

# la vague.

c3p.org

le magazine

de la pharma et des biotechs

octobre - novembre - décembre 2025

n°87

Deep dive on CCS  
understanding.  
Part 1.

How to leverage  
mathematics & IT  
tools for driving  
improvement?

Le secret des produits  
pharmaceutiques et  
cosmétiques réussis,  
de la formulation à  
l'application.

The next generation of  
reagents for Endotoxin  
Testing - for the next  
generation of scientists  
in the pharmaceutical  
/ medical device  
industry.

No detail left  
behind: A holistic  
approach to opening  
authorization in Sterile  
Manufacturing.



## Congrès de Biarritz. Sterile Manufacturing ICHQ10

Sommaire

n°87

- 3 Édito → L'éducation
- 4 Billet d'humeur → Une nouvelle dynamique pour le comité de lecture de la Vague
- 5 Contributeurs → Ils ont participé à ce numéro 6 Evènement A3P → Congrès International de Biarritz
- 9 Actualités A3P → Agenda 2026
- 11 Réglementaire → Ring et l'espace adhérent
- 12 Annex1 & CCS → How to leverage mathematics & IT tools for driving improvement?
- 18 CCS → Part 1. Deep dive on CCS understanding
- 25 Quality → No detail left behind: A holistic approach to opening authorization in Sterile Manufacturing
- 32 Production of incretin mimetics → Weight under control
- 35 Endotoxin → The next generation of reagents for Endotoxin Testing - for the next generation of scientists in the pharmaceutical / medical device industry
- 39 Rhéologie → Le secret des produits pharmaceutiques et cosmétiques réussis, de la formulation à l'application
- 44 Technology → A Toolbox for an Effective Technology Transfer
- 48 Environnement → Excess heat in pharmaceutical industry

la vague.

octobre - novembre - décembre 2025

Numéro offert aux adhérents de l'Association (valeur 10€)

Directrice de la Publication  
Anne RIGOULOT

Rédacteur en chef  
Frédéric BAR

Comité de lecture  
Delphine BOIVIN, Marie BUNEL,  
Frédéric ESTASSY, Arnaud MARGUIER,  
Hervé TASSERY, Lauriane ZUCHUAT

DA, conception & Coordination  
Sophie TORGUE  
storgue@a3pservices.com

Impression  
VL développement  
42000 Saint-Just-Saint-Rambert

Editeur  
A3P Association  
30, rue Pré Gaudry - 69007 Lyon

Dépot légal à parution  
N° d'ISSN : 1298-0471

Tous droits réservés. Les articles publiés n'engagent que la responsabilité de leurs auteurs.

Tirage : 2000 exemplaires. Imprimé sur du papier issu de forêts durables.



Édito.

Yves MOINARD → Membre du CA A3P & Antoine AKAR → Humanim Life Sciences

Chers lecteurs.

Au moment où notre association se réunit à Biarritz pour son congrès annuel, les thématiques qui nous rassemblent – la production stérile, l'ICH Q10 et les enjeux environnementaux, rappellent avec force que la qualité d'un médicament stérile repose d'abord sur les femmes et les hommes qui en assurent la production. Au-delà des technologies, des normes et des référentiels, la clé reste l'éducation des personnes qui assurent cette responsabilité au quotidien.

De l'Académie de Platon à la Renaissance, l'histoire montre que les civilisations les plus avancées sont celles qui ont fait de l'éducation un socle de leur prospérité. De la même manière, les sociétés pharmaceutiques qui se distingueront seront celles où l'éducation est considérée comme la fondation d'une culture Qualité forte et intégrée aux valeurs de l'entreprise.

De la formation à l'éducation. Un changement de paradigme

Dans notre industrie, la formation reste trop souvent réduite à la transmission d'instructions détaillées avec une focalisation sur l'exécution d'une tâche, dans un esprit de conformité réglementaire.

Le "quoi faire" occupe l'essentiel des efforts, au détriment du "pourquoi faire". Sans cette compréhension du "pourquoi", les erreurs deviennent inévitables et l'on s'étonne, à tort, de voir les écarts se répéter.

L'éducation change la donne : elle donne du sens, elle motive, elle responsabilise. Un opérateur ou un technicien de laboratoire qui comprend le "pourquoi" derrière la procédure sera plus attentif et saura réagir à l'imprévu. L'éducation permet au personnel de s'approprier son activité et de s'impliquer dans l'amélioration continue.

L'éducation est un investissement stratégique

Considérer l'éducation comme un investissement, c'est reconnaître qu'elle demande du temps, des ressources et de l'énergie – mais que le retour est immense. Les bénéfices sont tangibles : une meilleure qualité, une sécurité patient renforcée, une maîtrise durable de la contamination, et une performance industrielle qui progresse dans la durée. Ainsi, l'entreprise peut gagner la confiance des autorités et fidéliser ses collaborateurs.

Et parce que l'éducation est stratégique, elle s'inscrit dans le long terme. Elle ne se limite pas à une initiative de quelques mois, faisant suite par exemple à une inspection difficile, mais elle s'inscrit dans une politique d'entreprise durable et intégrée à la culture qualité.

L'éducation est aussi une attente réglementaire

Cette vision s'inscrit en pleine cohérence avec les évolutions récentes du cadre réglementaire.

Le congrès de Biarritz met en lumière deux références majeures : l'Annexe 1 et l'ICH Q10.

La nouvelle Annexe 1 des GMP européennes met l'accent sur la compréhension scientifique et la maîtrise holistique des procédés, soulignant l'importance d'une éducation solide et continue des personnels.

L'ICH Q10, avec son pilier du Knowledge Management, rappelle également que l'acquisition de la connaissance et la gestion de sa transmission constituent une dimension essentielle de la qualité pharmaceutique.

Des initiatives concrètes

Certaines entreprises l'ont compris et diverses initiatives dans l'industrie illustrent ce changement :

- Abandon du simple "Read & Understood" car la simple lecture d'une procédure n'assure pas une réelle compréhension.
- Mise en place formelle du principe de mentorat.
- Création de centres de formation permettant l'apprentissage sans interférence avec les activités de production.
- Intégration de temps significatif d'éducation dans les horaires de travail.
- Recours aux nouvelles technologies comme la réalité virtuelle et la réalité augmentée.
- Participation à des associations comme l'a3p.

Comme le dit une célèbre maxime, "si vous pensez que l'éducation coûte cher, essayez l'ignorance". Dans le monde de la production stérile, les implications d'une erreur sont très souvent significatives. L'investissement stratégique dans l'éducation est donc, de fait, une obligation en regard de notre responsabilité collective pour la santé des patients.

Bon Congrès 2025 et profitez de ces quelques jours pour apprendre et partager vos connaissances !

Les avantages de l'adhésion.

Inscrivez le site\* de votre entreprise et faites bénéficier de toute la base documentaire à vos collaborateurs !

Depuis votre espace personnalisé sur le site a3p.org, accédez à la plus importante base documentaire de l'Industrie du propre & stérile ! Structurée et qualifiée humainement tous les jours, elle regroupe tous les contenus techniques, réglementaires et scientifiques de plus de 30 ans de retours d'expérience, de guides pratiques, de conférences, d'articles, etc. À partir de cette richesse, vous avons pensé un moteur de réponses intelligent, propulsé par IA pour vous accompagner dans votre quotidien

Mieux qu'un moteur de recherche : le moteur de réponses du Propre & Stérile, généré par l'IA



+ 5500 adhérents à notre réseau



+ 2000 supports de conférences scientifiques & techniques



+ 200 articles d'experts du Propre & Stérile



+ 20 guides opérationnels (GST)



+ 1700 documents réglementaires & techniques : FDA, PICs,...

→ Toutes les infos sur [www.a3p.org/adhesion/](http://www.a3p.org/adhesion/)

\*La cotisation Site fait référence à une adresse postale d'un laboratoire de production d'une société prestataire / fournisseur ou d'un siège social. Le montant est défini selon le nombre de salariés attachés au site. Cotisation valable 1 an de date à date et dans tous les pays où l'Association A3P est représentée.



# Billet d'humeur. Une nouvelle dynamique pour le comité de lecture de la Vague.

Anne RIGOULOT → Membre du CA a3p

"Sans les rédacteurs d'articles, ce magazine n'existerait pas, c'est pourquoi nous les remercions chaleureusement pour le temps consacré et la transmission de leurs connaissances"

Depuis sa création, le comité éditorial La Vague n'a eu de cesse d'évoluer pour enrichir les contenus et anticiper les évolutions afin de se positionner comme un vecteur de référence pour la diffusion des retours d'expérience, des innovations techniques et scientifiques et des exigences qualité et réglementaires au sein de notre communauté a3p.

Cette qualité de contenu nous la devons aux rédacteurs mais aussi à l'engagement et au professionnalisme du comité éditorial, véritable garant de la pertinence, de la rigueur scientifique et de la neutralité des articles.

Ce comité éditorial est composé :

- d'un directeur de la publication, administrateur a3p, responsable de la gestion et de la diffusion des contenus en garantissant la qualité et la conformité légale des publications ;
- d'un rédacteur en chef, administrateur a3p, responsable de la ligne éditoriale et de la qualité du contenu publié ;
- d'un coordinateur de la conception, a3p services, en charge de la mise en page et de la vérification finale des articles et de la publication ;

- d'un comité de lecture, administrateur ou adhérent a3p, en charge de trouver des rédacteurs d'articles en lien avec la ligne éditoriale, de relire les articles pour s'assurer de la qualité et de l'adéquation du contenu avec les règles d'a3p, de définir le chemin de fer et enfin de proposer une ligne éditoriale annuelle qui sera ensuite validée par le conseil d'administration.

Comme toute organisation, le comité éditorial se doit lui aussi d'évoluer régulièrement pour anticiper les attentes des professionnels qui nous lisent.

Depuis janvier 2025, nous avons décidé d'avoir un comité de lecture composé de 3 membres permanents issus du conseil d'administration et 3 membres temporaires identifiés pour 3 ans hors conseil d'administration avec un changement partiel annuel pour renouveler les centres d'expertise et assurer une meilleure représentativité sectorielle.

Pour 2025 – 2028, nous avons l'honneur d'accueillir au sein du comité éditorial en tant que membre temporaire :

- Marie BUNEL, Merck Life Science
- Arnaud MARGUIER, IWT
- Lauriane ZUCHUAT, Corden Pharma

Nous tenons à remercier très sincèrement **Arnaud Huc**, Académie de la Qualité Efficace qui a fait partie du comité de lecture pendant plusieurs années, pour sa très forte contribution à la diversification des articles et des rédacteurs. De part son réseau, il nous a permis d'accueillir de nouveaux rédacteurs et d'étendre les thématiques abordées.

Nous n'oublions pas de remercier, **Sophie Torgue**, notre coordinatrice a3p services, personne clé dans la conception et

diffusion du magazine depuis de longues années pour son professionnalisme et surtout sa patience et son écoute.

Sans les rédacteurs d'articles, ce magazine n'existerait pas, c'est pourquoi nous les remercions chaleureusement pour le temps consacré et la transmission de leurs connaissances et nous réfléchissons actuellement à un mode de reconnaissance plus marqué qui sera communiqué prochainement.

Nous comptons sur vous pour continuer à faire vivre la vague, en proposant vos articles, en partageant vos expériences et pourquoi pas, en rejoignant à votre tour le comité de lecture de demain.

Bonne lecture et cap sur l'excellence partagée au travers de la vague et lors de ces 3 jours du Congrès International a3p dans ce fabuleux décor de Biarritz.

Le comité éditorial a3p,

- **Hervé TASSERY**, membre permanent et administrateur a3p,
- **Frédéric BAR**, rédacteur en chef et administrateur a3p,
- **Anne RIGOULOT**, Directrice de la publication et administratrice a3p.



# Merci à eux ! Ils ont participé à ce numéro.

Rédacteurs de " No detail left behind: A holistic approach to opening authorization in Sterile Manufacturing "

**Clémence LAMBERT**,

→ Aktehom

She holds a doctorate in pharmacy and a diploma in chemical process engineering (ENSIC). With almost ten years' experience in the healthcare industry, notably as a manufacturer of parenteral products, she specializes in asepsis. She offers her expertise to help manufacturers comply with the new Annex 1. Clémence also has solid experience in C&Q and project management.

**Michel HERTSCHUH**,

→ Aktehom

Michel has almost 30 years' experience in the pharmaceutical and medical device industries. His expertise covers aseptic operations (technical and regulatory expertise), technology transfer, CCS implementation, process validation in aseptic and biocontamination processes, regulatory compliance and plant design reviews. He's a Partner and co-founder of AKTEHOM.

Rédactrice de " Le secret des produits pharmaceutiques et cosmétiques réussis, de la formulation à l'application "

**Sylvia IMBART**,

→ ebi

Rédactrice de " The next generation of reagents for Endotoxin Testing - for the next generation of scientists in the pharmaceutical / medical device industry "

**Veronika WILLS**,

→ Associates of Cape Cod

Rédacteur de " Excess heat in pharmaceutical industry "

**Rodolphe HENRIETTE**,

→ GIC Performance  
environnementale

Rédacteur de " A Toolbox for an Effective Technology Transfer."

**Rui ALMEIDA**,

→ ValGenesis

This article was originally published in the PDA Letter on May 1, 2025 and is republished with permission of PDA, Inc.

Rédacteur de " How to leverage mathematics & IT tools for driving improvement? "

**David DA CUNHA**,

→ D2CLifescience

Rédacteur de " Production of incretin mimetics Weight under control "

**Markus BURKERT**,

→ Syntegon Technology

Rédactrice de " Part 1. Deep dive on CCS understanding."

**Darine BEHLOUL**,

→ Sanofi

I am a pharmacist working in the pharmaceutical industry for over 20 years, I had the opportunity to work in several fields: qualification/validation, quality assurance, regulatory affairs, engineering, technology transfer, production, project management and sterility assurance. These experiences have given me a strong and transversal knowledge of the pharmaceutical industry and have consolidated my understanding of processes throughout the product life cycle.

I would like to share my insights on CCS with the pharmaceutical industry network to help benefit and save time in understanding and implementing a sustainable and robust contamination control strategy. Therefore, why not use CCS as a catalyzer for industrial performance. ....

**Vous aussi, vous souhaitez participer aux prochains numéros ? Faites-nous parvenir vos propositions d'articles qui seront étudiées par le comité de lecture pour approbation.**

→ Coordonnées des contacts page 2 ←

## 2026 edition topics.

**Jan./Feb./Mar. ....N°88 ..... CCS Cleaning - Biocleaning**

(booking deadline: November, 1 2025)

**April/May/June ....N°89 ..... Microbiology & Supply**

(booking deadline: February 1, 2026)

**July/Aug./Sept. ....N°90 ..... eCompliance & Visual inspection**

(booking deadline: end of April)

**Oct./Nov./Dec. ....N°91 ..... October Biarritz Hot topics**

(booking deadline: July, 30)



# International Congress of Biarritz

→ Biarritz, France  
7, 8 & 9 October 2025

Pharmaceutical Quality System ICH Q10 / Sterile Manufacturing

3 days  
15 conferences  
20 workshops  
120 exhibitors

## Conferences

### Tuesday, October 7 / Bellevue

|                                                                                                                    |                                                              |
|--------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|
| Sterility Assurance Management: opportunities and challenges                                                       | Elodie DECONINCK → GSK & Antoine AKAR → HUMANIM              |
| PDA/ANSI Standard 06-2025: Assessment of Quality Culture Guidance Documents, Models, and Tools                     | Rebecca WALDEN → PDA & IRISH BLOOD TRANSFUSION SERVICE       |
| Viable environmental monitoring strategy                                                                           | François GUILLOU → DELPHARM & Thomas PEREZ → SANOFI          |
| Aseptic Process Simulation: answers to the challenges of Annex1 on implementing an APS strategy                    | GIC Assurance Stérilité                                      |
| Sterilization of Indirect product contact parts for isolators: new challenges from regulators                      | GIC AS / TB                                                  |
| Annex 1 and manufacturing of cytotoxics, what possible configurations and review of current and future innovations | Franck PAVAN → AXYS NETWORK & Yannick PIRIOU → FAREVA PAU    |
| Using Artificial Intelligence to process deviations                                                                | Laurent CLAUSS → CEVA                                        |
| Employee experience for the benefit of the ICHQ10 Quality system                                                   | Julien DELEARDE → GXP DESIGN & Nora BONNOT → PIERRE FABRE SA |
| Product and process knowledge capitalization: toward a new quality culture serving users                           | Ludovic JOUANOLOU & Manon MARGAI → OCTAPHARMA                |
| Knowledge Management as a lever for efficiency: Feedback from the pharmaceutical industry                          | Gaëlle LE CLAIR → LFB & Lucie BLANCHOT → AKTEHOM             |

### Thursday, October 9 / Bellevue

|                                                                                                                                   |                                                                                    |
|-----------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|
| The environmental challenges of a sterile production process.                                                                     | Samah RINGA → VEOLIA & Rodolphe HENRIETTE → NOVONORDISK SAS                        |
| Aseptic Manufacturing                                                                                                             | ANSM                                                                               |
| Advancing Pharmaceutical Quality: Insights from the FDA's Quality Management Maturity (QMM) Pilot Program and Roche's Experience. | Maria AMAYA → ROCHE                                                                |
| Contamination Control Strategy: when, why and how. A review of case studies and the most common challenges.                       | Alessio ROSATI → PQE GROUP & Paolo MONTAPPONI PATHEON, by Thermi Fisher Scientific |
| Developing a CCI control strategy for a new product manufactured on a new line.                                                   | Henri HEBTING → LILLY FRANCE                                                       |

