GUIDEGXP SERIES · PHARMA ENGINEERING

OPERATIONAL GUIDE

CLEANING, CIP & SIP

SYSTEMS IN GMP

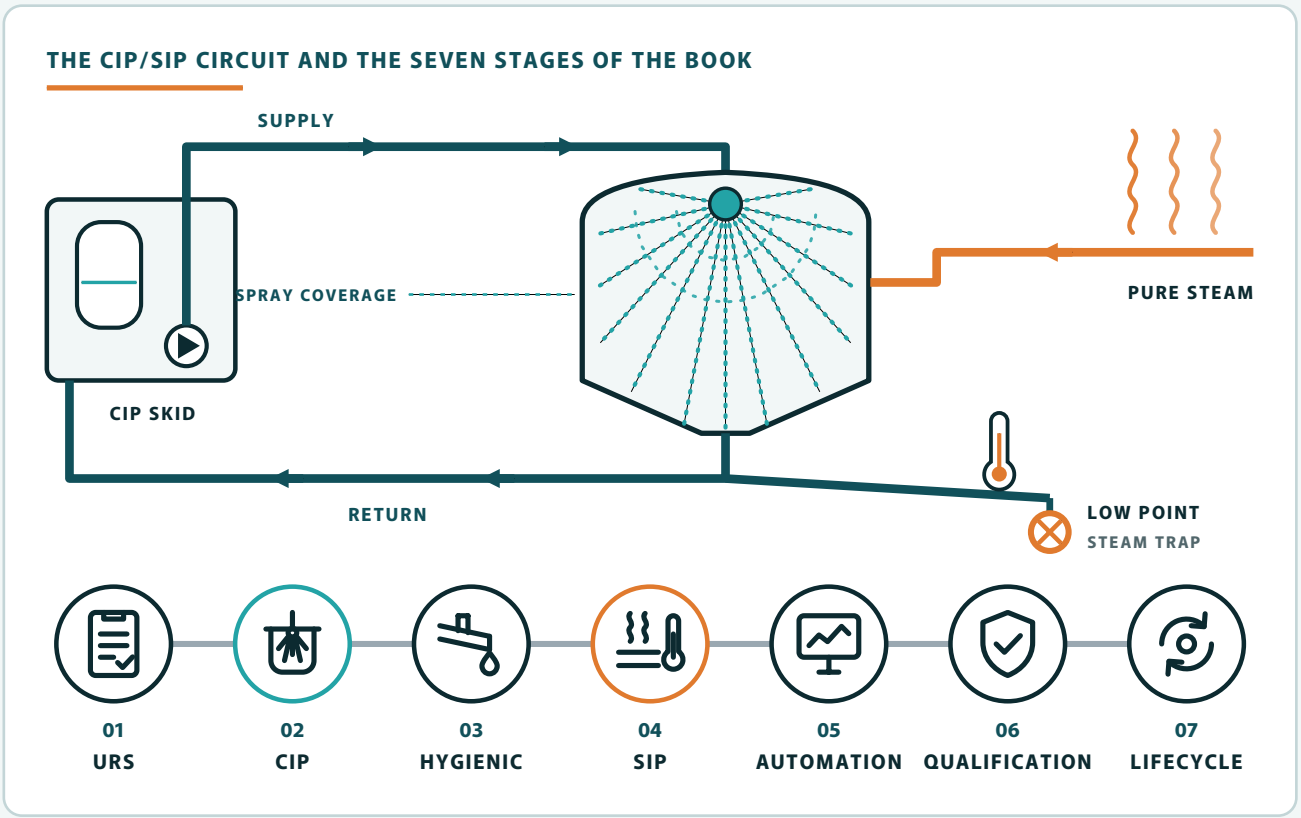
Requirements, Hygienic Design, Steam-in-Place, Automation, Qualification and Lifecycle Control

285 PAGES · PDF A4 · 24 WORD + EXCEL TOOLS · ENG EDITION

FROM THE URS TO A SYSTEM UNDER LIFECYCLE CONTROL

FIRST EDITION · OCTOBER 2026 · V1.0 · CUT-OFF 01/10/2026

FREE SAMPLE



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About this guide

The guide supports those who specify, design, qualify and govern the cleaning, CIP and SIP systems of a pharmaceutical or biotech company — CIP skids and circuits, spray devices, sterile boundaries and SIP cycles, recipes, instrumentation and data — from the URS to the evidence that holds up in an inspection. For every point it says which text governs it, with what force and in which jurisdiction, which value it gives (or does not give) and of what nature, what the company has to decide and where the decision is recorded. No universal values: velocities, slopes, L/d ratios, temperatures, times, F0, endpoints and the number of runs remain company decisions, taken with a written criterion.

This sample contains, exactly as they appear in the full edition: the regulatory status box and the label system; the complete table of contents; a technical extract from Chapter 7 on dead legs and drainability, with its example; an extract from Chapter 11 on the start condition of the SIP cycle; Case C from Chapter 24 in full; real pages of three toolkit tools; the list of what the purchase contains. First edition, October 2026, v1.0; regulatory cut-off 01/10/2026.

