Full Compliance Manual for Vitamin B12　Global Pharmacopoeia & Regulatory Standards from HiSiaddi

Complete collation of 7 major categories with official original links, core standard key points, PDF access channels, foreign trade/pharmaceutical application scenarios, customs clearance & registration requirements

Unified Basic Information

Common Name: Vitamin B12; Chemical Name: Cyanocobalamin; EC Number: 200-680-0; Molecular Formula; Molecular Weight: 1355.37

1. USP-NF Cyanocobalamin – United States Pharmacopoeia Monograph (Mandatory Standard for Pharmaceuticals & Dietary Supplements)

Official Documents & PDF Access

- Current Edition: USP 49-NF44 Monograph Cyanocobalamin (updated with 2026 revision bulletin)
- Official DOI Source Page: https://doi.usp.org/USPNF/USPNF_M20750_03_01USP
- Free Preview PDF: https://trungtamthuoc.com/pdf/cyanocobalamin-usp-2025.pdf
- Revision Bulletin PDF: https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/revisions/cyanocobalamin_rb_notice.pdf

Core Mandatory USP Specifications

1. Assay (dry basis): 96.0% ~ 102.0%
2. UV Identification: A361/A278=1.70~1.90; A361/A550=3.15~3.40
3. Loss on Drying ≤12.0%; Residue on Ignition ≤0.1%
4. HPLC Related Substances: Total impurities ≤3.0%, single unknown impurity ≤0.2%
5. Heavy Metals: Pb≤10ppm, As≤3ppm, Cd≤1ppm, Hg≤1ppm

Application Scenarios

Exports of US API, dietary supplements, oral/injectable formulations; USP-version COA + TDS mandatory for client customs clearance

2. Ph.Eur / EP Cyanocobalamin European Pharmacopoeia Monograph 0547

Official Documents & PDF

- Monograph No.: Ph.Eur. 11th Ed Monograph 0547 (universal for EU pharmaceutical manufacturers)
- Historical Version PDF (Full EP6.0): http://www.uspbpep.com/ep60/cyanocobalamin%200547e.pdf

- EP Reference Standard CRS: LGC Official Cyanocobalamin CRS (EPC3000000)

Key EP Clauses Differentiated from USP

1. Clearly classified impurities with separate limits for Impurity A/B/C
2. Mandatory HPLC chromatogram of related substances as core review basis for CEP certificates
3. Stricter microbial limits suitable for injectable grade API
4. Storage requirement: Hermetically sealed at 2–8°C away from light with full nitrogen protection

EU Applicability

EU pharmaceutical API registration, CEP certificate filing, EP-standard COA mandatory for European pharmaceutical factory procurement

3. FCC Food Chemicals Codex – Food-Grade Vitamin B12 Standard

Compliance Basis

- Current Latest Version: FCC 12; FDA 21CFR 184.1945 directly cites FCC specifications as GRAS judgment criteria
- Access Channel: Full paid PDF available on US National Academy of Sciences (NAS) official website; summary FCC version usable for customs & foreign trade

Core FCC Food-Grade Specifications (Distinguished from Pharmacopoeia)

1. Simplified impurity requirements without precise HPLC single impurity control
2. Microbiological indicators: Total aerobic count ≤100 CFU/g, all pathogenic bacteria negative
3. Heavy metal limits aligned with food contact safety standards
4. No endotoxin or sterility requirements for injectable grades

Application Scenarios

Food additives, health supplement raw materials, beverages, meal replacements, infant complementary food exports to the US / Canada

4. EFSA EU Feed Additive Safety Assessment Report (Feed Additive Use)

Official Authoritative Downloadable PDF Reports

1. Universal species assessment for fermentation strain Ensifer adhaerens CGMCC 21299 (2024)
   DOI: https://doi.org/10.2903/j.efsa.2024.8752
   Direct PDF Link: https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2024.8752

2. Assessment for Strain CGMCC 19596 (2023)
   PDF Link:
   https://pmc.ncbi.nlm.nih.gov/articles/PMC10118293/pdf/EFS2-21-e07972.pdf

Core EFSA Conclusions (Key for Feed Compliance)

1. Cyanocobalamin is safe for all livestock and aquatic animals with no maximum authorized addition limit
2. Production strains contain no viable bacteria or residual DNA with no GMO risks
3. Dust poses mild respiratory sensitization risk, which must be labeled in SDS
4. Regulatory compliance basis: EC 1831/2003 (EU Feed Additive Regulation), EC 429/2008 Implementing Rules

Export Application

EFSA safety assessment report copy mandatory for customs clearance for EU feed mills and premix manufacturers

5. FDA 21CFR 184.1945 GRAS Compliance Statement (US Food Market Access)

Official Regulatory Full-Text PDF

21 CFR Title21 Part184 Full PDF: https://www.govinfo.gov/content/pkg/CFR-2024-title21-vol3/pdf/CFR-2024-title21-vol3-sec184-1950.pdf