## Workshops

### Wednesday, October 8 / Bellevue & Casino

|                                                                                                                                                                                                                                          |                                                                                                              |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|
| Workshop 01: Validation des SI intégrant l'intelligence artificielle : approche pratique.                                                                                                                                                | Hervé CLUZEAUD → EXPLEO France & Arnaud DUIGOU → DATA BOOST                                                  |
| Workshop 02: La surveillance des performances des procédures analytiques au service de l'amélioration continue.                                                                                                                          | Marc FRANCOIS-HEUDE → AKTEHOM & Gérald DE FONTENAY → CEBIPHAR                                                |
| Workshop 03: Construire une approche bracketing en APS process.                                                                                                                                                                          | GIC Assurance de Stérilité                                                                                   |
| Workshop 04: Implementation of an APS process bracketing approach. 🇫🇷                                                                                                                                                                    | GIC Assurance de Stérilité                                                                                   |
| Workshop 05: Mise en application de la CPV selon le guide A3P.                                                                                                                                                                           | David DA CUNHA → D2C LIFE SCIENCE & Khelif RIM → SANOFI                                                      |
| Workshop 06: Décontamination des entrants en Classe B et des lignes de remplissage en Classe A. Par une approche du risque, comment mettre en place des procédures robustes et les valider pour répondre à la réglementation en vigueur. | Clémence PRETTE → THERAXEL & Sonia BUISSON → LEO-PHARMA                                                      |
| Workshop 07: Découverte de l'industrie pharmaceutique.                                                                                                                                                                                   | Gwenaëlle CLECH → 5M<br>Mats MICKOS → PHARMTEC<br>François MOREL → CABINET MOREL & Delphine BOIVIN BEY → A3P |
| Workshop 08: How Define URS? should be focused on the aseptic filling with fully automated systems using robotics incl. material transfers and Isolator Systems. 🇫🇷                                                                      | Richard DENIK → SKAN AG & Daniel MUELLER GMP-INSPECTORATE                                                    |
| Workshop 09: ICHQ10 implementation Quality management with the support of Cultural excellence. 🇫🇷                                                                                                                                        | Maria AMAYA → ROCHE & Jean-François DULIERE → ISPE                                                           |
| Workshop 10: Inspection readiness, où en êtes-vous ?                                                                                                                                                                                     | Nathalie BRICARD → EXPLEO & Olivier ANTOINE → SANOFI                                                         |
| Workshop 11: Pas de problème = pas d'amélioration. Les outils Lean, l'état d'esprit LEAN et des solutions concrètes pour augmenter les performances.                                                                                     | Ronan LE FLOC'H → SANOFI R&D & Vincent PHILIBERT → QP PHARMA                                                 |
| Workshop 12: Développez votre leadership situationnel pour révéler le potentiel de vos équipes.                                                                                                                                          | Dominique BEN DHAOU & Nicolas QUOEX → POINTNORTH INTERNATIONAL                                               |
| Workshop 13: Investigations des non conformités microbiologiques avérées ou supposées en production pharmaceutique.                                                                                                                      | Thierry BONNEVAY → SANOFI & Arnaud CARLOTTI → EUROFINS                                                       |
| Workshop 14: Towards a Sustainable Pharmaceutical Industry: Decarbonization, energy savings and much more...                                                                                                                             | Samah RINGA → VEOLIA & Mickael FORMET → VETOQUINOL                                                           |
| Workshop 15: Hot topics in Sterility Assurance & Contamination Control. 🇫🇷                                                                                                                                                               | Patrizia MUSCAS → ELI LILLY & Walid EL AZAB → QP PRO SERVICES                                                |
| Workshop 16: Construire l'URS d'une ligne d'inspection automatique.                                                                                                                                                                      | Grégory DUVAL → TEOXANE & Djonny RIGOT → SANOFI                                                              |
| Workshop 17: Concevoir l'HVAC d'une unité de remplissage aseptique : technologies et interfaces.                                                                                                                                         | Cedric DESARMENIEN → LAPORTE EURO & Christophe AUSSOURD → LABORATOIRE SERVIER                                |
| Workshop 18: Pharmaceutical water installations for aseptic production: what does Annex 1 say?                                                                                                                                           | Aurélien PERIQUET → MERCK & Frédéric MONNIER → VEOLIA                                                        |
| Workshop 19: Le pilotage des systèmes des Déviations et des CAPA.                                                                                                                                                                        | Amélie GERARD → SEPTODONT & Arnaud HUC → ACADEMIE DE LA QUALITE EFFICACE                                     |
| Workshop 20: Stratégies de Classification Environnementale pour la Production de Substances Médicamenteuses à Faible Bioburden : Utilisation de l'Analyse de Risque en lien avec l'Annexe 1 et la CCS.                                   | Fanny BUTHIER → MERCK & Gilles TRIMBORN → UCB                                                                |

## a3p Human Conference

### Wednesday, October 8 / Casino

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p><b>Quand la maladie devient moteur d'innovation !</b></p> <p>Diagnostiqué à seulement 29 ans avec une forme précoce de la maladie de Parkinson, Guillaume Brachet, pharmacien et chercheur, a choisi de transformer cette épreuve en un projet de vie profondément inspirant.Fondateur de CXS Therapeutics, il développe aujourd'hui des traitements innovants contre les maladies neurodégénératives.Guillaume s'est lancé un défi hors norme : remonter 150 km à contre-courant sur la Loire en kayak, pour financer ses premières recherches et donner une voix à ceux qui luttent dans le silence. Pour rendre ce défi possible, un constructeur de kayak basé à Anglet a conçu un modèle sur mesure, adapté à ses limitations physiques. Une session A3P Human placée sous le signe du courage, de l'innovation et de la volonté farouche de faire avancer la science. Un moment fort, à ne pas manquer.</p> | <p><b>Guillaume BRACHET → CXS THERAPEUTICS &amp; Valentin MARCHAL → WAÏNA OUTRIGGER ORGANISATION</b></p> <p><b>Dominique BEN DHAOU → POINTNORTH INT. &amp; Anne CASSART → GROUP JANSEN</b></p> |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

Rejoignez  
la communauté  
Linkedin



→ Biarritz, France  
7, 8 & 9 October 2025

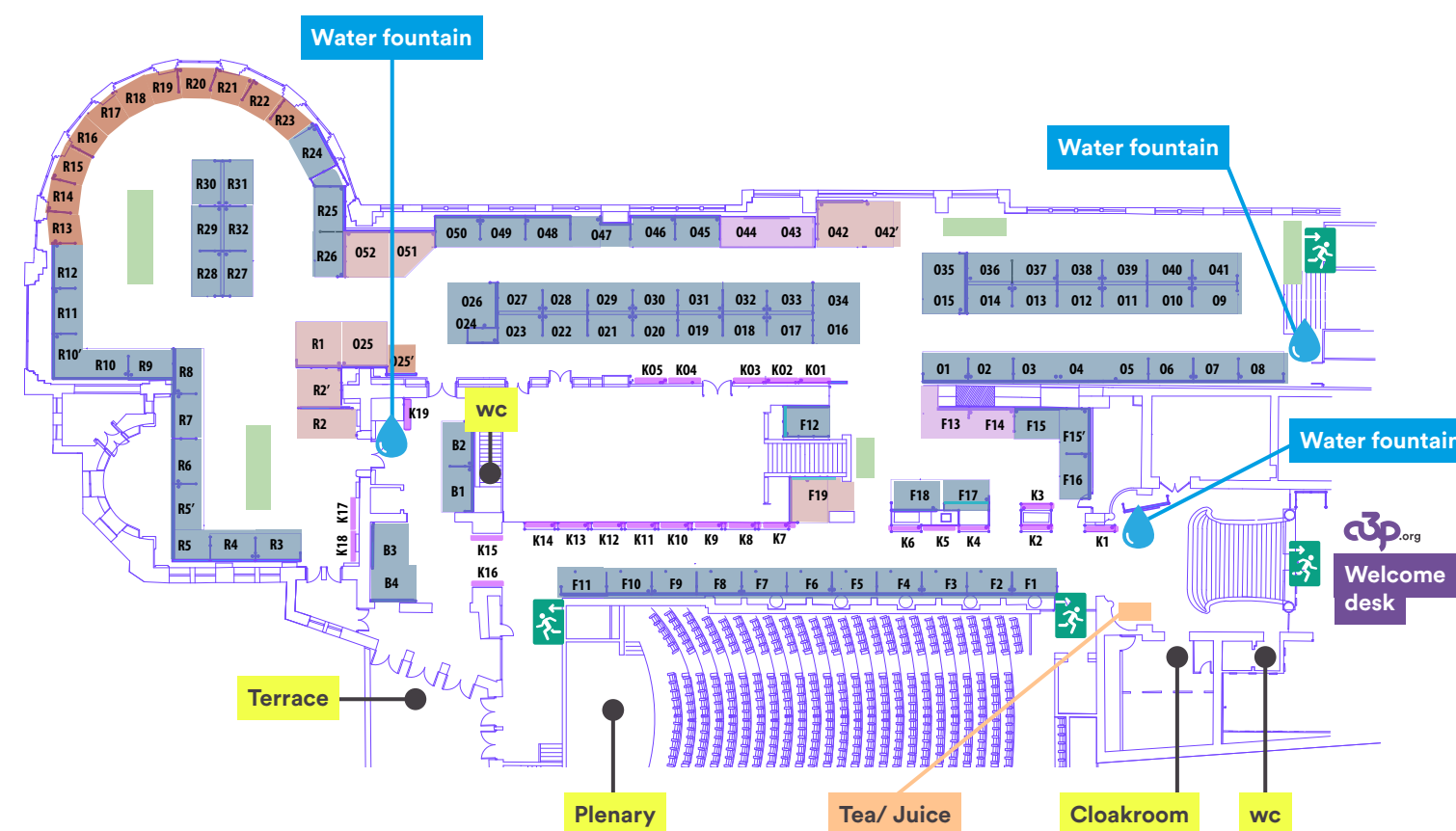
Pharmaceutical Quality System ICH Q10 /  
Sterile Manufacturing

3 days  
15 conferences  
20 workshops  
120 exhibitors

| Exhibition |                            |
|------------|----------------------------|
| O14        | ABC TRANSFER               |
| F2         | ACTINI GROUP               |
| K3         | ADIS PHARMA                |
| KO4        | ADVANCED INSTRUMENTS       |
| O6         | AEROMETRIK                 |
| F19        | AKTEHOM                    |
| R28        | ALBHADES                   |
| R23        | AMSONIC - HAMO             |
| O9         | ASEPTIC GROUP              |
| K5         | ASEPTIC TECHNOLOGIES       |
| R5 / R5BIS | ASSOCIATES OF CAPE COD     |
| O13        | ATRYON                     |
| K7         | AVN                        |
| R12        | BATIMPRO CHARRIER          |
| R7         | BAUSCH+STRÖBEL             |
| O22        | BECKMAN COULTER FRANCE     |
| B1         | BECTON DICKINSON           |
| O43 / O44  | BIOMERIEUX                 |
| O38        | BIOPHARMA TECHNOLOGIES     |
| O42        | BWT                        |
| R2         | CAELIS                     |
| K15        | CAP INGELEC                |
| R9         | CARSO PHARMA               |
| K16        | CATALENT PHARMA SOLUTIONS  |
| K6         | CCIT                       |
| O10        | CHARGEPOINT TECHNOLOGY     |
| R26        | CHARLES RIVER LABORATORIES |
| F4         | CHRISTEYNS LIFE SCIENCES   |
| K13        | CLEVER CULTURE SYSTEMS     |
| O2         | CONFORMAT                  |
| O37        | CONTEC INC                 |
| O48        | COPHACLEAN                 |
| O16 / O34  | CYTIVA                     |
| R22        | DEVEA                      |
| B3 / B4    | ECOLAB                     |
| O24 / O26  | ELIS CLEANROOM             |
| K4         | ELLAB                      |
| KO1        | ELSCOLAB - OPTEK FRANCE    |
| R30        | ENDRESS+HAUSER             |

|               |                                  |
|---------------|----------------------------------|
| R29           | EREA                             |
| F15 / F15 BIS | EUROFINS BPT FRANCE              |
| R24           | EXYTE PHARMAPLAN                 |
| O11           | GASPOROX                         |
| K19 / B2      | GETINGE                          |
| O3 / O4 / O5  | GIVE & TECH                      |
| F12           | GROUPE ICARE                     |
| F1            | HEX GROUP + SAFYR                |
| O50           | HOF SONDERANLAGENBAU             |
| K17           | HONEYWELL PROCESS SOLUTION       |
| F10           | ILC DOVER                        |
| F16           | IMA FRANCE                       |
| O30           | INITIAL CLEANROOMS               |
| O1            | INTERSCIENCE                     |
| O27           | INTERTEK FRANCE                  |
| O42 BIS       | IWT PHARMA                       |
| O51 / O52     | JCE BIOTECHNOLOGY                |
| O19           | KÖRBER                           |
| R27           | LAPORTE EURO                     |
| O21           | LDI - LOURD'INNOV - JBT BOURSIER |
| K14           | LIGHTHOUSE FRANCE                |
| O45           | LONZA COLOGNE                    |
| F7            | MARCHESINI FRANCE                |
| O25BIS        | MCP SOLUTIONS                    |
| F13 / F14     | MERCK                            |
| R4            | MESALABS                         |
| O28           | MGA TECHNOLOGIES                 |
| O40           | MK VERSUCHSANLAGEN               |
| K8            | NEOCERAM                         |
| KO3           | NIKKA DENSOK LIMITED             |
| R20           | NOVATEK INTERNATIONAL            |
| O36           | O&M HALYARD                      |
| O46           | OPTIMA PHARMA                    |
| R25           | OXYPHARM                         |
| K9            | PACOSPHARM                       |
| F5            | PARKER HANNIFIN                  |
| O33           | PARTICLE MEASURING SYSTEMS       |
| O41           | PEMFLOW                          |
| O7            | PFEIFFER VACUUM                  |
| F6            | PHARM-ALLIANCE                   |
| K18           | PHARMADULE MORIMATSU             |

|                       |                                          |
|-----------------------|------------------------------------------|
| O47                   | PHARMASEP                                |
| O39                   | PLAIR                                    |
| O23                   | PMT FRANCE                               |
| KO5                   | PQE GROUP                                |
| K2                    | PROMEPLA                                 |
| O32                   | RAPID MICRO BIOSYSTEMS                   |
| R21                   | RAUMEDIC                                 |
| R14                   | REALCO                                   |
| F11                   | ROMACO                                   |
| R8                    | ROMMELAG                                 |
| K1                    | RT2i                                     |
| F9                    | SALAMANDERU                              |
| O20                   | SCHOTT PHARMA                            |
| O49                   | SCHREINER MEDIPHARM                      |
| O29                   | SCHÜLKE                                  |
| K12                   | SGD PHARMA                               |
| O17                   | SGS FRANCE                               |
| O8                    | SIDJI                                    |
| F3                    | SKAN                                     |
| R15                   | SOFINN - PHARMTEC                        |
| R31                   | SOLIDFOG TECHNOLOGIES                    |
| O12                   | SOURCIN                                  |
| K11                   | SPC GROUP                                |
| F8                    | STAXS®                                   |
| O18                   | STERILINE                                |
| R16 / R17 / R18 / R19 | STERIS                                   |
| R3                    | SWAN                                     |
| F17 / F18             | SYMBIOSE ENVIRONNEMENT                   |
| O25 / R1              | SYNEXIN                                  |
| R10 / R10BIS          | SYNTEGON - TELSTAR                       |
| R6                    | TECHNIP ENERGIES                         |
| R13                   | TECHNOCHIM                               |
| O31                   | TEG                                      |
| KO2                   | TEMPRIS                                  |
| O15 / O35             | TERANGA GROUPE                           |
| K10                   | TERUMO PHARMACEUTICAL SOLUTIONS DIVISION |
| R11                   | THERAXEL                                 |
| R32                   | VALTRIA                                  |
| R2BIS                 | VEOLIA WATER TECHNOLOGIES                |
| R7                    | WILCO                                    |



## Actualité.

## Tous vos rendez-vous a3p en 2026.



Programmes  
& inscription  
[www.a3p.org](http://www.a3p.org)



## Experts de la formation dans les 5 domaines du "Propre & Stérile"

Maîtrise de la contamination  
Procédés  
Qualité et Réglementaire  
Qualification / Validation / Projet  
Systèmes informatisés

- + 60 sessions de formation inter et intra
- + 1500 personnes formées
- + 10 ans d'expérience
- + certifié Qualiopi



Calendrier des formations

# Espace adhérent. Focus sur Insight, le moteur de réponses.

La base documentaire a3p est le socle de l'espace adhérent. Aujourd'hui, elle est la **plus importante et spécialisée de l'industrie pharmaceutique**. Structurée et qualifiée humainement tous les jours, elle regroupe tous les contenus techniques, réglementaires et scientifiques de plus de 30 ans de retours d'expérience, de guides pratiques, de conférences, d'articles, etc.