Regulatory status box

⚠ NOTICE

Regulatory and technical status as of 01/10/2026 In the EU, EudraLex Vol. 4 CURRENT REGULATORY REQUIREMENT in the EU: Chapter 1 (revision 3, since 31/01/2013), Chapters 3 and 5 (since 01/03/2015), Chapter 4 (since 30/06/2011), Part II (since 01/09/2014), Annex 1 (since 25/08/2023; 8.123 since 25/08/2024), Annex 11 (since 30/06/2011), Annex 15 (since 01/10/2015), which for active substances is still "supplementary optional guidance". - PIC/S PI 006-4 'Recommendations on Qualification and Validation' CURRENT GUIDANCE has been in force since 01/10/2026 and replaces PIC/S PI 006-3 (2007) ~~SUPERSEDED~~. PI 006-4 is a PIC/S recommendation for inspectors and industry: it illustrates inspection expectations on Annex 15 but is not an EU legal act; in the EU the binding reference remains EU GMP Annex 15. - Other documents CURRENT GUIDANCE : PIC/S PE 009-18 (in force since 24/09/2026), PI 043-1, PI 046-1, PI 052-1, PI 053-1, binding only where an authority adopts them; EMA guidelines on HBEL (since 01/06/2015), sterilisation (since 01/10/2019) and water quality (since 01/02/2021) and EMA Q&A 246844/2018; ICH Q7, Q8(R2), Q9(R1) (in the EU since 26/07/2023), Q10, Q12; WHO TRS 1019 Annex 3, TRS 1033 Annexes 2 and 3, TRS 1044 Annex 2. - **In the USA**, 21 CFR 211, 600.11 and Part 11 CURRENT REGULATORY REQUIREMENT in the USA; FDA guidance on Part 11 (August 2003), aseptic processing (September 2004), Process Validation (January 2011), Q7 (September 2016) and data integrity (December 2018), the CGMP Q&A "Equipment" and the Inspection Guides 1991–1994 CURRENT GUIDANCE in the USA; the CSA guidance of 03/02/2026 concerns medical devices only. - **In the United Kingdom**, Human Medicines Regulations 2012, reg. 37 CURRENT REGULATORY REQUIREMENT in the United Kingdom. - **Pharmacopoeias.** As of 01/10/2026 the applicable texts are Ph. Eur. 12th Edition up to Issue 12.3 and USP–NF 2026, Issue 5 (official from 01/10/2026); USP–NF 2027, Issue 2 has been published but applies only from 01/04/2027. Ph. Eur. texts were not consulted directly: the information reported (WFI monograph, chapters 5.1.1, 5.1.2, 5.1.5) is as cited by official EU sources; for limits and methods the current Ph. Eur. text prevails. Informational USP chapter 〈1229.13〉 GUIDANCE: it sets no requirements or acceptance criteria and is a reference for the US market; the same applies to the other chapters numbered 〈1000〉 and above. - **Drafts.** Revision of EU GMP Annex 11, Chapter 4 and Chapter 1 and new Annex 22 DRAFT GUIDANCE: drafts consulted in 2025 (consultation closed); as of 01/10/2026 the final texts have not been published and the 2011 Annex 11 and Chapter 4 and the 2013 Chapter 1 remain in force CURRENT REGULATORY REQUIREMENT in the EU. The draft contents are proposals. ISO/DIS 14159 'Safety of machinery — General requirements for hygienic design' DRAFT has been under DIS ballot since 09/07/2026; ISO 14159:2002 remains in force CURRENT TECHNICAL STANDARD. - **In development.** Revision of EU GMP Annex 15 IN DEVELOPMENT: concept paper EMA/INS/GMP/163466/2026 of 19/01/2026 (consultation from 09/02/2026 to 09/04/2026) proposes making Annex 15 mandatory for active substance manufacturers and aligning it with ICH Q9(R1); the draft is planned for December 2026. As of 01/10/2026 the 2015 Annex 15 remains in force. The revision of ISO 13408-4 (ISO/AWI 13408-4) is IN DEVELOPMENT; ISO 13408-4:2005 remains in force. ASTM work items WK92599 and WK92659 IN DEVELOPMENT. - **Superseded.** PIC/S PI 006-3 (2007) ~~SUPERSEDED~~ was replaced by PIC/S PI 006-4 on 01/10/2026; its statements on three consecutive applications and on the 10 ppm and 0.1% dose criteria are not carried over into the current version. ISO 17665-1:2006 and ISO/TS 17665-2 and -3 ~~SUPERSEDED~~, replaced by ISO 17665:2024; FDA CSA guidance of 24/09/2025 ~~SUPERSEDED~~ since 03/02/2026. - **Technical standards.** ASME BPE-2026 was issued on 01/05/2026 and becomes effective six months after the date of issuance (i.e. on

01/11/2026, by calculation); as of 01/10/2026 ASME BPE-2024 remains effective CURRENT TECHNICAL STANDARD. Contracts must state the applicable edition. ISO 13408-4:2005, ISO 13408-5:2006, ISO 17665:2024, ISO 11138-1 and -3:2017, ISO 11140-1:2014, EN 285:2015+A1:2021, 3-A 605-04, ASTM E2500-25 and E3106-22, the EHEDG guidelines and the VDMA riboflavin sheet are CURRENT TECHNICAL STANDARD: they are voluntary standards and become binding only if referenced in a contract, a URS, a specification or a quality agreement. - **What is not there.** No regulatory value for CIP velocity, L/d, slope (EU), SIP temperature or duration, or F0 for SIP. No text in force in the EU sets a number of consecutive cycles to validate cleaning: EU GMP Annex 15 (10.13) requires an appropriate number based on risk assessment REGULATORY REQUIREMENT in the EU and PIC/S PI 006-4 has it defined in the protocol GUIDANCE. No verified FDA Warning Letter cites a failed CIP or SIP cycle. - **To be re-verified.** Final texts of Annex 11, Chapter 4 and Chapter 1; the Annex 15 draft; the effective date of ASME BPE-2026; Ph. Eur. Issue 13.1 (from 01/01/2027); ISO/DIS 14159 and ISO/AWI 13408-4; the status of USP 〈1119〉 and 〈1119.1〉; the FDA guidance on Computer Software Assurance for AI systems in drug manufacturing (on the CDER agenda, not published); the ISPE "C&Q Implementation Addendum" (announced).

Document	Status as of 01/10/2026	Dates not to be confused	Jurisdiction	Source
EU GMP Annex 1	CURRENT	adopted on 22/08/2022; operational since 25/08/2023	EU	FS-08
PIC/S PI 006-4; PI 006-3	CURRENT; ~~SUPERSEDED~~	01/10/2026; PI 006-3 in force since 25/09/2007	PIC/S	FS-20, FS-21
PIC/S PE 009-18	CURRENT	adopted on 22/09/2026; in force since 24/09/2026	PIC/S	FS-19
Revisions of Annex 11, Chapter 4, Chapter 1; new Annex 22	DRAFT	consultations closed on 07/10/2025 and 03/12/2025: closures, not adoptions	EU	FS-02, FS-05, FS-10, FS-14
Revision of Annex 15	IN DEVELOPMENT	concept paper 19/01/2026; draft planned for December 2026	EU	FS-12
ASME BPE-2026; BPE-2024	no label; CURRENT	issued on 01/05/2026, effective from 01/11/2026 by calculation	voluntary standard	FS-63, FS-64
USP–NF 2026, Issue 5	CURRENT	published on 27/03/2026; official from 01/10/2026	USA	FS-52

The labels in this book

Four labels state the status of a document, seven the nature of a statement, and one marks examples; status comes first, then nature, with the jurisdiction outside the brackets ("CURRENT in the EU").

Label	CIP/SIP example
CURRENT	EU GMP Annex 1, operational since 25/08/2023
DRAFT	2025 revision of Chapter 4: the draft proposes, it does not require
IN DEVELOPMENT	ISO/AWI 13408-4
~~SUPERSEDED~~	ISO 17665-1:2006, replaced by ISO 17665:2024
REGULATORY REQUIREMENT	temperature recorded at the SIP condensate drains (EU GMP Annex 1, 8.58) in the EU
COMPENDIAL REQUIREMENT	USP "Pure Steam" monograph in the USA
GUIDANCE	steam tests at points of use (PIC/S PI 006-4, 6.3.9)
TECHNICAL STANDARD	requirements for the manufacturer of biological indicators (ISO 11138-3:2017)
SCIENTIFIC PRINCIPLE	pressure–temperature relationship of saturated steam, in absolute pressure

Label	CIP/SIP example
GEP/QRM	blind branches oriented to displace air
GUIDEGXP RECOMMENDATION	annual revalidation of EU GMP Annex 1, 8.39 applied to SIP circuits
DEMONSTRATION EXAMPLE	F0 calculated on an invented SIP profile

The nature of a value is not a label: it is written in words next to the number and governs how the number may be used.

