solvent fed to vacuum stripper under -50 kPa, kettle temp ≤170°C; heterocycle crude product distilled overhead for subsequent crystallization refining; sulfolane discharged from tower bottom and sent to GMP solvent regeneration unit.

4 Industrial Extraction Solution for Cephalosporin & Macrolide Fermentation Broth

Fermentation broth contains mycelium, protein, polysaccharide and target antibiotics; traditional ester extraction causes severe emulsion and titer loss, sulfolane salting-out extraction validated for mass production by multiple cephalosporin API manufacturers.

4.1 Fermentation Broth Pre-Treatment

1. Plate & frame filter press to remove mycelium and clarify filtrate
2. pH adjusted to 5.0–6.5 (antibiotic stable range), 25% ammonium sulfate salting-out solution added to break protein emulsion system

4.2 Two-Stage Countercurrent Extraction for Cephalosporin C

1. Extraction temperature 30–40°C (high temperature triggers β-lactam ring cleavage)
2. Solvent ratio sulfolane:fermentation filtrate = 1:4, two-stage countercurrent
3. Separation effect: Cephalosporin C titer recovery ≥97%, protein & polysaccharide fully retained in aqueous phase
4. Back-extraction purification: Low-pH phosphate buffer added to transfer antibiotics back to aqueous phase, separating sulfolane for regeneration to simplify subsequent 7-ACA cleavage process

4.3 Differentiated Parameters for Erythromycin & Azithromycin

Lower polarity of macrolide lactone ring, solvent ratio adjusted to 1:2.5, extraction pH 7.0–7.8; vacuum of stripper increased to -60 kPa with kettle temp ≤165°C to avoid lactone hydrolysis.

4.4 Core Extraction Quality Control Points

1. Full light shielding, sulfolane accelerates oxidation & sulfonic acid generation under strong light
2. Full nitrogen blanketing, system dissolved oxygen <0.1 ppm
3. Rich solvent pH tested every 2 hours; fully activate ion exchange unit and increase MEA dosing once pH <6.5

5 Closed-Circuit Purification System for GMP-Compliant Solvent Regeneration

Per GMP Appendix 2 Clause 38 for APIs: Standardized regeneration SOP, full-index testing and complete traceability records mandatory for recycled solvent before reuse.

5.1 Two Parallel Regeneration Modes

5.1.1 Continuous On-Line Ion Exchange Light Purification (Non-Stop Daily Operation)

1. 3%~5% circulating solvent continuously passes through composite dual resin tower (cation resin for metal removal, strong base anion resin for sulfonate neutralization)
2. Operating parameters: 40–60°C, space velocity 2 h^{-1}; resin regenerated with dilute alkali every 7 days
3. Control target: Solvent pH stabilized 6.8~7.5, single metal ≤2 ppb, deep regeneration cycle extended to 30 days

5.1.2 Two-Stage High-Vacuum Deep Distillation Regeneration (Monthly Batch Purification)

Activated only when color >5 APHA, excessive acidity or total metal >3 ppb, all EP electropolished 316L equipment without carbon steel metal dissolution risk

1. Stage 1 light removal tower: Vacuum 4 kPa, kettle temp 160°C to remove water and low-molecular antibiotic degradation products
2. Stage 2 heavy removal tower: Vacuum 2 kPa, kettle temp 170°C, side draw of purified pharmaceutical grade sulfolane; tar & metal salt residue discharged from tower bottom for hazardous waste disposal
3. Regenerated solvent must pass full-index testing and issue independent COA before recycle to extraction section

5.2 Mandatory GMP Reuse Compliance Requirements

1. Complete solvent recovery validation report covering three consecutive batches to confirm no new API impurities introduced
2. Fresh/recycled solvent mixing ratio ≤1:3, full testing record retained for mixed batches
3. Cross-variety reuse prohibited (cephalosporin solvent cannot be used for heterocycle extraction to avoid cross-contamination impurities)
4. Maximum regeneration times per single solvent batch: ≤8 times; fully disposed as hazardous waste after exceeding limit to prevent cumulative trace impurities

6 Graded Resource Recovery & Harmless Treatment of Pharmaceutical Sulfolane Wastewater

Three categories of pharmaceutical waste liquid treated separately for solvent recovery, compliance and procurement cost reduction.