À partir de cette richesse, vous avons pensé un moteur de réponses intelligent "*Insight*", propulsé par IA. A partir de votre question la plus détaillée possible, *Insight* analyse l'ensemble de notre base documentaire et vous propose une réponse structurée, ciblée et adaptée à vos attentes, tout en précisant les documents références qu'il a utilisé pour formuler la réponse. Contrairement à des outils de type machine learning, notre moteur ne collecte, ni n'entraîne de modèles sur vos questions et aucune information n'est transmise à l'extérieur de notre serveur pour garder la confidentialité de vos données et de vos recherches.

### Sécurité des traitements

Données chiffrées  
IA sans apprentissage  
Respect du RGPD

### Souveraineté des données

a3p est propriétaire des données  
Infrastructure fermée et sécurisée  
Serveurs EU - ISO 27001

Je veux identifier les étapes indispensables pour créer la CCS (contamination Contrôle Stratégie) de mon laboratoire selon les obligations légales de la nouvelle Annexe 1 des GMP Européennes. Il me faut également identifier la nature des informations à recueillir et les services concernés. Je veux que les réponses soient classées dans un tableau. Merci de limiter les réponses au cadre des produits stériles injectables humains. Je représente un laboratoire sous-traitant (CDMO).

Voici un tableau synthétique présentant les étapes indispensables pour créer une Contamination Control Strategy (CCS) conforme à la nouvelle Annexe 1 des GMP Européennes, ainsi que la nature des informations à recueillir et les services concernés pour un laboratoire sous-traitant (CDMO) de produits stériles injectables humains.

| Étape clé                                         | Description                                                                                                               | Nature des informations à recueillir                                                            | Services concernés                        |
|---------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|-------------------------------------------|
| 1. Définir le périmètre et l'objet                | Identifier les processus et zones concernées par la CCS                                                                   | Description des chaînes de production, flux des matières et personnel                           | Qualité, Production, Microbiologie        |
| 2. Collecte et analyse des risques                | Réaliser une évaluation des risques spécifiques à la contamination microbiologique, particulière et endotoxique           | Données historiques de contamination, analyses de risques, points critiques (CPI, CCP)          | Assurance Qualité, Production, Ingénierie |
| 3. Conception du site et équipements              | Prendre en compte la conception des locaux, équipements, utilités et barrières (RABS, isolateurs)                         | Plans, qualifications des équipements, maintenance, système HVAC                                | Ingénierie, Maintenance, Qualité          |
| 4. Gestion des matières premières                 | Contrôle des matières premières, conteneurs et fermetures, qualification des fournisseurs                                 | Fiches matières, audits fournisseurs, certificats de conformité, analyses microbiologiques      | Qualité, Approvisionnement, Supply Chain  |
| 5. Définition et mise en place des procédures     | Rédaction des procédures opérationnelles et instructions concernant nettoyage, désinfection, décontamination, maintenance | Protocoles de nettoyage, plans de maintenance, logs de désinfection                             | Qualité, Production, Maintenance          |
| 6. Formation et habilitation du personnel         | Assurer la formation continue et le respect des bonnes pratiques aseptiques                                               | Registre des formations, habilitations, audits de compléances                                   | Ressources Humaines, Qualité, Production  |
| 7. Mise en place des contrôles et surveillance    | Surveillance environnementale, contrôle des pressions, tests APS, contrôle des filtres (PUPSIT)                           | Résultats de monitoring, plans de contrôle, résultats des tests d'intégrité                     | Microbiologie, Production, Qualité        |
| 8. Validation des procédés et équipements         | Validation des procédés aseptiques et des méthodes de stérilisation                                                       | Rapports de qualification et validation (DQ, IQ, OQ, PQ), rapports de stérilisation             | Validation, Qualité, Production           |
| 9. Suivi et amélioration continue                 | Analyse des tendances, investigations des écarts, actions correctives (CAPA)                                              | Rapports d'audit, CAPA, analyses des causes racines, indicateurs clés (KPI)                     | Qualité, Production, R&D, Maintenance     |
| 10. Documentation unique et synthétique de la CCS | Rédaction et mise à jour d'un document CCS clair, synthétique, intégrant tous les éléments nécessaires                    | Document CCS avec cross-références aux PQS (Système Qualité Pharmaceutique), photos, diagrammes | Qualité, Production, Validation           |
| 11. Revue périodique de la CCS                    | Mise à jour régulière en fonction des changements techniques, réglementaires ou suite audits                              | Rapports de revue, actions de mise à jour, intégration nouvelles exigences                      | Qualité, Production, Direction            |

Ce tableau s'appuie sur les exigences détaillées dans la nouvelle Annexe 1 des GMP et les bonnes pratiques proposées par l'ASAP. La CCS doit être un document vivant reflétant la stratégie globale de maîtrise des contaminations, adapté au contexte spécifique de votre laboratoire sous-traitant.

Pour approfondir et obtenir les modèles et guides pratiques, vous pouvez consulter les supports ASAP dédiés à la CCS, notamment le Guide ASAP Contamination Control Strategy et les supports de conférence associés, ainsi que la documentation réglementaire officielle disponible dans Ring (ANSM, EMA). Ces ressources vous permettront d'étayer votre démarche et d'assurer une conformité optimale aux exigences réglementaires.

**Contamination Control**

Conférence Les futures défis de la fabrication aseptique\_Liquorillo

CDMO - CDMO - CDMO

**Contamination Control**

Conférence 5 : Comprendre la dernière version de l'Annexe 1 et concevoir un point de vue - Pierre DUBOIS, Emma LAM

CDMO - CDMO - CDMO

**Contamination Control**

Workshop 1 : Contamination Control Strategy

CDMO - CDMO - CDMO

**Contamination Control**

10 GMP Annex 1 August 2023 - Manufacture of Sterile Products: CONTAMINATION CONTROL STRATEGY ASAP Guide & Template

CDMO - CDMO - CDMO

**ANSM**

Projet de transcription de l'Annexe 1 des bonnes pratiques de fabrication européennes

ANSM - WITNESS - Guideline

**ANSM**

Fabrication des médicaments stériles

ANSM - Effective - Guideline

Questionnez INSIGHT,  
le moteur de réponses à votre service





# Annex1 & CCS.

## How to leverage mathematics & IT tools for driving improvement?

David DA CUNHA → D2CLifescience



**The latest update to Annex 1 of the EU GMP guidelines marks a major shift in sterile medicinal product manufacturing. It moves away from strict compliance towards a more integrated, science and risk-based approach. A key addition is the requirement for a Contamination Control Strategy (CCS), which unifies all contamination control efforts into one documented framework.**

**The CCS is now a core element of quality assurance. It requires manufacturers to thoroughly assess all potential contamination sources and demonstrate a state of control through facility design, equipment, personnel behavior, monitoring, and more... The revised Annex 1 also introduces lifecycle thinking, treating contamination control as a continuous, evolving process.**

This shift raises expectations for manufacturers, demanding more transparency, traceability, and accountability. Annex 1 is now both a regulatory guide and a strategic tool, promoting collaboration and stronger risk awareness. At its center, the CCS ensures contamination risks are not only identified but actively controlled, supporting a culture of proactive quality for product safety.

### Gap versus Risk, what is the difference?

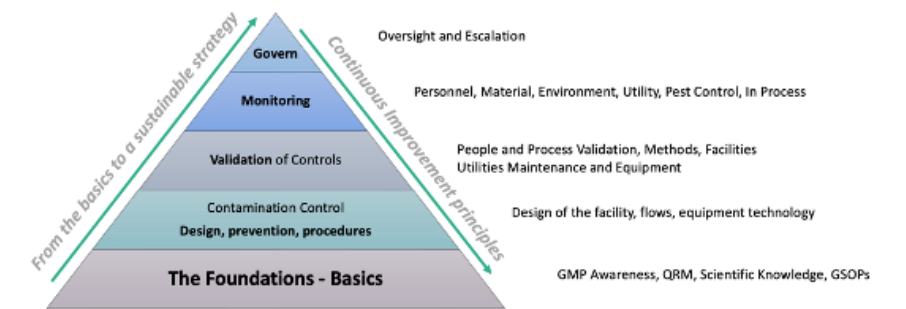
Gap assessment is a structured method used to identify the difference between a current state and a defined standard, goal, or requirement. It helps evaluating how well existing practices or systems align with expectations like regulations or quality standards. The “gap” is the shortfall between what exists and what is needed, and identifying it leads to corrective actions and ongoing improvement. The aim is not to assign blame but to clarify what is lacking and direct efforts where they are most needed.

On the other hand, Risk management is a decision-making process focused on identifying, understanding, and addressing uncertainty. It involves recognizing factors that may impact an organization's ability to meet its goals, assessing the likelihood and impact of these risks, and deciding how to respond. This may mean lowering the chance of the risk, limiting its impact, or accepting it if it's minor. The goal isn't to remove all risks (an unrealistic aim) but to make them visible and manageable.

### Application to Annex 1 and the CCS

By moving logically from compliance needs to risks identification and continuous improvement, the CCS provides regulators and internal stakeholders with clear evidence that contamination risks are understood, controlled and actively reduced over time.

The main drivers for the establishment of the site's Contamination control Strategy are in relation with the design, execution, and monitoring. The strategy is built on a foundation of essential principles and practices, each contributing to a comprehensive approach to ensuring product safety and quality. Key elements as described below basically give the skeleton of the Strategy.



↑ Figure 1: The CCS structure

#### BASICS

The contamination control strategy is grounded in Good Manufacturing Practices (GMP), quality risk management (QRM), and a culture of scientific awareness and procedural discipline. Employees are trained to see GMP not just as rules, but as essential to their daily responsibilities.

#### CONTROL

The strategy emphasizes preventing contamination through smart facility design, proper flows of people and materials, and strong cleaning and disinfection routines. All operations are structured to support cleanliness, with validated checks and proper waste handling to avoid contamination.

#### VALIDATION

Validation ensures all controls are effective. Rooms are qualified, cleaning and sterilization methods are tested, and aseptic process simulations confirm the system can reliably produce sterile products. Any issues trigger swift, risk-based actions.

#### MONITORING

Monitoring plays a central role. Environmental conditions, utilities, and products are regularly checked. This data helps detect trends and supports improvement. The system evolves through ongoing review and prioritization of risks.

#### GOVERNANCE

It keeps the strategy strong. Clear policies and procedures are maintained, compliance is monitored, and problems are resolved through defined escalation processes, ensuring a consistent and accountable contamination control approach.

### Integrating elements and building a Risk Based Strategy

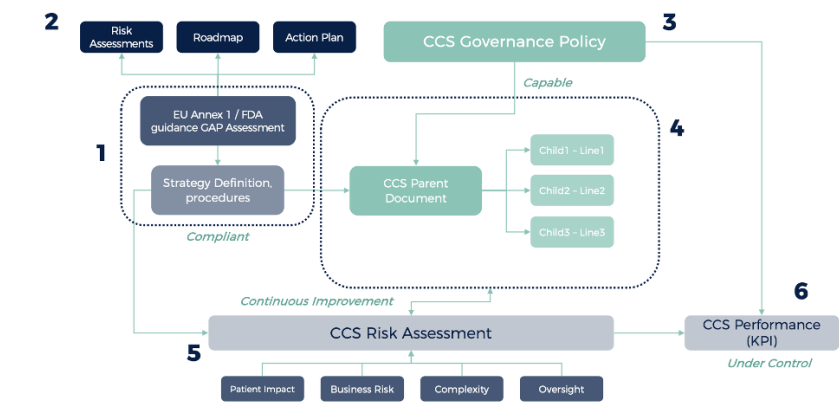
The Contamination control Strategy elaboration is a staged approach starting with Gap assessment and includes of course KPIs. The below model describes the entirety of the strategy elaboration, from the design to the monitoring

Once the Gaps have been identified and categorized from Compliance and Business perspective, the action plan must be rolled out, and in parallel the strategy defined for a sustainable sterility assurance. This is achieved through the use of Risk assessments, standards implementation, etc.

The strategy will be documented in a so called “CCS document” as per Annex one requirement, that aims to be easy to navigate and provide all necessary information supporting the contamination control strategy. The CCS structure may vary depending on the process, or the complexity, but will always provide the elements as described in figure 1.

The strategy for contamination control must be risk assessed to ensure its effectiveness. This will include criteria such as its added value on patient safety, its robustness from a business perspective, but must also include the complexity of the strategy, and the oversight from the Quality Organization. The CCS itself is subject to continuous improvement based on risks!





↑ Figure 2 : Strategy definition from Gap Assessment to KPIs

## A Gap Assessment, yes! But let's think different.

When performing a Gap assessment regarding compliance to Annex 1, several criteria may be used. The goal should not only be to respond to the question “Gap” or “no Gap”, it's never as simple as that, but rather to provide at the same time an information regarding the Risk related to the GAP. That's explained later in this article, but let's talk a little bit about mathematics first.

## Why thinking in ratios is better than considering differences?

When we compare two positive quantities, or values, we can look at their difference (subtract one from the other) or their ratio (how many times one fits into the other). The second approach gives a quicker and actionable information specifically when dealing with lots of Data.

## How our minds reinforce this

Experiments in psychology show that people detect change in proportion to the relative difference, not the absolute one. The tiniest change you can notice in a stimulus is roughly a fixed fraction of its current level. In other words, human perception is tuned to ratios.

That said, we can imagine that a Risk Assessment using Risk Priority Numbers can easily be compared to the maximum score possible, thus telling us how big the Risk is compared to the worst case situation of a 100% Risk. Interesting isn't it? But that's not all.

## Why a logarithmic scale helps

By writing each value as its logarithm (log a, log b). The distance between two points on a log axis is simply log (a ÷ b), the logarithm of the ratio. This single step gives several benefits:

- **Equal spacing for equal ratios.** Doubling, tripling, or halving always occupies the same visual width, so tiny numbers are not squashed and huge numbers are not stretched.
- **Multiplication becomes addition.** Logarithms turn products into sums, which are easier to plot, fit with straight lines, and analyze statistically. **Stable variability.** Data whose scatter is naturally multiplicative (e.g., growth rates) shows a constant spread after logging, making standard tools such as least-squares more reliable.
- **Unit-free comparison.** The log. distance is unchanged if every measurement is rescaled, preserving objectivity.

## What do we conclude out of it?

Ratios capture the true “relative size” of things, our brains naturally track change this way, and a logarithmic scale lays those ratios out in straight, even steps. That makes multiplication-based thinking, expressed through logs, the clearest and most efficient framework for comparing quantities at any scale.

Using a logarithmic calculation system, values are discriminated in the sense that lower values become less visible and higher values gain visibility.

This enables the use of the full range of measurements and helps to better discriminate Risks for an accurate prioritization.

For the calculation, we can use a Log10 referential and divide the result of the calculation by the maximum achievable score, to obtain a result ranging from 0 to 100%.

The graph (Figure 2) beside is generated from random data to calculate a RPN (Risk Priority Numbers) using 4 risk factors (f1 to f4) ranked from 1 to 5 using the formula described, and shows this differentiation between logarithmic ratio (green) and usual linear models (red).

The way data are plotted on the chart enables a better discrimination and subsequently a far more efficient decision making process when it's about setting priorities. Last but not least that doesn't affect the comparative positioning of each item. A low Risks keeps low, and a high risk keeps high, but better separated. Having GAPs visualized in such a way permits the elaboration of a structured action plan. Let's apply this to Annex 1.

## The Annex 1 Gap assessment

The risk scoring system used integrates five key factors: patient impact, business impact, compliance gap, inspection readiness, and likelihood of remediation failure. These are not weighed equally (gap severity carries the highest influence, followed by remediation effort, probability of failure, inspection preparedness, and patient safety impact.

Each factor is rated on a logarithmic scale (low, medium, high) and converted into weighted numerical values, allowing a Risk Priority Number (RPN) to be calculated for each compliance item.

## Company strategy

Should it be for a launch of the facility or a routine re-assessment, criteria will have a different weight. The example below shows the Gap (including all of these aspect for each requirement) will be very precisely evaluated in alignment with the context of the company.

Values are indicative.

The intermediate value (Medium) corresponds to the half of the logarithmic scale between low and max values.

## Gaps calculation

For each Gap, the calculation is made by multiplying the values for all of the 5 criteria, and dividing the log of the result by the log of the maximum values multiplied. It gives for each item of the standard a so called “success score”, not only based on Compliance (Gap/No Gap)

|        | Patient Impact | Business impact | Compliance Gap | Inspection Readiness | Remediation failure risk |
|--------|----------------|-----------------|----------------|----------------------|--------------------------|
| Low    | 1              | 1               | 1              | 1                    | 1                        |
| Medium | 7.7            | 8.9             | 10             | 8.4                  | 8.7                      |
| High   | 60             | 80              | 100            | 70                   | 75                       |

↑ Figure 3 : Weights and relative importance of assessment criteria

but integrating all aspects in terms of risks. In parallel, the calculation is made regarding pure Quality and compliance risks (using patient and compliance criteria), and business risks (using Business and Remediation failure risk).

Back to Annex 1, the compilation of all of these data provide a risk score representing all gaps for on given chapter (Indicative values):

When adding the Preparedness criteria (Inspection readiness), the areas of focus might be slightly different, and calculation (using ratio and logarithmic scale) enable an immediate visualization of areas of focus.