Nature of the value	Value and object	Document and point	Source
requirement	gas filters of 0.22 µm nominal or smaller, at the point of use, in the EU	EU GMP Annex 1, 6.19	FS-08
acceptable	three consecutive batches in process validation	EU GMP Annex 15, 5.20	FS-11
definition	dead leg beyond 3 internal diameters	EU GMP Annex 1, glossary	FS-08
guidance	WFI for the final rinse, CIP included, of sterile parenterals	EMA, water quality guideline, Table 5	FS-15
guidance for another scope	F0 ≥ 8 min for the medicinal product in the dossier; 1/100 slope for water systems	EMA, sterilisation guideline, 4.1.1; WHO TRS 1033, Annex 3	FS-18, FS-28
standard (target of a voluntary standard)	L/d ≤ 2 from the inner wall	ASME BPE	FS-65
test criterion	water at 12–25 °C, UV at 365 nm, "No visible fluorescence"	VDMA, riboflavin test	FS-77
convention	1.5 m/s (5 ft/s) per line, of dairy origin	3-A 605-04, Appendix K	FS-76
example	Re > 4000 in the recirculation of water systems	WHO TRS 1033, Annex 3, 8.6	FS-28
literature	critical wall shear stress of 3 Pa in the EHEDG method	Jensen and Friis, 2004	FS-92
draft	alarm limits and delays to be justified	Annex 11 draft, 8.2	FS-10

Full edition — complete table of contents: the map of the manual

The full edition comprises 24 chapters in six parts, named after the six areas of the Cleaning, CIP & SIP hub, plus six appendices, over 285 A4 pages. Chapters 2–23 follow the same seventeen-section path: the problem and the decision; scope and boundaries; data to collect; technical principles; requirements and sources; interpretation; risk; decision; reasoned procedure; evidence; audit readiness; example; errors to avoid; chapter checklist; toolkit tools and related articles; the decisions the chapter produces; chapter sources. Page numbers refer to the full edition, not to this sample.

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Technical extract — Dead legs and drainability

From Chapter 7, exactly as it appears in the full edition: the problem and the decision, the technical principles (physics of the dead leg, where L is measured from, slopes, drainable does not mean dry), the branch decision tree with its options, the calculated example, the errors to avoid and the chapter checklist. In the full edition the chapter also covers scope and boundaries, data to collect, requirements and sources, interpretation, risk, procedure, evidence, inspector questions and the D-07.n decisions.

The problem and the decision

A circuit can be cleaned, drained and sterilised only where its geometry allows: no recipe reaches an air-filled dead leg, empties a low point sloped the wrong way or washes a valve body that holds liquid. Hygienic design is decided before the order is placed and verified at installation: which dead leg definition and which measurement method, which slopes and which drainability test, which materials, finishes, welds, valves and elastomers, which exceptions to accept and with what mitigation. Engineering decides with QA (D-07.1–D-07.5).

Technical principles

Dead leg physics SCIENTIFIC PRINCIPLE. In a dead leg the liquid is renewed only by the vortex induced by the main line, which weakens towards the closed end. In CIP the enemy is air trapped in upward branches; in SIP it is air and non-condensable gases in upward branches and condensate in downward ones. A downward branch drains in CIP and collects condensate in SIP. Secondary summaries of the ASME STP-PT-065 study GEP/QRM report that without contact with the CIP solutions there is no cleaning and that orientation matters: downward branches, tees on vertical runs, short branches.

Where L is measured from. ASME BPE (BPE-2024 CURRENT TECHNICAL STANDARD) measures L from the inner wall of the main line; the historical six-diameter rule measured it from the axis. The same branch gives different numbers.

DEMONSTRATION EXAMPLE SCIENTIFIC PRINCIPLE

Branch (ID)	Maximum L for L/d 2 (mm)	L/d 3 (mm)	L/d 6 (mm)
BPE ½" (9.4 mm)	18.8	28.2	56.4
BPE 1" (22.1 mm)	44.2	66.3	132.6
BPE 2" (47.5 mm)	95.0	142.5	285.0

A 1" branch that is "6 diameters from the axis" of a 2" header (132.6 mm from the axis) measures 109 mm from the wall: L/d 4.93 by the BPE method. Mixing up the reference shifts the permitted length by 20–30%.

Slopes SCIENTIFIC PRINCIPLE:

Slope (in/ft)	%	mm/m	Degrees	Fall over 6 m (mm)
1/16	0.521	5.21	0.298	31
1/8	1.042	10.42	0.597	62
1/4	2.083	20.83	1.193	125

DEMONSTRATION EXAMPLE Hypothetical data, calculated only to illustrate the method: they are not acceptance criteria or parameters of a real system.

Drainable does not mean dry. After draining, a film remains, as does hold-up at low points and in valve bodies: air blowing, heat or time are needed SCIENTIFIC PRINCIPLE. The 1993 FDA inspection guide on cleaning validation CURRENT GUIDANCE in the USA states: "under no circumstances should stagnant water be allowed to remain in equipment subsequent to cleaning operations."

Finish and design. Surface finish reduces residue adhesion but does not compensate for dead legs, lack of drainability or trapped air: cleanability is designed first of all into the system geometry. ISO 13408-5:2006 CURRENT TECHNICAL STANDARD says so for SIP: "The most important issue to consider in establishing sterilization-in-place technology is the design of the system(s)" (introduction).

Materials, welds, valves, elastomers GEP/QRM. Steels and polymers are selected for residues, agents, temperature and steam; ICH Q9(R1) CURRENT GUIDANCE lists among the uses of QRM the "selection of stainless steel grade, gaskets, lubricants" (Annex II.4). Inspected orbital welds and diaphragm valves reduce standing liquid; elastomers age and become a maintenance item (see Chapter 22).

Decision

Branch decision tree GUIDEGXP RECOMMENDATION:

1. Is the run part of the CIP circuit, of the SIP sterile boundary or of both?
   - CIP only → go to 2.
   - SIP sterile boundary, even if cleaned by CIP → go to 3.
2. Is the branch flowed through by the fluid (flow-through) or is it blind?
   - Flow-through → **Outcome:** check of flow rate and wall shear stress in the run (Chapter 6).
   - Blind → **Outcome:** L/d with the declared method, orientation, coverage test or sampling access (D-07.1; Chapter 8).
3. Can the branch trap air (upward) or condensate (downward)?
   - Air → **Outcome:** vent or redesign; development thermocouple in the branch (Chapter 11).
   - Condensate → **Outcome:** low-point drain with steam trap, or redesign; thermocouple at the low point (Chapters 10 and 12).

Option	Advantages	Limitations	Dependencies	When to choose it
Short, correctly oriented branch	Removes the problem at source	Layout constraints	Initial design	Always as first choice
Flush-mounted diaphragm valve	No branch at all	Cost	Component availability	Points of use and sampling
Short-outlet tee	Reduced L	Not always available	BPE edition in the contract	Instruments and connections
Redesign	Permanent solution	Time and cost	Change control	Existing critical branches
Exception with mitigation	Avoids redesign	Mitigation must be maintained	Test, sampling or dismantling	Documented low risk

Dead leg criterion and measurement method `<to be defined>` (D-07.1); slopes and drainability criterion `<to be defined>` (D-07.2); materials, finishes, welds and contractual BPE edition `<to be defined>` (D-07.3): who decides, basis and record in the final section.