6.1 Grade 1 High-Concentration Washing Wastewater (Sulfolane 5–15 wt%) – Extraction-Distillation Coupling Recovery

1. Multi-stage dichloromethane extraction of sulfolane from wastewater, separate organic phase

2. Vacuum distillation to separate dichloromethane and sulfolane, recovered solvent purity ≥99.9% for recycle to regeneration unit, recovery rate ≥99.95%
3. Wastewater after distillation with sulfolane residue ≤35 mg/L sent to biochemical treatment

6.2 Grade 2 Low-Concentration Raffinate Wastewater (Sulfolane <1000 ppm) – Anaerobic + Aerobic Biochemical Treatment

1. Pre-treatment via water stripper to remove trace sulfolane for recovery
2. Combined anaerobic-aerobic biochemical process with COD removal rate >92%
3. Activated carbon terminal adsorption, discharged wastewater sulfolane <10 ppm meeting domestic & EU industrial discharge standards

6.3 Grade 3 Regeneration Tower Tar Residue (Hazardous Waste) – Harmless Incineration

1. Closed storage under nitrogen blanketing to prevent odor volatilization
2. Incineration by qualified pharmaceutical hazardous waste contractor with flue gas desulfurization to absorb SO_2
3. Complete hazardous waste transfer document filing for FDA & environmental inspection traceability

Environmental Cost-Reduction Benefit

Wastewater resource recovery cuts fresh sulfolane annual procurement by 25%~35% and reduces hazardous waste disposal cost, complying with EU CBAM carbon emission control.

7 Full GMP Standard for Workshop Use, Storage, Transfer & Equipment Cleaning Validation

7.1 Workshop Zone Classification Control

1. Solvent storage & regeneration area: Grade D clean pharmaceutical workshop
2. Extraction & water washing section: Grade C clean area
3. Finished solvent removal & crystallization (sterile API): Grade A/B isolated area with independent sulfolane pipeline to avoid cross-contamination

7.2 GMP Storage Specifications

1. Independent PTFE-lined electropolished 316L storage tank, mixing with other solvents forbidden
2. Storage temperature 20–30°C, 35°C warm water heat tracing to prevent crystallization (solidification point 26°C)

3. Continuous high-purity nitrogen blanketing (99.999%, dew point ≤-70°C), molecular sieve drying cylinder on breathing valve
4. Physical isolation of fresh solvent tank, qualified recycled solvent tank and unprocessed waste solvent tank with clear labeling

7.3 Material Transfer & Pipeline Material Standards

1. EP 316L pipeline, PTFE-lined diaphragm pump & PTFE ball valve; carbon steel and ordinary rubber forbidden
2. FFKM full fluorine gaskets without plasticizer dissolution risk
3. Pipeline design without dead leg, gradient slope for full drainage
4. Fully closed pipeline transfer, open drum transfer prohibited to reduce VOC and microbial contamination

7.4 GMP Equipment Cleaning Validation Protocol

Cleaning Medium

Purified water + dilute ethanol segmented washing, final nitrogen purge & drying

Acceptance Criteria for Swab Sampling

1. Sulfolane residue ≤10 μg/cm²
2. Total metal ion ≤1 ppb
3. Microbial limit ≤5 CFU/cm²
4. No preceding API residue detected via HPLC

Cleaning Cycle

Intermediate cleaning after every 5 consecutive batches for single-variety production; full cleaning plus three blank batches validation before variety switch with complete cleaning report retained

7.5 Personnel GMP Control

1. Anti-static clean suit, FFKM solvent-resistant gloves & chemical goggles for solvent contact positions
2. No eating, drinking or smoking in workshop with local exhaust ventilation
3. Specialized training on ICH residual solvent limit, solvent regeneration SOP and waste liquid emergency disposal with assessment records retained

8 Impurity Risk Analysis Linked to API Quality

8.1 Excessive Metal Ion Risk

Na/Fe/Cu >5 ppb coordinate with heterocycle & antibiotic nucleus to generate unknown heavy metal impurities, exceeding API related substance limits leading to finished product rework or scrapping during ICH/FDA inspection

Control: Procure pharmaceutical grade solvent with single metal ≤1 ppb, full ion exchange regeneration, EP polished storage & pipeline system

8.2 Excessive Water Risk (>20 ppm)

1. Hydrolysis of cephalosporin β-lactam ring, titer decline and excessive related substances
2. Hydrolysis side reaction of heterocyclic intermediates, yield drop >10%
   Control: Purchase solvent water ≤10 ppm, full nitrogen blanketing storage, deep dehydration via regeneration tower

8.3 Acidic Degradation Product Risk (Sulfonic Acid, Sulfuric Acid)

Oxidation & overheating of sulfolane generates acid to lower system pH, destroy heat-sensitive drug structures and accelerate pipeline corrosion with metal dissolution cycle