The outcome of this methodology is a multi-dimensional risk map, capturing both quality-related and business-related

areas of focus. These are used to build a focus matrix, visually distinguishing critical issues that combine high compliance risk and high remediation difficulty. The most urgent priorities emerge where compliance risk and difficulty intersect. Each plot of the map represents a requirement from annex 1.

To translate risk scores into action, a prioritization system is applied. This assigns a four-part code to each gap, derived from its overall success score and sub-scores in business urgency, preparedness, and failure risk. The resulting roadmap ensures that the most critical issues (those with high impact, difficult mitigation, and no solution) are addressed first.



↑ Figure 4 : Gaps all compiled from a Risk perspective, per chapter. Quality and Compliance / Business

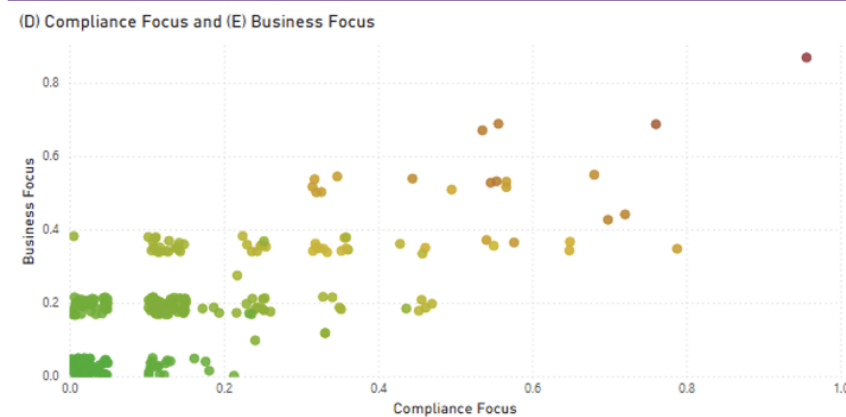


Figure 5 : multi-dimensional risk map, capturing both quality-related and business-related areas of focus



↑ Figure 6 : Priority Roadmap, identifying all actions to be implemented with ranking based on risks

These charts are being generated using Power BI capabilities based on calculation Data sets. enabling a possible periodic re-assessment using the tools, with updates sets of Data, after changes in the process, or regulatory updates for example.

This methodology goes beyond checklist compliance. It enables rational resource allocation, data-driven decision-making, and transparent communication. In doing so, it embodies the risk- and science-based mindset at the heart of Annex 1, where the aim is not only to meet standards, but to sustain a robust, justifiable state of control throughout the product lifecycle.

## And what about KPIs?

In the evolving landscape of contamination control, the ability to measure, interpret, and respond to performance indicators is no longer a complementary feature it is foundational. Within the framework of the Contamination Control Strategy (CCS), Key Performance Indicators (KPIs) are not simply dashboard metrics; they are the analytical backbone that transforms the CCS from static documentation into an operational, verifiable system of assurance.

The proposed process for an effective oversight consists in a multi-layered, data-driven approach. Each component of Annex 1, ranging from premises and utilities to quality control and environmental monitoring, is mapped against five strategic pillars: basics, controls, validation, monitoring, and governance. These pillars form the structure of the CCS, and the KPIs provide the continuous signals that show whether each part is functioning as intended. What emerges is a system where every requirement of Annex 1 is mirrored by at least one measurable indicator, ensuring that completeness, traceability, and trending capability are embedded from the outset.

Metrics are normalized on a 0–100% scale, turning qualitative assessments such as the adequacy of cleaning or personnel training, into quantitative, auditable values. These indicators feed a digital scorecard, visualized through a Power BI dashboard, that not only shows current status but also highlights deviations, risks, and missing data. By incorporating multiple timeframes—quarterly for operational metrics, rolling 12-month windows for seasonal or low-frequency events, and biennial checkpoints for governance activities—the system ensures both granularity and long-term oversight.



Beyond static reporting, the dashboard allows for slicing data by CCS element, department, facility, or even specific process lines. It empowers leadership and quality teams to analyze trends, benchmark performance, and initiate timely actions. For regulators, the KPI structure provides immediate confidence: they are presented not with anecdotal narratives, but with a transparent, continuously updated demonstration of aseptic control.

This KPI-centric model embodies the Annex 1 emphasis on lifecycle quality management. By making contamination risk measurable, comparable, and actionable, the CCS is no longer just a risk strategy, it becomes an engine for sustained GMP performance and inspection readiness. In this context, KPIs do not just inform: they govern.

# skan

Benefit from the excellent performance of our customized production lines

Our customized production isolators with the sophisticated skanfog decontamination technology and the integrated catalyst nanox guarantee a fast and safe cycle time and thus increase the total efficiency of production and filling lines.

With our predefined solutions, the isolator system can be easily tailored and precisely adapted to your production-specific requirements.



skan.com



For further information, please visit:

QP PRO SERVICES



# IT'S NOT THE VIAL WE SELL, BUT THE **EXPERTISE** IT CONTAINS.

*Delivering QP Excellence with a Pragmatic Tailored APPROACH.*

## OUR SERVICES

QP & RP Services

**Consulting** and  
**Operational** Support

Drug Product  
**EU Importation**



## TRUSTED FOR **CONTINUITY.**

Q P P R O S E R V I C E S

More information online



QP PRO SERVICES

[www.qpproservices.com](http://www.qpproservices.com)

[info@qpproservices.com](mailto:info@qpproservices.com)

[linkedIn|QPProServices](https://www.linkedin.com/company/QPProServices)



# CCS.

## Part 1. Deep dive on CCS understanding.

Darine BEHLOUL → Sanofi



Regulations for sterile medicinal products have evolved fundamentally and requirements for aseptic manufacturing are on the rise. Indeed, adherence to the current EU GMP Annex 1 is a significant concern for the pharmaceutical industries. In addition to their routine growth challenges to increase production capacity, efficiency and quality as well as simplifying processes and reducing waste, they are facing new operational challenges requiring technical and organizational adaptations.

Compliance of pharmaceutical companies with current regulatory requirements involves significant investment, extended lead times and expensive upgrades to equipment such as isolators and restricted access barrier systems (RABS) and implementing these measures can be challenging for small companies.

One of the significant changes in the current GMP Annex 1 requires manufacturers to implement a contamination control strategy (CCS). This involves implementing the most recent elements of the pharmaceutical quality system (PQS) and the extended use of quality management principles, as described in the International Council for Harmonization (ICH) guidelines, in particular ICH Q9: Quality Risk Management and ICH Q10: Pharmaceutical Quality System. A robust CCS implementation guarantees compliance, reduces the risk of contamination, enhances product quality and ensures patient safety.

In this first part, I will focus on the deep understanding of CCS by providing answers to the following questions:

- What is your understanding of CCS?
- Do you expect CCS to fit into the PQS (Pharmaceutical Quality System) and how does it interact with existing processes?
- What is the holistic understanding of CCS? Big Picture

### What is your understanding of CCS?

the first impression leads us to say that CCS involves the creation of a document that describes the production process, identifies contamination risks and the associated control measures in place to prevent contamination (microbial, pyrogenic and particulate).

This answer is not entirely false, but is not reflecting all dimensions that should the CCS have, as it focuses exclusively on the way the CCS is documented and misses the holistic approach, leading to the following assumption:

"Besides the documentary aspect, the purpose of setting up a CCS in a company is to develop a continuous oversight of contamination state of control during the manufacturing process of sterile and low bioburden products". What does this mean in concrete terms?

We need to explore more to have the response.....

### Do you expect CCS to fit into the PQS (Pharmaceutical Quality System) and how does it interact with existing processes?

Let's look at GMP Annex 1 requirements that are emphasizing CCS:

**Section 2.3:** "A Contamination Control Strategy (CCS) should be implemented across the facility in order to define all critical control points and assess the effectiveness of all the controls (design, procedural, technical and organizational) and monitoring measures employed to manage risks to medicinal product quality and safety. The combined strategy of the CCS should establish robust assurance of contamination prevention. The CCS should be actively reviewed and, where appropriate, updated and should drive continual improvement of the manufacturing and control methods. Its **effectiveness should form part of the periodic management review. Where existing control systems are in place and are appropriately managed, these may not require replacement but should be referenced in the CCS and the associated interactions between systems should be understood**"

**Section 2.4:** "Contamination control and steps taken to minimize the risk of contamination from microbial, endotoxin/pyrogen and particle sources **includes a series of interrelated events and measures. These are typically assessed, controlled and monitored individually but their collective effectiveness should be considered together**"

**Section 3.1:** "The manufacture of sterile products is a complex activity that requires specific controls and measures to ensure the quality of products manufactured. **Accordingly, the manufacturer's PQS should encompass and address the specific requirements of sterile product manufacture and ensure that all activities are effectively controlled so that**

**the risk of microbial, particulate and endotoxin/pyrogen contamination is minimized in sterile products"**

From sections 2.3 & 2.4, in particular, in the highlighted statements, we can understand that the regulation does not require to create new control systems or measures if they are already existing and well managed, but CCS is coming connecting the dots between these existing control systems, measures and events in order to have a holistic view of the contamination control state in the company.

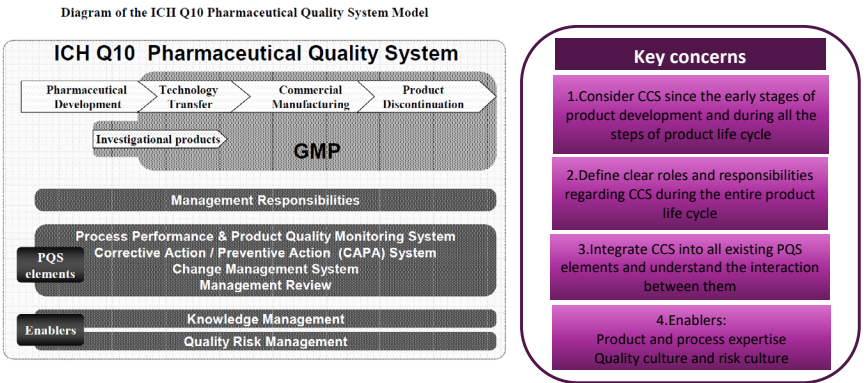
In the section 2.3, a very important element of PQS is pointed out: "**Periodic management review**", so we can understand that CCS should be integrated in the PQS and should interact with all PQS elements.

Finally, the section 3.1 clearly mentions that the manufacturer's PQS should embrace the specific requirements of sterile product manufacturing with the objective of identifying process and control vulnerabilities and the appropriate continuous improvement pathways. So, we can say that:

The CCS is coming to strengthen the PQS with a contamination control dimension (Figure 1)

### Key concerns to ensure a meaningful adaptation of the existing PQS with the contamination control dimension.

Considering contamination control requirements at early stages of projects and the product life cycle, implementing a high level of awareness of contamination risks, an efficient quality culture in the company and defining clear roles and responsibilities at all levels of the organization and during the entire life cycle of the product are key elements for CCS sustainability.



↑ Figure 1 : PQS & CCS interaction



## 1. Consider CCS since the early stages of projects and product development

Designing premises, facilities, equipment, utilities and processes is crucial to guarantee a good level of contamination control since the beginning and during the entire product lifecycle.

The building of a robust User's Requirement Specification (URS) is a Cornerstone in Pharmaceutical Qualification. For sterile processes, this document should capture all aseptic processing needs (Barrier Technology, RTP ports, easy set-up without opening the doors, CIP/SIP, quality oversight feasibility from windows...) and should set the stage for compliant, robust, and fit-for-purpose systems before any design or procurement begins.

Whatever the system or equipment to be qualified, a well-developed URS is the first line of protection against design weakness, regulatory issues and operational failures.

Design qualification is the key step in verifying that contamination control requirements have been met, for example:

- Suitability of the equipment for the specific characteristics of the sterile or low bioburden product and process.
- Positioning instruments and accessibility for periodic metrology testing without compromising product quality.
- Cleanability and hygienic design with easy disassembly for autoclaving.
- CIP/SIP possibility.
- Possibility and accessibility of requalification testing (ex: clean room reclassification, smoke studies exercises...).
- Accessibility for maintenance without compromising product quality.
- Contamination prevention for sterile or multi-product facilities (e.g., back-flow prevention, unidirectional flows, physical barriers, closed systems).
- Design minimizing interventions and, if necessary, interventions thought out carefully in advance, without breaking first air.
- Digital Traceability and Connectivity: equipment should allow automatic data collection for real-time monitoring, deviation detection, and integration into quality systems (e.g.: ERP, SCADA...) to facilitate investigations, trending and CCS effectiveness review.

Challenging engineers and suppliers is highly expected:

- To meet users' needs
- To propose innovative design to meet technical and operational expectations of GMP Annex 1 and other current regulations (ISO, USP...)
- To learn from manufacturing and inspection experience and difficulties (see role of suppliers part)

Every change or upgrade of the premise, facility or equipment must be an opportunity to improve contamination control and to introduce innovative solutions.

Using Quality by Design (QbD) approach is essential for designing processes and the associated control strategies

Contamination control of a new process/product needs to be assessed at various stages of the project: during product & process development, during technology transfer, validation and commercial manufacturing by using adapted risk assessment tools. The purpose of this contamination risk assessment is to improve the process continuously during the project life cycle, if some weakness or risks are identified

Product specifications (except for compendial testing) and sampling plan during the process should be representative and well-designed according to the identified contamination risks (eg. risk of endotoxin contamination, risk of particle and/or microbial contamination... product microbial proliferation properties) to maximize the detectability of any contamination issue and reinforce CCS.

Meeting high level design expectations for premises, facilities, utilities, equipment coupled with an optimized process design and specifications using a risk approach, will strongly reinforce CCS during product development and the

entire project phases leading to a high CCS performance for routine activities and consequently, a high level of industrial performance.

In the diagram below (Figure 2), contamination control requirements are represented as a V Model to provide a global understanding of existing interactions between product/process design and systems/equipment design. This customized CCS V Model works like an immune antibody to prevent and control contamination in the pharmaceutical industry.

## 2. Define clear roles and responsibilities regarding CCS during the entire product life cycle

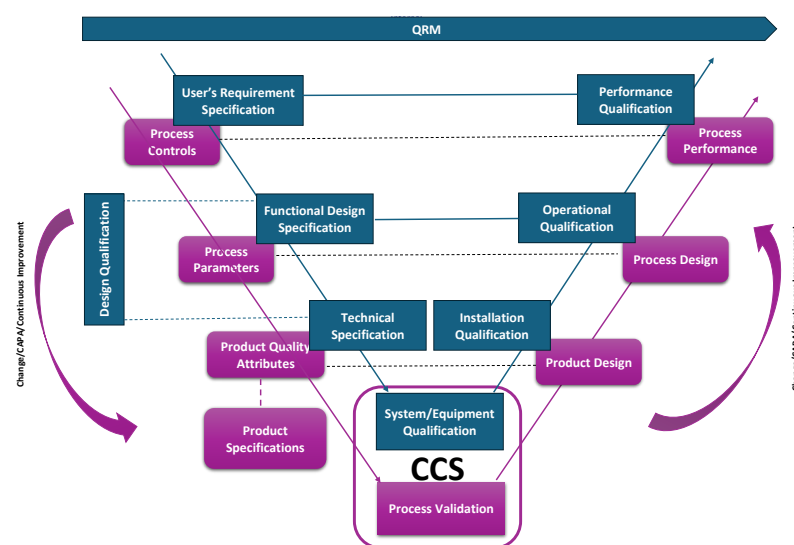
### Role of suppliers

For suppliers, at a time of increasing demand for innovative and accurate treatments, it's essential to have skilled process engineers who understand the complexity of sterile pharmaceutical manufacturing and manufacturer's needs.

The role of process engineering has never been more critical. Whether improving manufacturing efficiency or ensuring compliance with stringent regulatory standards, Supplier's process engineers play a key role in transforming complex processes into rationalized, cost-effective and innovative solutions (e.g. RMM, SUS, AI and digital solutions...)

It is strongly recommended that suppliers and stakeholders work closely together to facilitate understanding of regulatory concerns and challenges.

We can emphasize the potential of networking and innovation as an effective mean of improving suppliers' consideration of user needs.



↑ Figure 2 : CCS V Model

### Management of internal activities

Within pharmaceutical companies, CCS implementation at all levels requires the orchestration of all the impacted resources around a single objective and enables strong collaboration between different professions that previously did not work closely together (e.g. sterility Assurance, project leaders, production, QC, technical services.... quality assurance). The creation of a multi-disciplinary group of different business experts, who work together over the long term, is essential for success.

To create the favorable conditions in which these new challenges can be applied, it is essential to identify opportunities for adjusting the organization, the roles and responsibilities, ways of working and defining clear pathways of escalation.

Once a favorable organizational model has been identified, it must be validated by top management, clearly documented and communicated to all stakeholders.

For such a reorganization, the involvement of top management and stakeholders is fundamental

In fact, team engagement depends on top management's commitment to the strategy: budget available, resources allocated, inter-sector collaboration, all supported by a strong communication on the benefits/risks of implementing a CCS approach, as well as the commitment of the entire management team.