Example

DEMONSTRATION EXAMPLE Simulated case: Neravo Biologics S.r.l. is a fictitious company and the data are hypothetical.

Data. Register DLR-NB: 1" branch (ID 22.1 mm) on a 2" header (ID 47.5 mm), surveyed at 132.6 mm from the axis (six branch diameters). Specification MAT-NB rev. 3: 316L; Ra ≤ 0.5 µm mechanically polished (Areas P, U, D); train F electropolished with Ra ≤ 0.4 µm; orbital welds with documented borescope inspection; EPDM in CIP-only circuits; PTFE diaphragms with EPDM backing in SIP valves. Demonstration choice of a fictitious company: it is not a recommended or reference value.

Rule or method. BPE method (L from the wall); table of definitions; conversion formula L from the wall = L from the axis − line ID / 2 SCIENTIFIC PRINCIPLE.

Calculation. 132.6 − 47.5 / 2 = 108.85 ≈ 109 mm from the wall; L/d = 108.85 / 22.1 = 4.93.

Result. The same branch is "within 6D" under the historical rule from the axis, is a dead leg under the Annex 1 definition and exceeds the BPE L/d 2 target.

Reading. The number does not classify the branch without the method, the company criterion, the function and the orientation. No BPE designation is written in the Neravo specification: the Ra values are company choices, not standard designations.

Neravo decision. D-07.1: in DLR-NB, surveys taken from the axis are converted to the wall before comparison with the criterion. D-07.3: MAT-NB rev. 3; contracts reference BPE-2024 for projects contracted before 2026 (CIP-NB-02) and BPE-2026 for new ones. D-07.2: 5 min air blow with verification of no return flow and zero level at end of cycle. Low points LP-1 and LP-2 of LT-NB-503, with steam traps ST-503-1 and ST-503-2, are in the same register (see Chapter 10). ENG-PRJ-01 decides with QA-NB-01.

DEMONSTRATION EXAMPLE Hypothetical data, calculated only to illustrate the method: they are not acceptance criteria or parameters of a real system.

> ▣ EVIDENCE EXPECTED
>
> Register DLR-NB with the "L measurement method" column completed for every branch, the axis → wall conversion wherever the survey was taken from the axis, and the reference to specification MAT-NB rev. 3.

Errors to avoid

1. **"GMP 6D rule".** Annex 1 defines > 3 internal diameters; 6D is FDA history measured from the axis: state criterion, method and source.
2. **"L/d ≤ 2 is mandatory".** It is the target of a voluntary standard, binding only by contract.
3. **L measured from the axis against a criterion defined from the wall.** Convert and declare the method.
4. **The WHO 1/100 transferred to CIP as a requirement.** It is a recommendation for water systems: declare the analogy.
5. **"Electropolished, therefore cleanable".** Finish does not compensate for dead legs and air (ISO 13408-5).
6. **"Drainable, therefore dry".** PI 006-4, 7.7.3 asks for dry storage: air blow and verification.
7. **EHEDG Doc 8 cited in its 3rd edition.** The 4th edition (December 2025) is in force.

Chapter checklist

No.	Check	Evidence (record)	Outcome
CL-07.1	Every branch has L, measurement method and L/d	CS-TK-06 (Branches)	Y / N / NA
CL-07.2	The dead leg criterion states source and nature	CS-TK-06 (Criteria)	Y / N / NA
CL-07.3	SIP branches are classified by air or condensate risk	CS-TK-06	Y / N / NA
CL-07.4	Slopes are measured in the field, with date	CS-TK-06 (Slopes)	Y / N / NA
CL-07.5	Drainability of lines and vessels is tested	CS-TK-06 (Drainability)	Y / N / NA
CL-07.6	Dry storage is verified at end of cycle	Recipe; cycle report	Y / N / NA
CL-07.7	Materials and elastomers have certificates	IQ dossier	Y / N / NA
CL-07.8	Finishes are measured against the specification	Ra measurements	Y / N / NA
CL-07.9	Welds are inspected and documented	Weld reports	Y / N / NA
CL-07.10	No unassessed ball valve in product-contact runs	CS-TK-07 (section 6)	Y / N / NA
CL-07.11	BPE and EHEDG editions are cited correctly	URS; contract	Y / N / NA
CL-07.12	Exceptions have mitigation and approval	CS-TK-06 (Exceptions)	Y / N / NA

Technical extract — SIP cycle: what starts the exposure

From Chapter 11, exactly as it appears in the full edition: the problem and the decision and the example of the SIP recipe of a transfer line, with the run in which the low point never reaches temperature while the PLC closes the cycle normally. Case C, on the following pages, follows the same event from the deviation to the requalification.

The problem and the decision

The PLC counts exposure time from an event: which event, measured by which probe, decides whether the slowest point of the system receives the treatment or stays outside the count. Cycle development fixes that event and the parameters around it (pressure, band, duration, cool-down, sterile hold, post-cycle checks) on the real plant, with thermocouples in addition to the routine probes, before qualification. The typical case: the supplier's recipe starts exposure when the most convenient probe reaches the threshold, and the first "successful" steam-in-place (SIP) cycle becomes the basis for qualification. CQV decides with engineering and QA; QA decides sterile hold and post-cycle checks (D-11.1…D-11.5).

Example

DEMONSTRATION EXAMPLE Simulated case: Neravo Biologics S.r.l. is a fictitious company and the data are hypothetical.

Data. Recipe RC-SIP-503 (FH-NB-502 → LT-NB-503 → V-NB-504), v4 since 2019, v5 since 13/03/2026. Demonstration choice of a fictitious company: it is not a recommended or reference value (applies to the whole table).

Phase	Neravo conditions	D code
Prerequisites	Clean-in-place (CIP) of F-02/F-03 completed and drained; filter installed; system closed	D-11.1
Air purge	8 min; steam from the top; high vents and low drains open	D-10.2
Heat-up	1.20 barg (2.213 bara; Tsat 123.4 °C) at PCV-503	D-10.6, D-11.1
Start of exposure	TT-503-1, TT-503-2, TT-504 (since 13/03/2026 also TT-503-2B) all ≥ 121.5 °C with 1 min stability	D-11.2
Exposure	30 min; band 121.5–125.0 °C on all routine probes	D-11.1
Cool-down	Steam shut off; sterile filtered air from AF-503 held at 0.3 barg	D-11.3
Sterile hold	Up to 72 h at ≥ 0.2 barg	D-11.4
After SIP	Integrity test of the FH-NB-502 filter before use	D-11.5

Run 1 of the requalification on 09/02/2026 (Case C, see Chapter 12), with recipe v4, after replacement of ST-503-2 during the shutdown: routine probes ≥ 121.5 °C from 14.0 min, exposure from 15.0 to 45.0 min; thermocouple TC-11, at the bottom of low point LP-2, never reaches 121.5 °C (108.0 °C at the start of exposure, plateau at 111.5 °C); TT-503-2, on the vertical drop above LP-2, reads steam at 122.3 °C.