Control: Full oxygen isolation, ion exchange continuous neutralization, regeneration kettle temp capped at 170°C

8.4 Residual Solvent Compliance Risk

Sulfolane residual >160 ppm in finished API violates ICH Q3C limit and blocks domestic & overseas drug registration

Process control: Extended vacuum holding time of solvent stripper, terminal activated carbon adsorption; purchase low-impurity pharmaceutical grade solvent to reduce stripping load

9 API Factory Procurement Selection, Inventory & Annual Consumption Calculation Guide

9.1 Procurement Grade Selection by Production Line

1. Cephalosporin/Erythromycin fermentation line: Antibiotic special pharmaceutical grade (single metal ≤1 ppb, water ≤10 ppm), PTFE-lined IBC bulk supply with long-term fixed-price contract
2. Heterocycle fine intermediate line: High-purity pharmaceutical grade (metal ≤5 ppb) for cost balance
3. Lab pilot & small trial: 200 L clean drum packaging of pharmaceutical grade for flexible small-batch supply

9.2 GMP Safety Inventory Standard

- Stable regular production: 1-month total circulating solvent volume
- Annual overhaul & overseas long shipping cycle (Japan/Korea/Europe/America): Increase to 1.5-month buffer inventory
- Predicted global solvent shortage in 2027: Reserve 2-month inventory to avoid production shutdown

9.3 Annual Fresh Solvent Procurement Calculation Formula

Annual fresh procurement = Annual feedstock processing volume × Unit loss benchmark − Waste solvent recovery volume

Loss benchmark explanation: 0.07~0.09 kg/t feed with full regeneration & wastewater recovery; 0.18~0.22 kg/t feed without recovery system

9.4 Mandatory Supplier Qualification Checklist for Bidding

1. CNAS/CMA full-index testing qualification for pharmaceutical grade sulfolane
2. REACH/TSCA/K-REACH global chemical registration certificate
3. ISO9001/14001/45001 & ISO17025 lab certification
4. Self-owned two-stage vacuum distillation production line & clean filling workshop certificate
5. ICH Q3C impurity spectrum & microbial limit test report
6. Supporting solvent regeneration process validation documents for pharmaceutical factory audit

10 Full Compliance Document List for Global Pharmaceutical Factory Audit

Basic Documents Attached to Each Batch

1. Chinese & English TDS exclusive for pharmaceutical grade sulfolane
2. Full-index batch COA with CNAS lab seal (ICP metal, water, microbial limit & impurity spectrum included)
3. 16-Chapter GHS English SDS (ICH/EU/North America customs compliant)
4. Original pharmaceutical grade compliance letter
5. PTFE drum/IBC packaging material dissolution test report

Extra Documents for FDA/EMA European & American Pharmaceutical Clients

1. REACH registration, EU OR authorization & DoC compliance statement
2. Complete ICH Q3C Class 2 solvent PDE toxicology report
3. Distillation PFD & clean workshop ISO certification
4. Supplier impurity spectrum research & full-process metal control document
5. Solvent recovery validation template for pharmaceutical factory process verification

Extra Documents for Japan & South Korea API Factories

1. Bilingual Japanese SDS, K-REACH registration copy
2. Raw ICP-MS metal spectrum per batch
3. Nitrogen purity test report of clean filling workshop

GMP Supporting Technical Documents Delivered with Manual

1. Sulfolane extraction Aspen Plus simulation parameters

2. Standardized solvent regeneration SOP template
3. Equipment cleaning validation swab sampling limit standard
4. Wastewater resource recovery process flow chart
5. Annual solvent consumption calculation Excel template

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4 Technical Solution for Sulfolane-Based Acid Gas Sweetening & Purification

Target Users

Natural gas processing plants, coal chemical syngas facilities, gas field procurement buyers from the Middle East & Central Asia, petrochemical trading groups

Application Scope

High-sulfur natural gas, coal chemical crude syngas containing H_2S, CO_2, COS, methyl mercaptan and dimethyl sulfide; covers sulfolane-amine composite system comparison, absorption efficiency test data, low-temperature operating parameters, solvent regeneration and procurement budgeting

Catalog

1 Core Process Principle of Sulfolane-Amine Synergistic Absorption

Sulfolane is a strong polar physical solvent compounded with alkanolamine (MDEA/DIPA) to form mixed sweetening liquid with dual absorption advantages:

1. Low partial pressure (<0.1 MPa acid gas): MDEA chemical reaction dominates for deep H_2S removal to meet pipeline standard 6 mg/m³