### Management of outsourced activities

Contamination control can also be affected by several outsourced activities (e.g. QC testing, cleaning of classified area, sterilization of materials...) which underlines the importance of subcontractor/ service provider management that should include for a minimum:

- Assessment of the quality system of the subcontractor/ service provider (e.g., change control, change notification of customers, deviation management, good documentation practice).
- In the quality agreement between the customer and the subcontractor/ service provider, consider URS requirements (related to contamination control).
- In the quality agreement between the customer and the subcontractor/ service provider, specify the expectation to have a CCS and its related effectiveness review.
- Regular on-site audits performed by the customer.

When using a CMO or CDMO for manufacturing pharmaceutical products, the implementation of CCS is the responsibility of the CMO or CDMO and should be specified in the quality agreement between the two parts. The customer should have a quality oversight of the CCS.

## 3. Integrate CCS into all existing PQS elements and understand the interaction between them

The elements specified in Figure 1 are the main pillars of the PQS model. They are intended to be used appropriately and consistently throughout the product lifecycle. They should facilitate acknowledgement of opportunities for identifying continuous improvement pathways for contamination control. How can this be achieved using standard PQS elements?

### Changes, deviations and CAPA Management

If we include the CCS in the PQS, the CCS becomes an integral part of the product lifecycle and can evolve as new knowledge is acquired or changes occur. This may involve the modification/adjustment of certain control measures which are an integral part of the CCS. PQS components such as deviation and CAPA management, as well as change management, are triggers for any revision of the CCS.

Therefore, introducing a systematic assessment of the impact on the CCS when dealing with deviations, changes and defining CAPAs (e.g. Change in cleaning & disinfection program, change in personal gowning for a specific operation, CAPA adding a new control measure...) is very useful for having a contamination control strategy that is permanently up to date and under control, acting proactively to prevent deviations and recurrences.

This encourages us to place even greater importance on the accurate definition of root causes, the definition of immediate actions when possible and appropriate CAPA to reduce the risk of contamination and eliminate recurrences. The definition of suitable effectiveness reviews is extremely important.

Some adjustments may be necessary to facilitate data collection, which is very important for the holistic analysis carried out when reviewing the effectiveness of the CCS (for example, categorizing deviations according to CCS elements to facilitate follow-up. eg. glove test integrity failures, EM excursions, sterility testing failures, product leakage... failure in GXP equipment requalification, APS failure, critical alarm occurrence, repeat and recurrent significant events).

## Process performance & Product Quality monitoring system and Management Review

Giving a particular importance to contamination control in all quality management processes is very helpful:

- In starting the reflection about contamination risks at each stage and being able to alert and escalate as early as possible.
- In preparing the needed data for CCS effectiveness review.

The type of monitoring can also be adjusted (in type, number and frequency) using adapted risk management tools to be able of detecting any drift in the level of control. A well-designed monitoring programs (EM program, cleaning program, utility monitoring, deviations, complaints.... QC testing trending, alarm trending) will help to select the adapted Metrics for the CCS effectiveness review.

The purpose of performing the CCS effectiveness review at a regular basis is to evaluate CCS performance during the life cycle of the product and identify any improvement or remediation actions. This CCS effectiveness review should form part of the periodic management review (Section 2.3 of GMP annex 1) already in place (eg. PQR, APR, CPV...)

In order to better understand the functioning of all these existing quality reviews and product monitoring, their relationship should be clarified to make sense and take benefit of the outcome of each exercise for performing the holistic review of CCS performance.

And you, has your company redesigned its existing PQS systems to include a contamination control dimension?

## 4. PQS Enablers:

As illustrated in Figure 1, two key enablers are identified in the PQS model:

- Product and process expertise
- Quality & risk culture

Let's make a focus on contamination control applicability

### Product and process expertise:

For manufacturers of sterile products, developing skills and competencies in product knowledge, contamination control, microbiological fundamentals, investigation tools and root cause analysis is required for key positions participating in the steps of design, qualification/validation, contamination risk assessment, routine manufacturing according to well-designed procedures, maintenance in clean area, trending analysis, investigations, CAPA definitions, Quality Assurance and Quality Control.



this expertise grows over time and during the product life cycle (changes, process adaptations, regulatory evolution...), underlining the importance of a long-term organization with the identification of SMEs in critical fields.

An individual and collective development plans should be in place for each employee according to the needs of his function. A special focus should be done on contamination control risk identification, proactive evaluation before the problems occur, continuous improvement actions and escalation paths. Networking with peers and potential suppliers as well as attending conferences on regulatory evolutions, microbiology days and aseptic production is highly recommended and should not be limited to quality employees.

All these elements will impact positively shaping the pharmaceutical future with innovative technologies and optimized design

#### Quality & risk culture

Embracing an efficient quality culture in our day-to-day activities is a real challenge nowadays for pharmaceutical companies, with the increasing expectations of sterile product manufacturing. Agile and innovative solutions should be implemented at all levels of the organization to give sense and should use a variety of smart educational tools adapted to each audience. Practical and interactive case studies have a real added value for developing the mindset of employees to better understand risks and act appropriately.

Companies' top management and the quality department are the essential actors for promoting quality culture. It is essential that managers lead by example, incarnating quality values in their daily actions, decisions and orientations. Their awareness about the added value that a sustainable quality culture can have on our way of working, on our performance and on the company's brand image will help for setting strategic orientations and objectives of the company every year.

Close collaboration between operational stakeholders (e.g. the production department, engineering and technical services....) and human resources is crucial for defining the targeted agile initiatives to promote these principles: regular culture talks (about : risk management, continuous improvement and contamination control management) , continuous campaign of awareness on contamination control , agile projects focused on continuous improvement, new working methods, dedicated quality weeks, quality podcasts, targeted training,

ongoing collaboration with operational staff and creative ways of engaging teams in this important subject.

Implementing a strong quality culture is not only a matter of compliance or the only business of the quality department but the business of all the company from the top management to the operational directly involved in manufacturing, packaging operations and distribution.

As required by GMP annex 1(section 3.1): "the risk management is applied in the development and maintenance of the CCS, to identify, assess, reduce/eliminate (where applicable) and control contamination risks. Risk management should be documented and should include the rationale for decisions taken in relation to risk reduction and acceptance of residual risk".

This clear requirement emphasizes the importance of risk culture and the use of QRM for supporting a robust CCS in the company. Other regulations such as, The CFR - Code of Federal Regulations, ICH, PIC/S have in recent years incorporated in their guidance's, the requirements for using QRM during the entire product life cycle. The added value of using QRM principles is to identify our existing risks, to cote their criticality, mitigate them by proposing continuous improvement actions. Embracing a proactive risk approach is a key element for preventing and reducing contamination

As precised for quality culture, risk culture is also a prerequisite for CCS implementation and should be promoted by the company's leadership. It's useful not only for risk assessments redaction but also useful for everyone to embrace a risk behavior. It means that every employee should be able:

- To identify quality and contamination risks,
- To assess the risk with relevant bodies contribution,
- To act appropriately according to defined procedures,
- And to escalate if it is assessed critical for patient safety and/or product quality and/or business continuity.

#### What is the holistic understanding of CCS? CCS Big Picture (Figure 3)

According to this deep analysis supported by examples, experience, solution proposals to comply with regulatory requirements and enhance performance, we gained some maturity in CCS understanding. We can finally say with confidence, that CCS is much more than a regulatory document available

for inspections. In order to ensure its optimized working, CCS should be integrated in the PQS: Pharmaceutical Quality System at all levels and during the overall lifecycle of the product. For sterile and low bioburden products manufactures, **CCS is coming connecting the dots between PQS elements to enhance contamination control.**

This leads to the following statement:

"CCS is developing a corporate strategy/approach to mitigate the risks of contamination during the manufacturing process of sterile and low bioburden products. It requires:

- A corporate quality and risk culture at all operational levels.
- A Sterility Assurance expertise derived from comprehensive knowledge of the processes and a thorough understanding of the associated risks and vulnerabilities.
- A well-designed product process, facilities, premises, utilities and equipment using innovative technologies, qualified personal and well-designed contamination control measures.

The implementation of such strategy in a sustainable manner needs some organizational, technical, design and operational considerations (GMP Annex 1 section 2.3)".

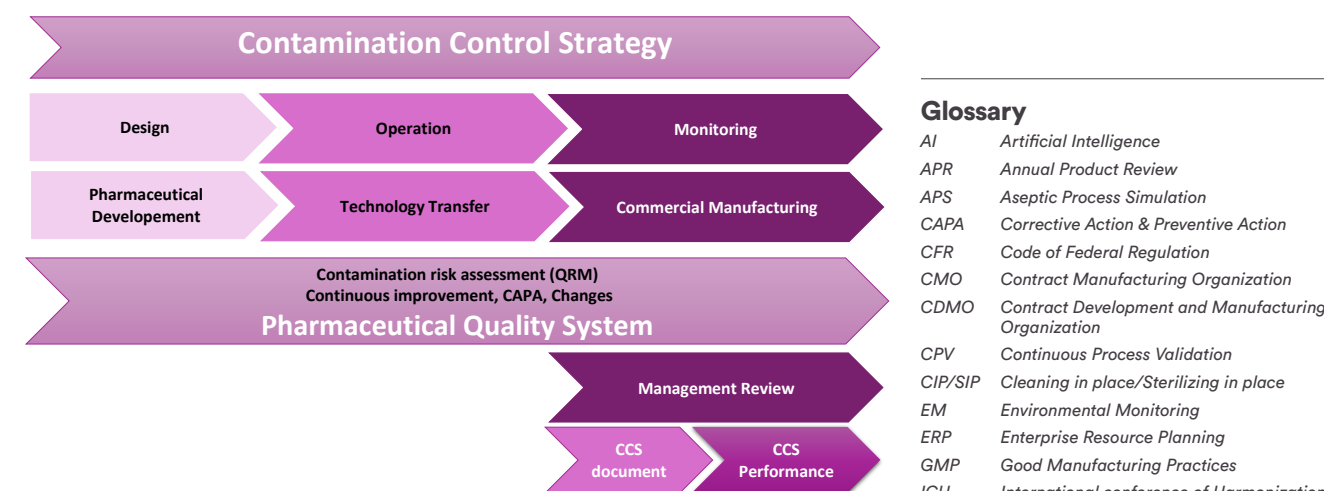
#### Conclusion

It should be noted that CCS is not a regulatory limitation. If well designed from the beginning and well managed throughout the product life cycle, it can be used as a quality and performance management tool. The purpose of CCS implementation is to reach a contamination control maturity level in the company. Therefore, we are aware of our risks, proactively manage them before a deviation occurs and introduce a continuous improvement approach to reinforce CCS on an ongoing basis.

CCS Mindset needs a strong involvement of sites leaderships & management and is strongly enhanced by:

- Promoting **QUALITY CULTURE** at all operational levels: by using agile tools for approaching all employees and enhancing Sterility Assurance awareness and expertise.
- Promoting **QRM CULTURE** at all operational levels: by embracing proactive risk management with adapted tools and organization.
- Promoting **CONTINUOUS IMPROVEMENT CULTURE**: by overcoming resistance to change.

Please keep in touch for the next parts to continue CCS story....



↑ Figure 3 : CCS Big picture

#### References

1. GMP Annex 1: Manufacture of Sterile Medicinal Products
2. A3P CCS guide : CONTAMINATION CONTROL STRATEGY, A3P Guide & Template, VOL. N° 13 // December 2022
3. A3P QbD guide : Le QbD, une approche visant à mieux connaître le procédé, pour mieux le piloter et non le subir (Stages 1 & 2), VOL. N° 8 // Janvier 2022
4. CCS PDA guide (TR90): Contamination Control Strategy Development in Pharmaceutical Manufacturing
5. ICH Q9: Quality Risk Management
6. ICH Q10: Pharmaceutical Quality System

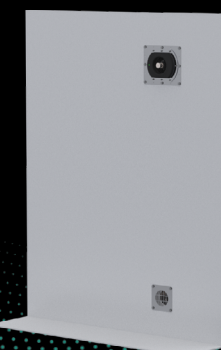
#### Glossary

|         |                                                     |
|---------|-----------------------------------------------------|
| AI      | Artificial Intelligence                             |
| APR     | Annual Product Review                               |
| APS     | Aseptic Process Simulation                          |
| CAPA    | Corrective Action & Preventive Action               |
| CFR     | Code of Federal Regulation                          |
| CMO     | Contract Manufacturing Organization                 |
| CDMO    | Contract Development and Manufacturing Organization |
| CPV     | Continuous Process Validation                       |
| CIP/SIP | Cleaning in place/Sterilizing in place              |
| EM      | Environmental Monitoring                            |
| ERP     | Enterprise Resource Planning                        |
| GMP     | Good Manufacturing Practices                        |
| ICH     | International conference of Harmonization           |
| PIC's   | Pharmaceutical Inspection Co-operation Scheme       |
| PQR     | Product Quality Review                              |
| PQS     | Pharmaceutical Quality System                       |
| QbD     | Quality by Design                                   |
| QC      | Quality Control                                     |
| QRM     | Quality Risk Management                             |
| RMM     | Rapid Microbiology Method                           |
| RTP     | Rapid Transfer Port                                 |
| SCADA   | Supervisory Control and Data Acquisition            |
| SME     | Subject Matter Expert                               |
| SUS     | Single Use System                                   |
| USP     | United States Pharmacopeia                          |
| ISO     | International Organization for Standardization      |

## Phileas® AIRLOCK : Le meilleur de la technologie DSVa de Devea, intégrée



A l'extérieur du sas



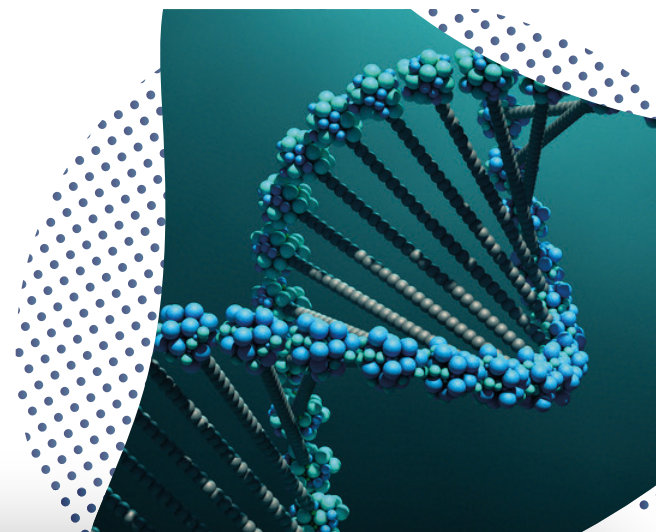
A l'intérieur du sas

- **Encombrement minimal**  
Module de diffusion affleurant, pas de perte de place à l'intérieur du sas
- **Sécurité maximale**  
Sonde H<sub>2</sub>O<sub>2</sub> intégrée, sécurité avant démarrage, contrôle des portes
- **Process intégré**  
Automate industriel, communication modbus avec la GTC (CTA, portes) : lancement de la DSVa en un seul clic
- **Idéal pour sas neuf ou revamping**





L'alliance des compétences  
pour répondre aux exigences  
des biomédicaments



TERANGA vous accompagne pour vos tests de sécurité biologique et les essais physico-chimiques permettant de caractériser ou contrôler vos matières premières, produits intermédiaires et produits finis dans des conditions GMP ou R&D.



## Spécialisé en tests de biosécurité

### Microbiologie :

- Tests de stérilité, charge biologique, pureté et viabilité, tests sur les endotoxines bactériennes
- Identification microbienne (MS Maldi TOF, MicroSeq)

### Virologie, biologie moléculaire et immunoessai :

- Quantification des acides nucléiques
- Détection de mycoplasmes (qPCR), ADN résiduel et protéines résiduelles, contaminants, impuretés (ELISA)
- Détermination des protéines totales et de leur pureté



## Spécialisé en physico-chimie

- Développement analytique à façon, de la R&D jusqu'au stade commercial
- Contrôle Qualité des matières premières et produits finis
- Recherche spécifique d'impuretés et d'agents de transfection
- Etudes de stabilité



### NOTRE VISION

Être un partenaire fiable et disponible au delà d'une simple relation client-fournisseur.



### NOS MISSIONS

Apporter des solutions techniques et réglementaires durant les différentes phases de développement et de contrôle de vos produits.



### NOS VALEURS

Le sens du service, notre proactivité et l'épanouissement de nos équipes sont des éléments clés de la réussite de vos projets.



info@acmpharma.com  
30-36 avenue du 21 août 1944, 45270 Bellegarde  
+33 (0)2 38 90 40 01  
Faculté des Sciences Pharmaceutiques  
35 Chemin des Maraîchers, 31400 Toulouse  
+33 (0)5 82 95 20 50



contact@cebiphar.com  
1 rue de la Bodinière, 37230 Fondettes  
+33 (0)2 47 42 48 48  
3 rue des Satellites, Canal Biotech 2, 31400 Toulouse  
+33 (0)5 82 95 90 68

# Quality Assurance.

## No detail left behind: A holistic approach to opening authorization in Sterile Manufacturing.

Clémence LAMBERT & Michel HERTSCHUH → AKTEHOM



The process of obtaining authorization to open a pharmaceutical site in France is governed by a standardized form issued by the ANSM. This form is structured into three main sections: the applicant's identity, detailed information about the future pharmaceutical site – including the name of the responsible pharmacist – and a technical note that precisely outlines all planned activities at the new location.