Rule or method. Annex 1, 8.52 and 8.63; Neravo F0 calculation rule: Tref 121.1 °C, z 10 °C, only readings ≥ 110 °C, actual Δt of 0.5 min, half-open window from 15.0 to 45.0 min (end excluded).

Calculation. F0 of TC-11 during exposure: 2.8 min. The other 15 thermocouples remain between 121.8 and 123.2 °C.

Result. The PLC closes the cycle normally: the v4 start condition contains no probe at the low point.

Reading. The 2019 qualification had found the cold spot at LP-2 and had correlated TT-503-2 with it (0.3 K), with the original trap; once the trap was changed, the probe kept reading steam. Without a routine probe at the low point, the v4 start condition let a maintenance change through. Version v5 adds TT-503-2B at the bottom of LP-2: a similar change today would block the start of exposure.

Neravo decision. D-11.2: since 13/03/2026 start condition with TT-503-2B (RC-SIP-503 v5, CC-NB-26-012); D-11.1, D-11.3, D-11.4, D-11.5 as in the table. CQV-01 decides with ENG-PRJ-01 and QA-NB-01.

DEMONSTRATION EXAMPLE Hypothetical data, calculated only to illustrate the method: they are not acceptance criteria or parameters of a real system.

> ▣ **EVIDENCE EXPECTED**
>
> Development report SIPD-503 with the table of times to reach 121.5 °C per thermocouple, the ranking of the slowest locations and the justification for the choice of routine probes; alongside it, the revision of recipe RC-SIP-503 that implements that choice.

Integrated case — Case C, the low point in SIP

From Chapter 24, which holds four (A new CIP skid, B coverage after the spray-device retrofit, C cold spot in SIP, D endpoint drift), all linked to the toolkit with the same identifiers. Case C is reproduced in full. Neravo Biologics is a fictitious company: data, dates and codes are hypothetical.

Case C — The low point of LT-NB-503

DEMONSTRATION EXAMPLE Scenario built for teaching purposes. Simulated case: Neravo Biologics S.r.l. is a fictitious company and the data are hypothetical.

Context. Annual requalification of the SIP of train F (FH-NB-502 → LT-NB-503 → V-NB-504) after the shutdown from 19/01/2026 to 06/02/2026; frequency chosen as a prudent interpretation of EU GMP Annex 1 CURRENT REGULATORY REQUIREMENT in the EU, 8.39 (see Chapter 12). Initial qualification QR-SIP-503-19: cold spot TC-11 in low point LP-2, routine probe TT-503-2 on the downleg above LP-2, correlated with a 0.3 K difference. **Problem.** Requalify a train on which maintenance has changed a sterile-boundary component. **Risk.** Condensate in the low point of the filtered product path, invisible to the routine probe. **Decisions.** Approved spare part codes for the steam traps; TT-503-2B in the start condition; 16 thermocouples, three justified runs, correlation; annual requalification plus triggers; like-for-like only with quality approval. Criteria: all thermocouples within 121.5–125.0 °C during exposure; equilibration ≤ 5.0 min; F0 ≥ 25.0 min at every thermocouple; BIs negative. Demonstration choice of a fictitious company: it is not a recommended or reference value. **Activities and data.** Run 1: routine probes ≥ 121.5 °C from 14.0 min, exposure from 15.0 to 45.0 min; TC-11 at 108.0 °C at the start of exposure, plateau at 111.5 °C, F0 2.8 min (Tref 121.1 °C, z 10 °C, readings ≥ 110 °C, Δt 0.5 min); the other thermocouples between 121.8 and 123.2 °C. LP-2 BIs: expected reduction 2.8 / 1.8 = 1.6 log on 2.0 × 10^6 spores, about 5.6 × 10^4 survivors, consistent with the physics. INV-NB-26-007: subcooled condensate in the downleg and in LP-2 because of the ST-503-2 element and the missing insulation; TT-503-2, above the condensate level, read steam at 122.3 °C. During heat-up the section produces 1.26 kg of condensate (53.6 kg of steel). B runs: TC-11 at 121.5 °C at 16.0 / 15.5 / 16.5 min, then at 122.0 / 122.1 / 121.9 °C over the 30 min of exposure; F0 36.9 / 37.8 / 36.1 min; equilibration 4.0 / 3.5 / 4.5 min; in B1 lowest F0 at TC-14 (35.2 min), slowest to heat TC-11.

Date and time	Event	Record	Who
20/11/2019	Initial qualification: cold spot TC-11; TT-503-2 correlated with a 0.3 K difference	QR-SIP-503-19	CQV-01; QA-NB-01
26/01/2026	ST-503-2 replaced as like-for-like; insulation removed	WO-NB-26-0112	MNT-01
09/02/2026	Run 1: TC-11 at 111.5 °C, F0 2.8 min; deviation	RQ-SIP-503-26; DEV-NB-26-007	CQV-01; QA-OPS-01
16/02/2026	LP-2 BIs positive (2 of 2)	QC-MIC-BI-26-004	QC-MIC-01
24/02/2026	Change control; RC-SIP-503 v5 with TT-503-2B	CC-NB-26-012	QA-NB-01
02/03/2026–04/03/2026	Three requalification runs	RQ-SIP-503-26-B	CQV-01
11/03/2026	B-run BIs negative	QC-MIC-BI-26-009	QC-MIC-01
13/03/2026	Report approved; deviation closed; CAPA	RQ-SIP-503-26-B; CAPA-NB-26-006	QA-NB-01

Documents. In addition to those in the chronology: MAP-503-26, INV-NB-26-007, SOP-NB-MNT-012. **Evidence.** Tables per thermocouple; two rankings; correlation of TT-503-2B with TC-11; hypothesis matrix. **Outcome as of 01/10/2026.** Production resumed on 16/03/2026, no batch produced on train F between 26/01/2026 and 13/03/2026; CAPA-NB-26-006 with an effectiveness check over three quarters of TT-503-2B come-up times within the trend band (D-16.3). **Three lessons.** Like-for-like is a quality decision based on equivalence quantities. A mapping with positions in the low points sees what routine

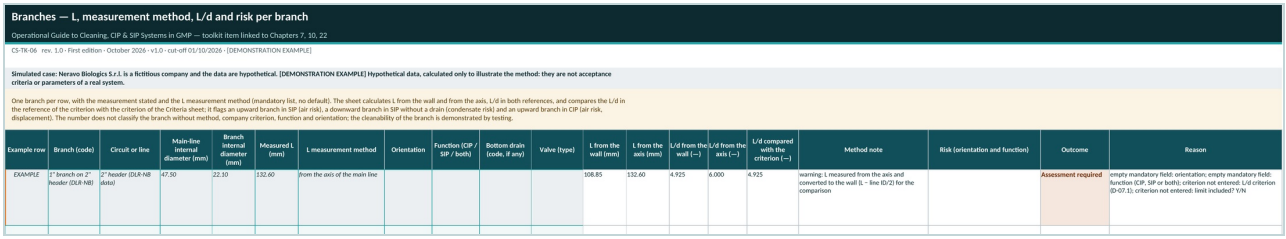
monitoring does not. Cold spot and slowest-to-heat location can be different positions (TC-14, TC-11): the start condition must see the slowest. **D codes.** D-10.3, D-11.2, D-12.1–D-12.5, D-16.3, D-21.5, D-22.1. **Tools used.** CS-TK-09 → CS-TK-10 → CS-TK-11 → CS-TK-12 → CS-TK-21 → CS-TK-22.