Core Clause Translation

1. §184.1945 Vitamin B12 (Cyanocobalamin, CAS 68-19-9) produced via microbial fermentation
2. Products must meet FCC food-grade specifications to be recognized as GRAS (Generally Recognized As Safe)
3. Scope of use: Nutritional fortifiers, dietary supplements, infant formula milk powder
4. Dosage only restricted by GMP (Good Manufacturing Practice) with no mandatory upper limit
5. No historical ban or restriction, directly applicable for food production within the United States

Supporting Compliance Documents Required

US food exports must provide: 21CFR screenshot + FCC TDS + English COA + GRAS statement

6. CEP/COS Certificate Explanation & US DMF Drug Master File Interpretation (For Major Pharmaceutical Clients Only)

6.1 CEP / COS Certificate of Suitability (EU API Market Access)

1. Definition: Certificate of Suitability issued by EDQM to verify cyanocobalamin complies with EP 0547 monograph
2. Applicability: API sales to EU pharmaceutical factories, finished drug marketing authorization filing
3. Valid existing CEP case for Vitamin B12: R1-CEP 1998-140 Rev05 (Bulk API registration)
4. Dossier Composition: Full production process, impurity research, stability data, validation documents, batch COA complete set
5. Function: EU customs and pharmaceutical factories exempt from full re-testing for rapid clearance

6.2 US DMF US Drug Master File (Type II API Category)

1. Classification: Type II DMF (API Master File), confidential technical dossier filed with FDA
2. Public Vitamin B12 Case: DMF No.4095 (Active and Valid)
3. DMF Contained Content:

- Full fermentation/synthetic process, impurity profile, analytical method validation, stability testing, quality control specifications
- Plant GMP audit, contamination control, residual solvents, full heavy metal data

1. Commercial Value: US finished drug clients may directly reference the manufacturer’s DMF when filing ANDA generic drug applications, drastically shortening declaration cycles
2. Delivery: Only accessible to major pharmaceutical clients with signed non-disclosure agreements; full dossier cannot be circulated externally

6.3 Comparison Table: CEP vs DMF

Document	Issuing Authority	Applicable Region	Core Purpose
CEP/COS	EDQM (European Directorate for the Quality of Medicines)	EU / EEA	API factory incoming inspection, finished drug registration

Document	Issuing Authority	Applicable Region	Core Purpose
US DMF	FDA (U.S. Food and Drug Administration)	United States, Puerto Rico	ANDA generic drug filing, injectable API market access

7. REACH Annex VI Vitamin B12 Registration Dossier Abbreviated Version (Mandatory for EU Importers)

Basic REACH Determination (CAS 68-19-9 EC 200-680-0)

1. Substance Classification: Organic cobalt vitamin, non-hazardous substance with no GHS hazard classification
2. Registration Threshold Rules:

- Annual import volume <1 ton/year: Exempt from main REACH registration, only simple importer notification required
- Annual import volume ≥1 ton: Complete REACH substance registration with full dossier submission mandatory

1. Annex VI: REACH regulatory substance inventory recording official CAS/EC numbers, nomenclature and hazard classification for cyanocobalamin

Mandatory Modules of Abbreviated REACH Dossier (Customs Clearance Documents for Importers)

1. Substance Identity: CAS, EC, structural formula, purity, impurity composition
2. Physicochemical data (reused from EP/USP standards)
3. Toxicology summary (LD50＞5000mg/kg, practically non-toxic)
4. Exposure assessment: Extremely low release volume for food/feed/pharmaceutical applications with no environmental risks
5. SDS (16-section REACH-standard English safety data sheet)
6. Exemption / registration certificate, tonnage declaration form

Key Compliance Reminder

Vitamin B12 contains no SVHC Substances of Very High Concern and is not listed on the REACH restricted substances list; dust generation during operation is the sole operational risk

Supplementary Domestic General Regulations (Export Auxiliary Materials)

1. GB 30613-2014 Food Additive Cyanocobalamin (Vitamin B12)
2. Chinese Pharmacopoeia CP 2025 Cyanocobalamin API Monograph

3. GB 7300 Feed Additive Vitamin B12 Specification Standard

Document Matching Suggestions by Market

1. US Food / Health Supplements: FCC TDS + 21CFR184.1945 + English COA + SDS
2. US Pharmaceutical Clients: USP Monograph + Type II DMF Materials + USP COA
3. EU Pharmaceutical Market: EP0547 + CEP Certificate + REACH SDS
4. EU Feed Market: EFSA Safety Assessment Report + Abbreviated REACH Dossier
5. Global General Customs Clearance: Basic three-document set TDS+SDS+COA, supplemented with regional regulatory attachments