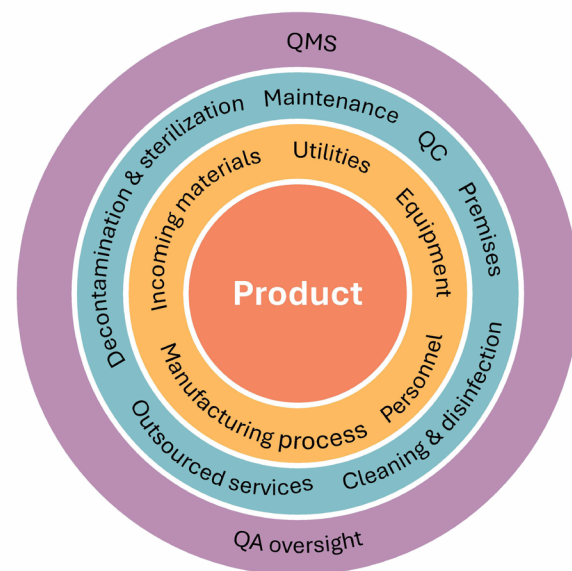
In the context of modifying an industrial site to accommodate a new sterile product manufacturing unit, any change to the pharmaceutical site must be reported to the health authorities. While the ANSM provides a formal framework, the structure and content of the modification request – particularly the description of its impact on existing operations – remain relatively flexible. The applicant is free to present the changes and their implications in the manner they consider most appropriate.

However, the responsibility for ensuring the completeness of the modification description lies entirely with the applicant. This task can be particularly challenging, as feedback from the authorities often resembles a detailed reminder of GMP. The goal of this article is to support pharmaceutical industrials in achieving a comprehensive submission by highlighting the key elements that should be described and included in the modification request. In some cases, the reminders provided in the various sections directly address specific expectations from health authorities.

The article outlines critical points to consider when submitting a request to modify the opening authorization of a pharmaceutical site. These points are organized into 12 sections, each corresponding to a specific activity or function within an industrial site.

All the sections discussed in this article aim to bring the product – positioned at the center of [Figure 1](#) – under control.

The first circle of elements to be put under control when initiating a change request in the regard of the obtained opening authorization. It includes those



↑ *Figure 1 : A quality product - the target of manufacturers*

directly related to the product: incoming materials, utilities, equipment, personnel, and the manufacturing process. The following circle corresponds to support production activities, i.e. cleaning and disinfection, decontamination and sterilization, maintenance, QC, premises, and outsourced services. Finally, the QMS and QA oversight are intended to ensure the sustainability of processes to guarantee the overall product quality.

## Section 1: Utilities

The sterile product manufacturing unit may follow a single-use approach, a conventional approach, or a hybrid of both, depending on the strategy chosen for the project. The utilities involved in such modifications are not always the same. In this case, we are addressing a

modification that requires the full range of utilities, namely various pharmaceutical-grade waters, clean steam, and process gases.

As part of this, the modification request must include a description of the creation and/or changes to the production/distribution systems for water, gases, and steam, along with the proposed design. The applicant must also justify the requirements for each utility involved (expected quality, point of use, use or not of terminal filtration). When filters are to be included in the installations, the control strategy for these filters must be detailed.

In certain cases, it may be relevant to describe the other utilities used – particularly when they are involved in controlling critical process parameters

manufacturer status or the importer status, when their activities are limited to batch release.

- For manufacturers of medical gases, the addition of a storage room for packaged gases.
- Administrative change such as change in the legal form of the company, change in the corporate name of the company, appointment of a new responsible pharmacist, transfer of the registered office, change in the wording of the address of a pharmaceutical site, discontinuation of an activity or pharmaceutical operation (see Article R5124-10-1).

All other modification should be mentioned in the annual state declaration.

or clean utilities. For example, if temperature maintenance is required for critical process steps, it is appropriate to describe the technical elements used to control temperature (description of the planned monofluid system, such as glycol water, industrial steam, chilled water, silicone oils, liquid nitrogen).

## Section 2 : Equipment

The new Annex 1 of the GMP guidelines emphasizes barrier technologies over conventional filling line configurations. It is the responsibility of the manufacturer to demonstrate the relevance of its technical choices. The operating principles of the newly implemented equipment must be explained, along with the proposed qualification approaches. Particular attention is expected regarding flow management, especially when barrier technologies are introduced on a site that previously did not have them.

In the modification request form, it is advisable to list the main equipment added, including their planned location, function, and operating principles. Depending on the case, this may include:

- Preparation area (weighing of raw materials, formulation tanks, storage tanks, filtration)
- Filling line (washing machine / depyrogenation tunnel / filling machine / capping machine / labelling machine / RABS / isolator)
- H<sub>2</sub>O<sub>2</sub> airlocks / transfer isolators / autoclaves / RTP transfers / stopper preparation
- Freeze-dryer (including loading/unloading and tray handling if applicable)
- CIP/SIP systems for all equipment
- Packaging equipment

Special attention must be paid to the material flow into the cleanrooms. The transfer of materials through airlocks and cleanrooms must be described in detail, including the specific requirements related to transfer between different cleanroom classifications and any class breaks.

This section must also include the qualification principles for the equipment, specifying the parameters to be studied based on the equipment involved.

Finally, if the unit is to be equipped with a RABS or an isolator, the modification request must provide sufficient information on its design, airflow management and first air strategy, disinfection, integrity testing methodology and glove replacement, as well as cleaning and decontamination inside the barrier system.

## Section 3: Personnel

Any request of opening authorization modification requires an assessment of human resource needs, both in terms of staffing and skills. New practices must be identified particularly if the asepsis mindset isn't yet implemented.

The planned production capacity, particularly the number of batches, may justify the adequacy of current or future resources with the introduction of new activities. A structured training plan must be established, including qualification, authorization, and disqualification procedures for personnel.

In the case of new technologies or pharmaceutical forms being introduced, specific strategies for microbiological monitoring and training must be implemented and described – particularly for operators, QC, and maintenance teams. The technical note must indicate – if the new unit requires additional resources in terms of skills or staffing – which departments are impacted by the change.

It is essential to justify this by specifying the expected capacity of the new unit in terms of the number of batches produced. The objective is to demonstrate that the resources available now or in the future will be aligned with the needs for implementing the new pharmaceutical activities.

The technical note must describe the training process planned for the new activities. It may also outline the procedures already in place for qualifying and authorizing personnel for their roles, or for temporarily disqualifying them depending on the context.

In the context of the new activity – especially if it involves the introduction of a new technology (e.g., barrier technology) – a strategy for microbiological monitoring of operators must be described in the technical note. The asepsis mindset is essential and should be outlined (major procedures like gloves management, aseptic behavior). If parenteral products – which by definition require sterility assurance – are introduced on site, all production and QC personnel must be trained not only in sterility sampling and testing procedures, but also in environmental and product microbiological control.

The personnel section in the request form should not only focus on the resources involved in the manufacturing or control of new products, but also on the entire chain of personnel involved, up to the release of the new products.

In particular, if the new activity involves a new pharmaceutical form (e.g., lyophilized product, vaccine, etc.), the staff responsible for certifying the finished product must be trained for the new product type or new process steps.

It is strongly recommended to specify that training plans will be updated specifically to incorporate this new pharmaceutical form – for all relevant roles: production, QC, and maintenance in particular.

## Section 4: Manufacturing process including holding times, visual inspection

To facilitate the evaluation and approval of the request for modification, the process and all planned operations should be described. The proposed validation aspects must be outlined and explained, covering not only the manufacturing and filtration processes but also the filling steps and all auxiliary processes.

The description of the process and planned operations may be presented in the form of a flowchart to ensure easy understanding and to provide a comprehensive overview for the authorities.

The validation aspects of the new process must be detailed in the technical note, and should include but not limited to the following:

- Validation of the aseptic process, including the definition of critical operations and process times through a risk analysis,
- Validation of CIP processes, specifying the intended method,
- Validation of SIP processes,
- Depyrogenation validation,
- Validation of the overall process (concerning the new unit).

It is important to specify that the various critical durations introduced by the modification will be verified as part of these validation activities. The durations to be considered in the technical note include, among others: time between the start of manufacturing and sterile filtration, filtration duration, filling duration, loading time of a freeze-dryer (between sterile filtration and lyophilization), time out of refrigeration if applicable, as well as dirty holding time, sterile holding time, clean holding time.

Additional elements must be included, notably the flow between the exit of the fill & finish area and the visual inspection zone. Linked to the visual inspection activities holding times, monitoring of

## When should you submit a modification request to the health authorities?

The list of modifications requiring a request to the ANSM is specified in Articles R5124-10 and R5124-10-1 of the Public Health Code :

- The manufacture or importation of a new category of products among medicinal products for human use, investigational medicinal products for human use, cannabis medicine, any system containing a radionuclide (generator, kit, precursor).
- The manufacture or importation of a new pharmaceutical form or a pharmaceutical product not covered by the current opening authorization.
- The implementation of a new

pharmaceutical operation related to manufacturing, importation, or exploitation.

- The creation of premises where pharmaceutical operations such as manufacturing, importation, wholesale distribution, or storage are carried out.
- The removal of premises where production and quality control operations are performed, or any removal of premises (including the change of holder of part of the authorization to open a pharmaceutical site).
- Changes to the storage conditions of drugs classified as narcotics.
- Modification of the distribution territory mentioned (for distributors).
- Relocation within the same site of a pharmaceutical site holding the



time out of refrigeration, description of the intermediate storage area, time since terminal sterilization should be described.

The new Annex 1 of GMP also places significant emphasis on the filtration process and its associated requirements. Therefore, the product filtration modalities must be described, particularly the position of the filter relative to the filling point. The technical note must specify the validation strategy for the product sterilizing filter.

### Section 5: Incoming materials (i.e. raw materials, components, single-use systems, consumables)

The opening of a new manufacturing unit is often accompanied by the introduction of a new product at the site in question. New product means new incoming materials, with supply conditions that may be more or less standardized. The addition of the handling of these raw materials, components, and consumables required for the production of the new product – and their impact on existing flows – must be assessed in relation to current material flows.

It is therefore essential to declare all new raw materials and consumables, particularly any new active substances. These changes must be subject to an impact assessment with respect to existing flows to ensure full control over the risk of cross-contamination. In particular, the management of any GMOs introduced as a result of the modification must be specified.

This section may also describe the implementation of SUS, where applicable.

### Section 6: Premises

The addition of a sterile manufacturing unit can be implemented in several ways, e.g. by extending an existing building, integrating it into an active production area, or building an entirely new facility. Regardless of the approach, such a project inevitably alters the site's infrastructure.

When referring to infrastructure, this includes both the structural elements (e.g., building shell) and the production environment, with particular attention to confinement and air handling systems. Beyond these structural components, it is essential to provide a detailed description of all anticipated flows within the new manufacturing unit.

A comprehensive flow description should encompass product/intermediates movement, sample handling, personnel circulation, all types of materials, raw materials (including weighed materials), and waste management. The more holistic and detailed flow mapping, the better it supports regulatory expectations.

Additionally, the implementation of infrastructure control systems – such as an EMS – must be clearly described to demonstrate how the environment will be monitored and maintained under control.

The construction of the structural works mainly involves the provision of site layout drawings and building drawings.

The finishing works must include the basic technical characteristics of the materials and technical principles used (e.g., confinement & glazing, doors, floors, ceilings, airlocks). Details must be provided regarding the management of piping and drainage systems planned in the cleanrooms, particularly concerning

cleanability, maintenance, and disinfection aspects. Measures planned for the visualization of activities in Grade A/B areas must be described, and the area drawings should allow identification of glazed surfaces.

Air treatment systems are one of the key elements ensuring the sterility of manufactured products. Therefore, any request for modification must emphasize all related elements. Drawings showing cleanroom classifications, pressures, temperatures, and humidity levels (when controlled) must be attached to the request. When specific products such as plasmids or viral vectors are expected in the area, the specificities related to the nature of those products must be presented.

It is important to specify which AHUs will be newly installed or modified, as well as the list of rooms served by each AHU. The airflow principles applied to prevent any contamination (cross, particulate, or microbiological) must be described – for example, the use of low-level air intakes, implementation of sufficient air change rates, use of fresh or recirculated air, and the intended use of air extraction systems. Finally, the general operating principles of the air handling units, including during airborne decontamination phases, must be explained.

**Nota bene:** *If an H<sub>2</sub>O<sub>2</sub> airlock is used and if it is considered as an equipment instead of a room, the airlock must appear on drawings. It is strongly recommended to specify the classification of the airlock.*

Furthermore, the qualification procedures for rooms and airflow (airflow visualization studies at rest and in operation) must be documented, along with the methods for defining the number of people per room.

implemented, such as the temporal or physical segregation of flows (e.g., separation of material, personnel, and waste airlocks).



Cleanroom monitoring is generally ensured by EMS in which alert and action thresholds are defined, with appropriate delays depending on the criticality of the alert or action. The type of alarm reported (pressure, temperature, humidity) and the principle for defining alarms based on room types where alerts are triggered (e.g., airlocks but not Grade D areas) must be defined.

Another measure to control contamination risks is the management of flows both in the routine and during project, in case the production site is modified. All flows must be described, and should include but not limited to the following: personnel, raw materials, packaging items, consumables, bulk and semi-finished products, finished products, samples, dirty, clean, and sterile equipment, waste, and rejected units. In manufacturing unit designs which include Grade A and B areas, incoming and outgoing items must be managed with distinct unidirectional processes (either temporally or physically), meaning that entry and exit airlocks must be different. If such a design is not possible, the movement management of each type of item must be described in the technical note. Measures to prevent potential contamination of incoming items must be clearly specified. Measures planned to prevent cross-contamination must be described, and include a mandatory risk analysis detailing the means to protect the product, i.e. separation of flows in space or time, use of specific equipment such as BSCs, and application of personnel, material, and product flow rules.

If a modification is made in an active part of the building, it is recommended to carry out a risk assessment and define containment measures to ensure that the building works (risk of contamination, vibrations, dust, heat) and access by external personnel will not impact production areas near the new area in construction.

Finally, the arrangements for managing storage areas and associated environmental conditions must be described in detail.

### Section 7: Maintenance

Maintenance activities must take into account the introduction of new technologies such as a RABS, an isolator, or an automatic freeze-dryer loading system. The specificity of these interventions requires the development of appropriate maintenance procedures.

These procedures must consider the scenarios for introducing tools into the aseptic environment, whether through the use of RTP (Rapid Transfer Ports), or through a strategy involving the permanent presence of tools within the isolator or RABS. These procedures must be challenged and validated during APS exercises.

### Section 8: Quality control

When establishing a new area, the health authorities expect that new finished products – and therefore their associated controls – will be introduced, requiring analytical validation.

In addition, an in-process and finished product sampling plan must be outlined. Within this framework, sterility testing for each product must also be mentioned.

### Section 9: Cleaning & disinfection

The planned measures for contamination control through the cleaning and disinfection of premises and equipment must be specified, even if such practices are already in place on site. The overarching principles for validating these processes must also be documented.

This section should describe the cleaning of premises, including the nature of the products used (disinfectants, sporicides, process-specific agents such as virucides, fungicides, biocides for plasmid removal). The cleaning of equipment – detailing the strategy for product-contact surfaces and, similarly to premises, the external surfaces and indirect product-contact parts of the equipment should also be described.

In the case of SUS, any remaining product-contact surfaces requiring cleaning must be clearly identified in the change request.

### Section 10: Decontamination & sterilization

Since decontamination and sterilization are parts of contamination control in sterile product manufacturing areas, the request for modification of opening authorization must outline the planned approach. In particular, the technical note must present how critical elements will be controlled. It should mention the definition of the equipment concerned, the establishment of detailed loading patterns, and the acceptance parameters for the various cycles. The validation approach must be documented.

A list of materials to be decontaminated in the H<sub>2</sub>O<sub>2</sub> airlock or autoclaved for introduction into Grade B areas must be provided. It is also necessary to announce the creation (or the update) of procedures detailing the loading configuration for the airlock, autoclaves, isolator, or RABS, to ensure complete surface decontamination or sterilization.

Acceptance parameters for H<sub>2</sub>O<sub>2</sub> cycles (relative humidity / temperature / H<sub>2</sub>O<sub>2</sub> quantity) or autoclave cycles (pressure / temperature) used in routine must be provided.

The strategy implemented for components in indirect contact with the product at the filling machine level, including washing, autoclaving procedures, and control measures for hidden surfaces or those exposing the first air must be presented.

Concerning validation/qualification aspects:

- H<sub>2</sub>O<sub>2</sub> decontamination validation should include but not limited to residue measurement and the use of biological indicators.
- Sterilization processes must also be supported by biological indicators results.
- Processes combining sterilization and surface/air disinfection of equipment in indirect contact with the product must also be described and validated.

In any case, those exercises must be supported by a risk analysis.

### Section 11: Outsourced service

When submitting a request for opening authorization modification, although no specific documentation is formally required by the authorities, it is important to recall that all outsourced activities must be governed by a written contract with clearly defined responsibilities. This applies even if the outsourced activities are not directly impacted by the project.

Furthermore, the contracting organization retains ultimate responsibility for the review and evaluation of records and results provided by the subcontractor.

### Section 12: Quality Management System & QA oversight

The existing quality system is, in principle, applicable even in the context of new projects. Any necessary adaptations of the system for the new facility must be clearly described and must take into account aseptic control aspects.