DEMONSTRATION EXAMPLE Hypothetical data, calculated only to illustrate the method: they are not acceptance criteria or parameters of a real system.

> **▲ COMMON MISTAKE**
>
> The SIP cycle closes normally on the PLC while the low point stays at 111.5 °C: with a routine probe above the condensate level the controller sees steam and counts the time. The positive BIs are consistent with the physical measurement, which remains the basis of the decision (EU GMP Annex 1, 8.36 and 8.42); the correction is a probe at the bottom of the low point in the start condition, not a longer exposure.

The toolkit: real pages of three tools

The images are pages of the delivered files — Neravo filled-in examples from the 07_Examples folder, English edition — converted to PDF without retouching. In the clean templates of folders 01–06 the same sheets are empty: no operational value is preloaded and no sheet declares a system clean or validated.



Branches — L, measurement method, L/d and risk per branch

Operational Guide to Cleaning, CIP & SIP Systems in GMP — toolkit item linked to Chapters 7, 10, 22

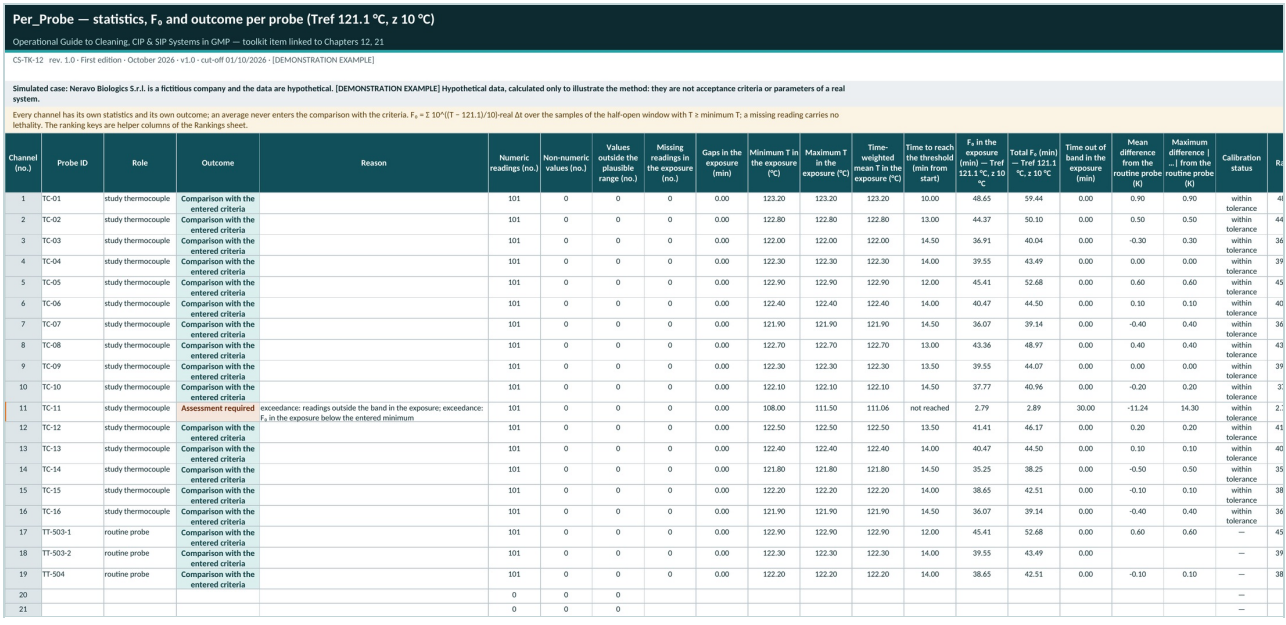
CS-TK-06 rev. 1.0 · First edition · October 2026 · v1.0 · cut-off 01/10/2026 · [DEMONSTRATION EXAMPLE]

Simulated case: Neravo Biologics S.r.l. is a fictitious company and the data are hypothetical. [DEMONSTRATION EXAMPLE] Hypothetical data, calculated only to illustrate the method: they are not acceptance criteria or parameters of a real system.

One branch per row, with the measurement stated and the L measurement method (mandatory list, no default). The sheet calculates L from the wall and from the axis, L/d in both references, and compares the L/d in the reference of the criterion with the criterion of the Criteria sheet; it flags an upward branch in SIP (air risk), a downward branch in SIP without a drain (condensate risk) and an upward branch in CIP (air risk, displacement). The number does not classify the branch without method, company criterion, function and orientation; the cleanability of the branch is demonstrated by testing.

Example row	Branch (code)	Circuit or line	Main-line internal diameter (mm)	Branch internal diameter (mm)	Measured L (mm)	L measurement method	Orientation	Function (CIP / SIP / both)	Bottom drain (code, if any)	Valve (type)	L from the wall (mm)	L from the axis (mm)	L/d from the wall (—)	L/d from the axis (—)	L/d compared with the criterion (—)	Method note	Risk (orientation and function)	Outcome	Reason
EXAMPLE	1" branch on 2" header (DLR-NB data)	2" header (DLR-NB data)	47.50	22.10	132.60	from the axis of the main line					108.85	132.60	4.925	6.000	4.925	warning: L measured from the axis and converted to the wall (L − line ID/2) for the comparison		Assessment required	empty mandatory field: orientation; empty mandatory field: function (CIP, SIP or both); criterion not entered: L/d criterion (D-07.1); criterion not entered: limit included? Y/N

CS-TK-06 — Dead Leg and Drainability Register (Excel) · branches sheet: L from the wall and from the axis, L/d and comparison with the criterion



Per_Probe — statistics, F_0 and outcome per probe (Tref 121.1 °C, z 10 °C)

Operational Guide to Cleaning, CIP & SIP Systems in GMP — toolkit item linked to Chapters 12, 21

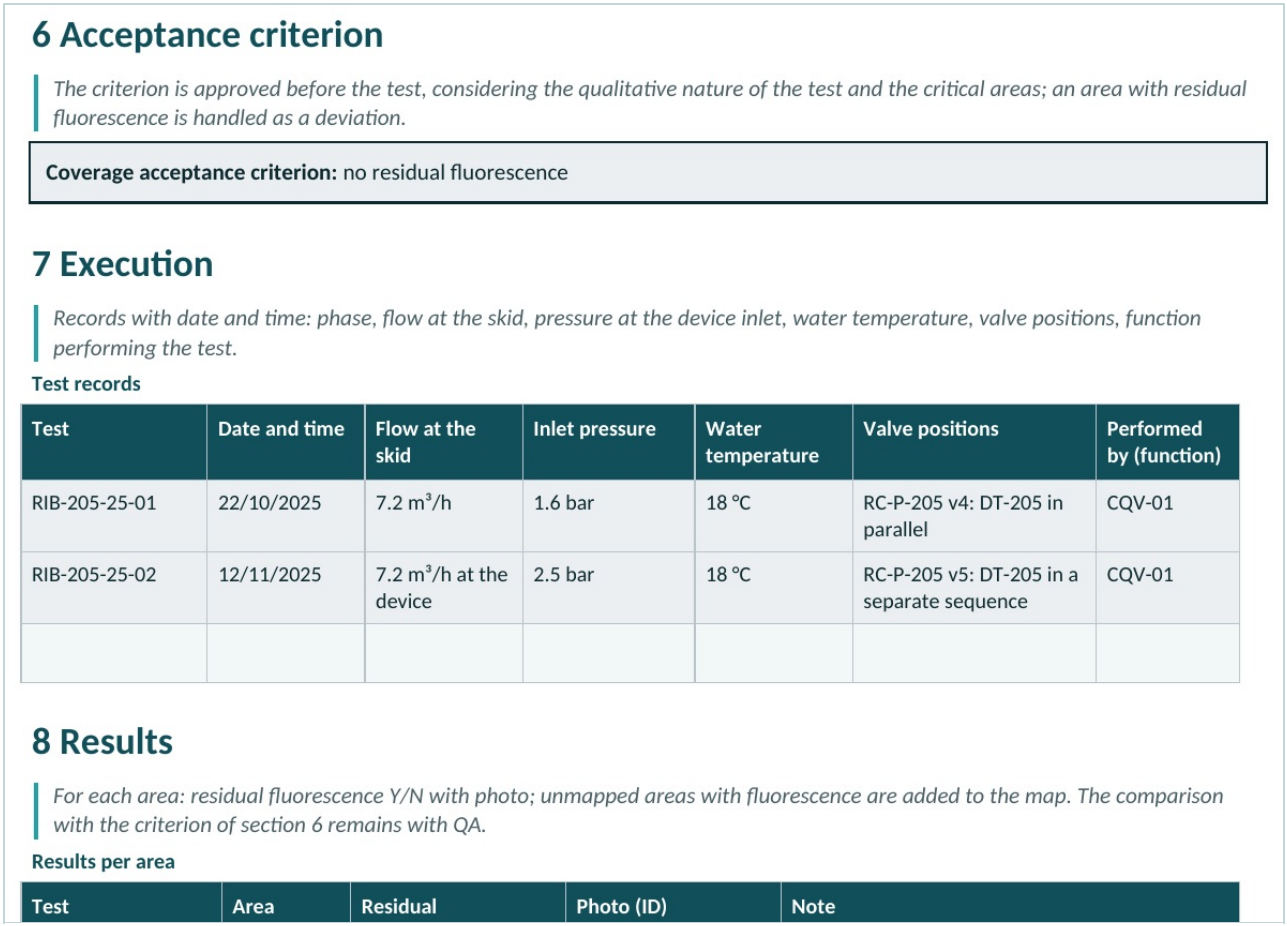
CS-TK-12 rev. 1.0 · First edition · October 2026 · v1.0 · cut-off 01/10/2026 · [DEMONSTRATION EXAMPLE]

Simulated case: Neravo Biologics S.r.l. is a fictitious company and the data are hypothetical. [DEMONSTRATION EXAMPLE] Hypothetical data, calculated only to illustrate the method: they are not acceptance criteria or parameters of a real system.

Every channel has its own statistics and its own outcome; an average never enters the comparison with the criteria. $F_0 = \Sigma\ 10^{(T - 121.1)/10}$·real Δt over the samples of the half-open window with T ≥ minimum T; a missing reading carries no lethality. The ranking keys are helper columns of the Rankings sheet.

Channel (no.)	Probe ID	Role	Outcome	Reason	Numeric readings (no.)	Non-numeric values (no.)	Values outside the plausible range (no.)	Missing readings in the exposure (no.)	Gaps in the exposure (min)	Minimum T in the exposure (°C)	Maximum T in the exposure (°C)	Time-weighted mean T in the exposure (°C)	Time to reach the threshold (min from start)	F_0 in the exposure (min) — Tref 121.1 °C, z 10 °C	Total F_0 (min) — Tref 121.1 °C, z 10 °C	Time out of band in the exposure (min)	Mean difference from the routine probe (K)	Maximum difference | …| from the routine probe (K)	Calibration status	R
1	TC-01	study thermocouple	Comparison with the entered criteria		101	0	0	0	0.00	123.20	123.20	123.20	10.00	48.65	59.44	0.00	0.90	0.90	within tolerance	4
2	TC-02	study thermocouple	Comparison with the entered criteria		101	0	0	0	0.00	122.80	122.80	122.80	13.00	44.37	50.10	0.00	0.50	0.50	within tolerance	4
3	TC-03	study thermocouple	Comparison with the entered criteria		101	0	0	0	0.00	122.00	122.00	122.00	14.50	36.91	40.04	0.00	-0.30	0.30	within tolerance	3
4	TC-04	study thermocouple	Comparison with the entered criteria		101	0	0	0	0.00	122.30	122.30	122.30	14.00	39.55	43.49	0.00	0.00	0.00	within tolerance	3
5	TC-05	study thermocouple	Comparison with the entered criteria		101	0	0	0	0.00	122.90	122.90	122.90	12.00	45.41	52.68	0.00	0.60	0.60	within tolerance	4
6	TC-06	study thermocouple	Comparison with the entered criteria		101	0	0	0	0.00	122.40	122.40	122.40	14.00	40.47	44.50	0.00	0.10	0.10	within tolerance	4
7	TC-07	study thermocouple	Comparison with the entered criteria		101	0	0	0	0.00	121.90	121.90	121.90	14.50	36.07	39.14	0.00	-0.40	0.40	within tolerance	3
8	TC-08	study thermocouple	Comparison with the entered criteria		101	0	0	0	0.00	122.70	122.70	122.70	13.00	43.36	48.97	0.00	0.40	0.40	within tolerance	4
9	TC-09	study thermocouple	Comparison with the entered criteria		101	0	0	0	0.00	122.30	122.30	122.30	13.50	39.55	44.07	0.00	0.00	0.00	within tolerance	3
10	TC-10	study thermocouple	Comparison with the entered criteria		101	0	0	0	0.00	122.10	122.10	122.10	14.50	37.77	40.96	0.00	-0.20	0.20	within tolerance	3
11	TC-11	study thermocouple	Assessment required	exceedance: readings outside the band in the exposure; exceedance: F_0 in the exposure below the entered minimum	101	0	0	0	0.00	108.00	111.50	111.06	not reached	2.79	2.89	30.00	-11.24	14.30	within tolerance	2
12	TC-12	study thermocouple	Comparison with the entered criteria		101	0	0	0	0.00	122.50	122.50	122.50	13.50	41.41	46.17	0.00	0.20	0.20	within tolerance	4
13	TC-13	study thermocouple	Comparison with the entered criteria		101	0	0	0	0.00	122.40	122.40	122.40	14.00	40.47	44.50	0.00	0.10	0.10	within tolerance	4
14	TC-14	study thermocouple	Comparison with the entered criteria		101	0	0	0	0.00	121.80	121.80	121.80	14.50	35.25	38.25	0.00	-0.50	0.50	within tolerance	3
15	TC-15	study thermocouple	Comparison with the entered criteria		101	0	0	0	0.00	122.20	122.20	122.20	14.00	38.65	42.51	0.00	-0.10	0.10	within tolerance	3
16	TC-16	study thermocouple	Comparison with the entered criteria		101	0	0	0	0.00	121.90	121.90	121.90	14.50	36.07	39.14	0.00	-0.40	0.40	within tolerance	3
17	TT-503-1	routine probe	Comparison with the entered criteria		101	0	0	0	0.00	122.90	122.90	122.90	12.00	45.41	52.68	0.00	0.60	0.60	—	4
18	TT-503-2	routine probe	Comparison with the entered criteria		101	0	0	0	0.00	122.30	122.30	122.30	14.00	39.55	43.49	0.00			—	3
19	TT-504	routine probe	Comparison with the entered criteria		101	0	0	0	0.00	122.20	122.20	122.20	14.00	38.65	42.51	0.00	-0.10	0.10	—	3
20					0	0	0												—	
21					0	0	0												—	