### Best Practices for Managing Flows

Numerous flows must be brought under control in a pharmaceutical manufacturing facility. They are interconnected and, in some cases, may intersect or occur simultaneously.

The main flows concerned are as follows:

- Semi-finished product / sample flow
- Personnel flow
- Waste flow
- Consumables flow
- Sterile equipment flow
- Clean equipment flow

- Dirty equipment flow
- Raw material flow
- Weighed material flow

As part of a request for modification of opening authorization, it is essential to apply the core principles described in GMP during the design of production areas.

Although personnel are by definition central to the management of flows – most often being responsible for moving materials from point A to point B – special attention must be paid to the handling of waste and dirty equipment.

Preservation measures must be



The organization set up to ensure sterility assurance level should be described. The contamination control strategy planned should document means to ensure effective monitoring of the newly introduced aseptic process.

It is recommended that the CCS be established concurrently with the submission of the modification request. Quality Assurance oversight should be defined based on the CCS elements, in connection with the monitoring of the various activities.

## Conclusion

This article has provided an overview of the key expectations when submitting a request for opening authorization modification. This exercise should not be underestimated, as it plays a crucial role in building confidence with regulatory authorities and demonstrating technical mastery of the new operations. A well-prepared submission facilitates both the approval process and the successful launch of the new manufacturing area.

To achieve this, several critical domains must be brought under control and clearly described:

- **Premises:** Layout, zoning, and classification of cleanrooms.
- **Utilities:** HVAC systems, water and clean steam systems, compressed gases.
- **Equipment:** Qualification status, integration of new technologies (e.g., isolators, RABS, automated systems), flow managements.
- **Incoming Materials:** Control strategies for raw materials, packaging components, consumables, and single-use systems (SUS).
- **Manufacturing Process:** Description of the process flow, critical steps and aseptic operations, validation aspects.
- **Personnel:** Staffing, skills, training plans, qualification and disqualification procedures.
- **Maintenance:** Adapted maintenance plans for new technologies and aseptic environments.
- **Cleaning & Disinfection:** Procedures, agents used, and validation strategies for both premises and equipment.
- **Decontamination & Sterilization:** Control of critical parameters, loading patterns, and validation of H<sub>2</sub>O<sub>2</sub> and autoclave cycles.
- **Outsourced Services:** Contracts, responsibilities, and oversight of subcontracted activities.

- **Quality Control:** Analytical validation, in-process and finished product sampling plans, including sterility testing.
- **Quality Management System & QA Oversight:** Adaptations to the existing system, integration of the CCS, and QA involvement across all activities.

By addressing each of these items comprehensively, the submission will reflect a robust and proactive approach to quality and compliance, aligned with authorities expectations and industry best practices.

## Glossary

|      |                                                                     |
|------|---------------------------------------------------------------------|
| AHU  | Air Handling Unit                                                   |
| ANSM | Agence Nationale de Sécurité du Médicament et des Produits de Santé |
| APS  | Aseptic Process Simulation                                          |
| BSC  | BioSafety Cabinet                                                   |
| CCS  | Contamination Control Strategy                                      |
| CIP  | Cleaning In Place                                                   |
| EMS  | Environmental Monitoring System                                     |
| GMO  | Genetically Modified Organism                                       |
| GMP  | Good Manufacturing Practices                                        |
| HVAC | Heat, Ventilation and Air Conditioning                              |
| QA   | Quality Assurance                                                   |
| QC   | Quality Control                                                     |
| QMS  | Quality Management System                                           |
| RABS | Restricted Access Barrier System                                    |
| RTP  | Rapid Transfer Port                                                 |
| SIP  | Sterilization In Place                                              |
| SUS  | Single Use System                                                   |



# MAÎTRISEZ LA CONTAMINATION.

## Fabriqué à partir de fibre de carbone

Manche extrêmement léger sans perte de résistance.

## Manche télescopique

Cinq longueurs différentes disponibles de 32cm à 8m.

## Flexibilité totale

Compatible avec tous les cadres de tête de balai QuickConnect de Contec.

## Système de verrouillage facile

Ajuste la longueur rapidement et en toute sécurité selon les besoins.

Jusqu'à  
**60%**  
plus léger que les manches en acier inoxydable

## Voici les manches de balai en fibre de carbone QuickConnect de Contec.

Spécialement conçus pour les salles blanches, les manches en fibre de carbone améliorent considérablement l'ergonomie du nettoyage et de la désinfection grâce à leur poids réduit.

Pour plus d'informations ou pour organiser un essai, contactez-nous à l'adresse suivante : [infoeu@contecinc.com](mailto:infoeu@contecinc.com)



SCANNEZ-MOI

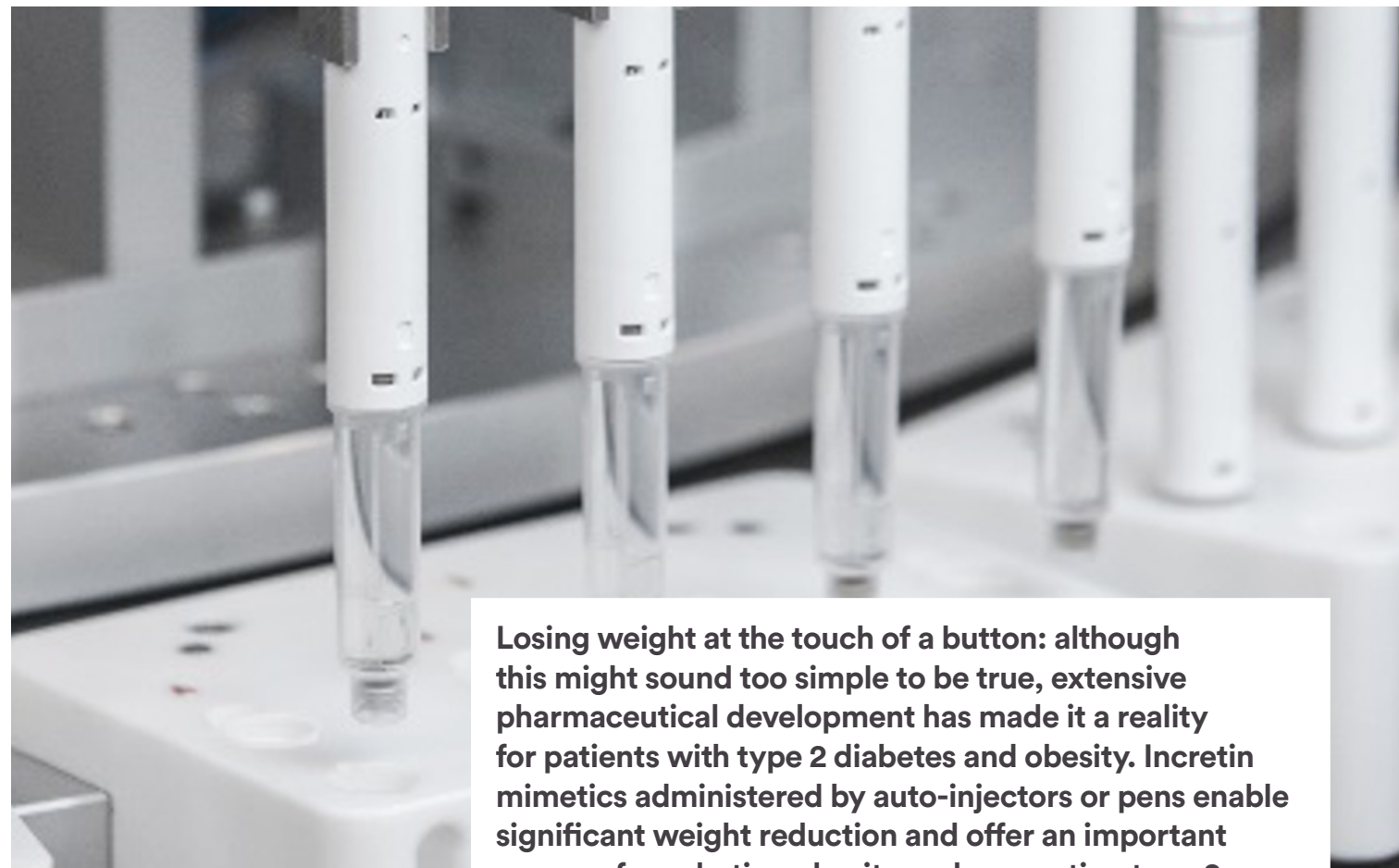
Quand le nettoyage est essentiel



# Production of incretin mimetics.

## Weight under control

Markus BURKERT → Syntegon Technology GmbH



**Losing weight at the touch of a button: although this might sound too simple to be true, extensive pharmaceutical development has made it a reality for patients with type 2 diabetes and obesity. Incretin mimetics administered by auto-injectors or pens enable significant weight reduction and offer an important means of combating obesity and preventing type 2 diabetes. Pharmaceutical manufacturers are currently investing heavily in development and production. However, timely market entry requires integrated processes. System providers act as technological partners and offer flexible solutions for high-volume production.**

Type 2 diabetes and obesity are not only widespread; they are also partly interrelated. People suffering from obesity have an increased risk of developing type 2 diabetes. According to estimates by the International Diabetes Federation, 540 million people worldwide are currently living with diabetes, more than 90 percent of whom have type 2. What's more, the World Obesity Federation estimates that around four billion people – half of the world's current population – could be severely overweight by 2035.

Whatever their condition, patients urgently need effective control: weight loss is the main objective for obese people, while type 2 diabetes requires a regulated release of insulin. Patients with type 2 diabetes can produce insulin themselves, but often not in sufficient quantities. Medicines based on incretin mimetics are proving to be an effective treatment option for both indications. The products are experiencing increased demand, as they can also be used for weight control following recent approvals. In 2022, the EU Commission greenlighted the marketing of Wegovy® from manufacturer Novo Nordisk, which the U.S. FDA had approved for the North American market a year earlier. Novo Nordisk has also been permitted to market Wegovy® for the treatment of heart disease since 2024. The company first launched semaglutide on the U.S. market under the brand name Ozempic® at the end of 2017 to lower blood glucose level. Eli Lilly, another major player in weight management and antidiabetic treatment, first marketed its GIP and GLP-1 agonist Mounjaro™ for type 2 diabetes in 2022 following an FDA approval the same year. Under the brand name Zepbound™ Eli Lilly has been marketing its type 2 diabetes drug for use in chronic weight management since 2023.

### Hormone-driven weight loss

Some of the high-dose, subcutaneously injectable medications only need to be administered once a week. Auto-injectors or pens enable easy self-medication: patients administer the exact dose by simply pressing a button. However, drugs based on incretin mimetics owe their success not only to their practical handling. Clinical studies have shown that the products can lead to weight reduction of more than 15 percent within a few months. The recombinant active ingredients also influence the patients' sensation of hunger: by stimulating the production of the hormone incretin in the

body, patients feel satiated for a longer period of time.

Meanwhile, the few approved weight management products that only need to be administered once a week have sparked a veritable race for more medicines. According to Globaldata, more than 50 drugs targeting the same mechanism were undergoing clinical trials at over 40 companies in early 2024. Most of the products are injectables, while some are administered orally. The liquid formulations are to be launched on the market either as pre-filled syringes in auto-injectors or as cartridge-based pens. Novo Nordisk and Eli Lilly opted for auto-injectors. However, Novo has approval from the European Medicines Agency (EMA) for both dosage forms. Unlike auto-injectors, pens can be used up to five times. Patients only need to change the needles before each use. Single-use auto-injectors do not require this step.

### Challenging glass cylinders

Cartridges, however, which are the main component of pens, present manufacturing companies with specific challenges: unlike the ready-to-use (RTU) syringes of auto-injectors, the glass cylinders are usually not pre-sterilized and not processed simultaneously in large quantities. On the contrary, manufacturers must ensure sterile individual filling, which includes flexible assembly and inspection in addition to high output – as well as additional upstream processes such as cleaning, siliconization, and sterilization. In case manufacturers rely on large-volume cartridges, which are filled as RTUs, the same systems can be adapted to accommodate this container type, resulting in leaner processes without the aforementioned upstream steps.

High-performance cleaning machines pave the way for aseptic filling: they remove product residues and other contaminants from the inside and outside of the containers so that potentially harmful substances can no longer compromise the safety of operators and patients. Advanced systems offer pre-treatment in an ultrasonic bath. Flexible configurations of cleaning stations also enable product-specific and efficient sanitization.

State-of-the-art cleaning systems further make sure that the cartridges are siliconized. The thin silicone layer inside the containers has a major influence on the speed of the rubber stopper during administration and hence on the pressure of the administered medication.

If the inner walls have too much silicone, the stoppers slide too quickly, and the pressure inside the patients' tissue increases excessively. Too little silicone, on the other hand, might have the stopper sliding too slowly and the drug not penetrating the tissue sufficiently. State-of-technology sterilization tunnels fixate the silicone layer thanks to even heat distribution and sterilization speed.

### High-volume filling and sealing

High-performance filling and sealing machines with an output of 600 units per minute are standard equipment for manufacturers who want to meet global demand and remain competitive. However, high quantities alone are not sufficient to meet the requirements of efficient production. The often small opening of the containers requires highly precise filling. Common equipment concepts therefore include time-pressure filling (TPF) systems with a large number of filling stations. For sound reasons: the sensitive GLP-1 agonists call for filling methods like TPF that don't expose them to thermal and mechanical stress. After the cartridge stoppers have been placed and checked with a sensor, the cartridges are filled at separate stations. Leading technology providers rely on sensor filling for maximum precision. This helps to achieve the optimum fill level and avoid air bubbles in the liquid, thereby reducing costly rejects.

Due to high sterility requirements, cartridges are filled in production environments that ensure strict separation of drugs and operators. The new version of EU GMP Annex 1 places additional emphasis on effective separation: isolator technology will establish itself as the long-term standard in filling, as it guarantees automatic bio-decontamination and a stable pressure difference to the operator environment.





Customized Assembly

The filled and sealed cartridge is the centerpiece of the pen, which is ideally assembled on flexible platforms. Although the numerous pen and injector types on the market have similar components, they vary in terms of size, material, and shape. Leading machine manufacturers have developed solutions that combine standardization and customization in close cooperation with their customers, resulting in platforms that offer the required flexibility and capacity and can process both auto-injectors and pens.

Common pen assembly machines are designed for standard four-part disposable pens, which consist of a pen cap, a cartridge holder, the cartridge, and a dispensing mechanism. These solutions allow companies to choose between manual, semi-automated, and fully automated assembly with quick, tool-free changeovers. Small manual workstations have proven to be the ideal solution for initial clinical trials. As soon as commercial production begins, semi-automated or fully automated assembly systems come into play. Thanks to this scalable approach, process validation can be transferred from one assembly platform to another. This makes for

versatile processes with minimal downtime between batches, facilitating prompt time to market.

Containers without cracks or defects

Inspection plays an important role: this process step makes sure that cartridges do not break on the way to the patient or during use. It is the linchpin for patient safety and a regulatory requirement for parenterally administered medications. High production volumes require fully automated and highly flexible systems for comprehensive inspection: different systems for visual inspection and leak detection – preferably on a single platform – enable containers to be precisely checked for cosmetic defects, intrinsic and extrinsic contamination, and leaking closures. In view of the increasing global demand for weight control medicines, but also due to the expected focus on cartridges, this kind of system will become ever-more important – combined with even more flexible, safe, and efficient processes along the entire value chain.

Endotoxin.  
The next generation of reagents for Endotoxin Testing - for the next generation of scientists in the pharmaceutical / medical device industry

Veronika WILLIS → Associates of Cape Cod, Inc



The pharmaceutical industry—an exciting, fast-paced world where innovation changes the quality of human life. If you're a recent graduate stepping into this field, you are a part of a new generation poised to shake things up and make a difference. One topic where your fresh perspective is truly needed? Endotoxin testing. This critical process keeps patients safe because it ensures that injectable drugs and medical devices are free not only from viable harmful bacteria (subject to sterility testing) but also free from their ghost components – endotoxins.



ENERGY  
EFFICIENT  
WATER



Innover pour réduire et optimiser.

Engagé pour la qualité, la sécurité et l'environnement, BWT offre des solutions innovantes de traitement des eaux à usages pharmaceutiques et biotechnologiques. Grâce à nos technologies de pointe, **réduisez votre consommation d'eau et l'empreinte carbone de vos installations** tout en optimisant votre production. Optez pour une fabrication plus durable d'EPU, d'EPPI et de vapeur pure avec BWT, où notre expertise en efficacité environnementale est reconnue et valorisée.





Finished product testing supported by well-designed process control helps ensure the quality and safety of given sterile pharmaceuticals, from small molecules to complex biologicals and combination products <sup>(1)</sup>.

Testing for bacterial endotoxins has been an integral part of the process control for half a century (and prior to that as an in-vivo pyrogen test done in live rabbits since 1942)<sup>(2)</sup>. Starting in the 1980s, the use of live rabbits had been largely replaced by the Limulus Amebocyte Lysate (LAL) test, an in-vitro test. Since then, the LAL test has been the gold standard for endotoxin testing around the world <sup>(3, 4)</sup>! Saving millions of rabbits and humans. But here’s the catch—the LAL test is completely dependent on a natural resource derived from the blood of wild marine arthropods - the horseshoe crab <sup>(5)</sup>.