CS-TK-12 — SIP Temperature Mapping Data Analysis (Excel) · statistics, F0 and outcome per thermocouple



6 Acceptance criterion

The criterion is approved before the test, considering the qualitative nature of the test and the critical areas; an area with residual fluorescence is handled as a deviation.

Coverage acceptance criterion: no residual fluorescence

7 Execution

Records with date and time: phase, flow at the skid, pressure at the device inlet, water temperature, valve positions, function performing the test.

Test records

Test	Date and time	Flow at the skid	Inlet pressure	Water temperature	Valve positions	Performed by (function)
RIB-205-25-01	22/10/2025	7.2 m³/h	1.6 bar	18 °C	RC-P-205 v4: DT-205 in parallel	CQV-01
RIB-205-25-02	12/11/2025	7.2 m³/h at the device	2.5 bar	18 °C	RC-P-205 v5: DT-205 in a separate sequence	CQV-01

8 Results

For each area: residual fluorescence Y/N with photo; unmapped areas with fluorescence are added to the map. The comparison with the criterion of section 6 remains with QA.

Results per area

Test	Area	Residual	Photo (ID)	Note

CS-TK-08 — Spray Coverage Test Protocol Riboflavin (Word) · sections 6–8: criterion, execution, results per area

What the purchase contains

The purchase is digital: after payment you download a ZIP package with the guide and the toolkit in the language you chose. Choose one variant: **ITA - Italiano** or **ENG - English**; the two editions have the same structure, the same tools and the same codes.

- **The complete PDF guide** — 285 A4 pages, 24 chapters in six parts and six appendices (ITA/ENG glossary, source matrix, chapter–toolkit–article matrix, toolkit instructions, assumptions and limitations, revision); clickable table of contents and bookmarks.
- **24 editable tools** — 12 Word templates and 12 Excel workbooks, codes CS-TK-01...24, arranged in the six folders of the parts (list below).
- **24 filled-in examples** on the simulated Neravo Biologics case (folder 07_Examples).
- **Test Log** of the Excel workbooks (folder 08_Verification).

Folder and group	Code	Tool	Format
01_Requirements · Requirements and Cleaning Strategy	**CS-TK-01**	Project Brief and RACI Matrix	Word
01_Requirements · Requirements and Cleaning Strategy	**CS-TK-02**	Equipment Surface and Residue Register	Excel
01_Requirements · Requirements and Cleaning Strategy	**CS-TK-03**	Cleaning and SIP Risk Assessment	Excel
01_Requirements · Requirements and Cleaning Strategy	**CS-TK-04**	CIP SIP URS	Word
02_CIP_Design · CIP Design and Hygienic Engineering	**CS-TK-05**	CIP Hydraulic Calculator	Excel
02_CIP_Design · CIP Design and Hygienic Engineering	**CS-TK-06**	Dead Leg and Drainability Register	Excel
02_CIP_Design · CIP Design and Hygienic Engineering	**CS-TK-07**	Hygienic Design Review Checklist	Word
02_CIP_Design · CIP Design and Hygienic Engineering	**CS-TK-08**	Spray Coverage Test Protocol Riboflavin	Word
03_SIP · SIP and Thermal Process Control	**CS-TK-09**	Saturated Steam and F0 Lethality Calculator	Excel
03_SIP · SIP and Thermal Process Control	**CS-TK-10**	SIP Design and Sterile Boundary Checklist	Word
03_SIP · SIP and Thermal Process Control	**CS-TK-11**	SIP Cycle Development and Qualification Protocol	Word
03_SIP · SIP and Thermal Process Control	**CS-TK-12**	SIP Temperature Mapping Data Analysis	Excel
04_Automation_Monitoring · Automation and Process Monitoring	**CS-TK-13**	Recipe Sequence and Interlock Functional Specification	Word
04_Automation_Monitoring · Automation and Process Monitoring	**CS-TK-14**	Instrument and Calibration Register	Excel
04_Automation_Monitoring · Automation and Process Monitoring	**CS-TK-15**	CIP SIP Data Integrity and Audit Trail Assessment	Excel
04_Automation_Monitoring · Automation and Process Monitoring	**CS-TK-16**	Rinse Endpoint Trending	Excel
05_Qualification · Qualification and Cleaning Validation	**CS-TK-17**	CQ Plan and FAT SAT IQ OQ PQ Framework	Word
05_Qualification · Qualification and Cleaning Validation	**CS-TK-18**	Requirements Traceability Matrix	Excel
05_Qualification · Qualification and Cleaning Validation	**CS-TK-19**	Cleaning PQ Protocol CV Interface	Word
05_Qualification · Qualification and Cleaning Validation	**CS-TK-20**	Qualification Report and Release for Use	Word
06_Lifecycle · Lifecycle and Procurement	**CS-TK-21**	CIP SIP Deviation Investigation and CAPA	Word
06_Lifecycle · Lifecycle and Procurement	**CS-TK-22**	Maintenance Periodic Review and Requalification Planner	Excel
06_Lifecycle · Lifecycle and Procurement	**CS-TK-23**	RFP Checklist and Supplier Responsibilities	Word
06_Lifecycle · Lifecycle and Procurement	**CS-TK-24**	Technical Bid Evaluation and TCO	Excel

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