With the support of regulatory bodies, technology, and a strong push by investors, the industry has now started moving in a new, “greener” direction <sup>(6, 7, 8)</sup>. One that you can help shape! Let’s talk about how the next generation of reagents for endotoxin testing is more than just science—it’s about sustainability, secure supply chain, innovation, and making a difference.

### Why Endotoxin Testing Matters

Imagine this—you’ve created a groundbreaking new drug. It has passed rigorous trials and is set to help millions. But before it hits the market, it must be tested for endotoxins—tiny, invisible but toxic components of the cell envelope of Gram-negative bacteria. Endotoxins, if in abundance, circulating in our circulatory system or cerebrospinal fluid, can trigger severe, or even lethal reactions in patients. That’s why it’s a huge part of ensuring pharmaceutical product safety. Testing for bacterial endotoxins isn’t just an industry standard - it’s the law and a life-saving measure.

The first reagent for the bacterial endotoxins test was developed by the scientists who formed Associates of Cape Cod, Inc. (ACC) in the 1970s based on the discovery and research performed by Dr. Fredrick Bang and Dr. Jack Levin at the Marine Biological Laboratory (now University of Chicago) in Woods Hole, MA, USA<sup>(9)</sup>. The raw material for all LAL reagents is blue blood (aka hemolymph) donated by the horseshoe crab. The blood clotting cascade present within amebocyte’s granules detects endotoxins (regardless of the bacterial strain) with an extremely high sensitivity and specificity.

### The Biodiversity Challenge

Horseshoe crabs play a key role in coastal ecosystems and have done so for eons, surviving 5 mass extinctions and a meteor impact<sup>(6)</sup>. Their eggs are also a critical food source for migrating birds, and they have been part of the oceanic food chain for millions of years. While their collection and release for LAL production is highly regulated along the eastern seaboard of the United States, protecting the ecosystems and reducing the need of their blood cells is a responsibility of the LAL and pharmaceutical / medical device industry and regulators worldwide<sup>(10)</sup>. Reducing and/or eliminating the use of wild animals is a common and worthy goal across all borders. For the new generation of pharma professionals, this is where you can make a difference <sup>(11)</sup>!

### Innovating for Sustainability

- The future of endotoxin testing is innovation, and it's happening in ways that honor both science and sustainability. Meet the recombinant reagents for endotoxin testing (rBET): Recombinant Factor C (rFC) and Recombinant Cascade Reagents (rCR). Thanks to biotechnology that identified and cloned the key endotoxin-detecting proteins, they are now expressed in bioreactors without ever using a drop of horseshoe crab blood ever again<sup>(12, 13, 14, 15)</sup>!

Here’s why recombinant reagents are a game-changer:

- Ethical and Sustainable: It supports the pharmaceutical industry’s shift toward ethical practices by minimizing the impact on wild animals <sup>(16)</sup>.
- Innovative bringing improved reproducibility and specificity to

- endotoxins: rBET reagents are highly characterized, therefore their performance is highly reproducible, with no cross-reactivity with 1,3-beta glucans (unlike LAL reagents)<sup>(13)</sup>.
- Ready for automation: rBET reagents are compatible with various liquid handling systems, depending on the needs of the lab<sup>(7)</sup>.

The best part? Global regulatory bodies are not only increasingly accepting rBET as an alternative to LAL testing but strongly encouraging pharma to implement their use <sup>(17, 18, 19)</sup>.

### Supply Chain Resilience Starts with Innovation

Beyond protecting crabs and ecosystems, these advancements also strengthen global supply chain of these critical reagents<sup>(16)</sup>. Think about it—dependance on a single source of raw material (Limulus polyphemus, the north Atlantic horseshoe crab) to make most globally used LAL reagents in the US may introduce some risk. The supply chain could potentially be vulnerable to shortages, delays, and regional shipping disruptions. Secondly, all the raw material for LAL must be collected during a short season (which continues to shrink due to locally imposed restrictions). This can be further impacted by changing weather patterns and rising sea levels. Compare that to rBET grown in a bioreactor, which can be made on different continents, can be scaled up or down as needed and has no dependency on access to the horseshoe crabs. By adopting rBET reagents, pharmaceutical companies create a more resilient, reliable supply chain that’s better equipped to handle global stressors <sup>(20)</sup>.

Sustainability and resilience are no longer buzzwords—they’re necessities. And as someone new to the field, you can help push them from concept to reality just like Thomas Edison.



### Become an rBET Influencer

You might be thinking, “What can I do as someone just starting out?” The truth is, your voice and values matter more than they seem.

- 1.Stay Educated:** Keep learning about new advancements in pharmaceutical science. Technology moves fast, and staying informed ensures you’re ready to lead the way<sup>(21, 22)</sup>.
- 2.Ask Questions:** Get curious about the sustainability practices of your workplace. How are they adopting modern, ethical testing methods like rBET reagents? What steps are they taking to reduce their ecological impact?
- 3.Learn From the Pioneers in the Industry:** Read sustainability reports of other companies, research and interview their employees on how the other companies work towards sustainability<sup>(23)</sup>.
- 4.Champion Change:** Advocate for innovations that prioritize both patient safety and environmental stewardship. If your company isn’t using modern testing methods, speak up and suggest it<sup>(24)</sup>.

- 5.Collaborate for Biodiversity:** Partner with conservation organizations or support research into sustainable practices. Aligning the goals of pharma and environmental science can lead to incredible breakthroughs<sup>(5)</sup>.

### A Future You Help Shape

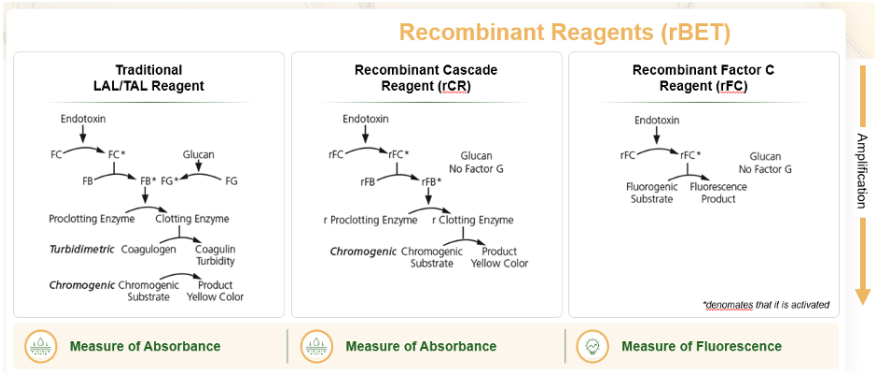
Every generation is known for demanding “better”—better ethics, better practices, and a better future - than your parent’s or grandparent’s reality. Your entry into the pharmaceutical world comes at a pivotal moment in healthcare history, as growing human population puts increasing demand on the industry and resources, technology and innovation step in to help answer the call. Endotoxin testing is just one piece of the puzzle, but it's a critical one.

By pushing for more sustainable solutions and supporting biodiversity, you're doing more than contributing to safe medicine. You're making a statement—that science and nature can thrive together in harmony. And in doing so, you'll leave a legacy you can be proud of.

Welcome to the new age in pharma, where resilience and sustainability are more than goals—they’re the foundation of everything we do. Now, it’s your turn to take the baton and help lead this change. Will you rise to the challenge?

### References

1. 2012 FDA Guidance for Industry: Pyrogen and Endotoxins Testing: Questions and Answers: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-pyrogen-and-endotoxins-testing-questions-and-answers>
2. US Pharmacopeia Chapter <51> Rabbit Pyrogen Test
3. US Pharmacopeia Chapter <85> Bacterial Endotoxins Testing
4. European Pharmacopeia 2.6.14 Bacterial Endotoxins
5. <https://horseshoecrab.org/>
6. US Pharmacopeia Chapter <86> Bacterial Endotoxins Testing Using Recombinant Reagents
7. Bolden J et. al. Currently available recombinant alternatives to horseshoe crab blood lysates: are they comparable for the detection of environmental bacterial endotoxins: A review. PDA J Pharm Sci Technol, 74 (5): 602 – 611 (2020)
8. <https://www.bnpparibas-am.com/en-ch/forward-thinking/talking-heads-why-biodiversity-loss-matters-to-investors/>
9. <https://www.aai.org/About/History/History-Articles-Keep-for-Hierarchy/Blue-Bloods-Bang,-Levin,-and-the-Horseshoe-Crabs>
10. [https://asmfc.org/wpcontent/uploads/2025/01/HorseshoeCrabStockAssessmentUpdate\\_April2024.pdf](https://asmfc.org/wpcontent/uploads/2025/01/HorseshoeCrabStockAssessmentUpdate_April2024.pdf)
11. <https://www.un.org/sustainabledevelopment/sustainable-development-goals/>
12. Mizumura H, Ogura N, Aketagawa J and et. al. Genetic engineering approach to develop next-generation reagents for endotoxin quantification. Innate Immunity, 23, 136–146 (2017)
13. Stevens I et. al. Advanced Recombinant Cascade Reagent PyroSmart NextGen® for Bacterial Endotoxins Test as Described in the Pharmacopeias, BPB, Vol.5, No. 5 105–114 (2022)
14. Shapovalova O V et. al. New direction in the determination of bacterial endotoxins: Analysis using recombinant Factor C. Pharmaceutical chemistry journal, 56, 1133–1139 (2022)
15. Kikuchi Y et. al. Collaborative study on the Bacterial Endotoxins test using Recombinant Factor C-based Procedure for Detection of Lipopolysaccharides (Part 3). Pharmaceutical and Medical Device Regulatory Science, 54 (4), 341–351 (2023)
16. <https://pscinitiative.org/bulletin?bulletin=888>
17. <https://www.usp.org/news/expert-committee-voting-on-endotoxin-testing-using-non-animal-derived-reagents>
18. <https://www.pmda.go.jp/files/000275359.pdf>
19. European Pharmacopeia Chapter 2.6.32 Test for Bacterial Endotoxins Using Recombinant Factor C
20. <https://www.njspotlightnews.org/2024/05/big-pharma-pharmaceutical-companies-meet-delaware-bayshore-consider-synthetic-test-versus-using-horseshoe-crab-blood-tests/>
21. <https://www.pda.org/global-event-calendar>
22. <https://www.a3p.org/en/event/>
23. <https://sustainability.lilly.com/>
24. <https://pharmascore.org/>
25. <https://www.acciusa.com/>
26. [https://www.acciusa.com/assets/files/pdf/PyroSmart\\_Brochure.pdf](https://www.acciusa.com/assets/files/pdf/PyroSmart_Brochure.pdf)



↑ Figure 1: Reagents for BET





## Your journey from LAL to rCR begins here.

As the pioneer in endotoxin detection Associates of Cape Cod, Intl, Inc. (ACC) proudly recognizes and supports the scientific and regulatory validation of recombinant technologies, which offer sustainable alternatives that align with the industry's increasing focus on principled sourcing and environmental responsibility.

With that said, inclusion of recombinant reagents in USP <86> is the beginning of a broader transition. Real-world implementation will require a phased, multi-tiered approach that takes into account several complex variables.

As you navigate your own transformation journey — from qualitative to quantitative to recombinant — count on ACC for the highest-quality products and support.



Are You Ready to Take the Journey?  
Contact Us for More Information.

[acciuk.co.uk](http://acciuk.co.uk)

# Rhéologie.

## Le secret des produits pharmaceutiques et cosmétiques réussis, de la formulation à l'application

Sylvia IMBART → ebi



La rhéologie, science qui étudie la déformation et l'écoulement de la matière, joue un rôle clé dans la performance des produits pharmaceutiques et cosmétiques. Qu'il s'agisse d'une crème hydratante au toucher soyeux, d'un gel médicamenteux à libération prolongée ou d'un sérum fluide et facile à appliquer, les propriétés rhéologiques déterminent non seulement la stabilité du produit, mais aussi son efficacité et son acceptabilité par les consommateurs. Des émulsions aux suspensions en passant par les gels, chaque texture résulte d'un équilibre précis entre viscosité, élasticité et thixotropie, soigneusement optimisé en laboratoire.

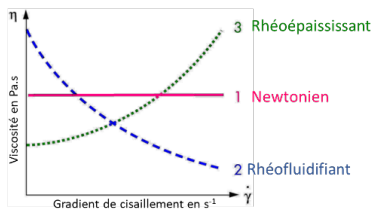


Dans cet article, nous explorons comment la maîtrise de la rhéologie permet de transformer une formule en un produit performant, depuis son développement jusqu'à son application finale, en passant par sa phase de production à l'échelle industrielle.

## Histoire de la Rhéologie

Le terme "rhéologie" a été introduit au début du XXe siècle par Eugene C. Bingham et Markus Reiner, inspiré de la maxime grecque "panta rhei" (tout coule). Cependant, l'étude du comportement des fluides et des solides visqueux remonte à l'Antiquité, avec des observations empiriques sur la déformation des matériaux. Des chercheurs comme Isaac Newton, qui a défini la viscosité newtonienne, et James Clerk Maxwell, qui a proposé un modèle de fluide viscoélastique, ont contribué à la fondation de cette discipline.

La rhéologie, l'étude du comportement d'écoulement et de déformation des matériaux, joue un rôle crucial dans de nombreux secteurs industriels, notamment la cosmétique et la pharmaceutique. Elle permet de caractériser et d'optimiser la texture, la stabilité et l'application des produits. La maîtrise des propriétés rhéologiques d'un produit permet de garantir à la fois l'efficacité technique et l'adhésion par le consommateur final.



↑ Figure 1 : Les Différents comportements rhéologiques

## Les comportements rhéologiques

En rhéologie, on distingue trois grands types de comportements (fig.1). Les deux premiers sont des comportements non newtoniens : le comportement rhéofluidifiant, où la viscosité diminue avec l'augmentation du cisaillement (la majorité des produits cosmétiques et pharmaceutiques), et le comportement rhéopaisissant produits qui contiennent de l'amidon (ou des polymères particuliers), où la viscosité augmente avec le cisaillement. Le troisième type est le comportement newtonien, pour lequel la viscosité reste constante (les huiles par exemple), quel que soit le cisaillement appliqué.

## Les méthodes de mesure en rhéologie

Les méthodes de mesure en rhéologie utilisent des approches complémentaires pour caractériser les propriétés des produits cosmétiques et pharmaceutiques. L'appareil qui réalise ces mesures est un rhéomètre (fig.2a).

La **rhéométrie rotative**  se distingue par sa capacité à analyser les comportements d'écoulement en appliquant un cisaillement contrôlé via des géométries spécifiques (cône-plan, cylindres concentriques ou plaques parallèles, fig.2b). Ces configurations permettent de mesurer la viscosité dynamique et d'établir des courbes d'écoulement en faisant varier le taux de cisaillement, ce qui est essentiel pour optimiser la texture des crèmes ou la fluidité des gels. Par exemple, la géométrie cône-plan offre un gradient de cisaillement uniforme grâce à son angle réduit (0,5° à 4°), idéal pour les échantillons à viscosité élevée comme les pommades, tandis que les cylindres concentriques, avec leur grande surface de contact, sont adaptés aux fluides peu visqueux tels que les lotions.

Les rhéomètres rotatifs modernes comme le MCR 302 de chez Anton Paar (fig. 2a) intègrent également des mesures

de contraintes normales, révélant des propriétés structurales critiques pour la stabilité des émulsions cosmétiques ou la résistance à la sédimentation des principes actifs pharmaceutiques. Cette technique est incontournable pour le contrôle qualité lors de la formulation, permettant de prédire le comportement lors de l'application cutanée ou de l'extrusion dans des tubes.

Combinée à la **rhéométrie oscillatoire** , qui permet de quantifier le module élastique  $G'$  (ou la partie solide) et le module visqueux (la partie liquide), forme un panel complet pour maîtriser les propriétés viscoélastiques depuis la R&D jusqu'à la production industrielle.

## Applications en Cosmétique et en Pharmaceutique

La rhéologie est déterminante dans la formulation et l'optimisation des produits:

### 1. Cosmétique

- **Crèmes et lotions:** Une bonne viscosité et un comportement rhéofluidifiant assure une application homogène et un confort sensoriel optimal. Sur la [figure 3](#), nous pouvons

voir le comportement rhéofluidifiant de 3 crèmes, la viscosité diminue en fonction du gradient de cisaillement. Ainsi, on peut conclure que les crèmes vont s'écouler sous l'action de l'étalement de la main. Les différentes viscosités obtenues (premier point de la courbe [fig.3a](#)) vont vérifier la valeur imposée dans le cahier des charges du produit. Enfin, grâce à la courbe d'écoulement ([fig.3b](#)), on peut mesurer la contrainte seuil, c'est-à-dire la force qu'il faut appliquer au produit pour qu'il s'écoule

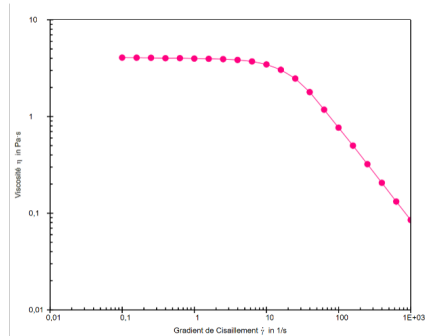
- **Maquillage :** La rhéologie influence la tenue et la facilité d'application des rouges à lèvres et fonds de teint. Il ne doit pas s'écouler du tube, doit s'étaler sur les lèvres et ne doit pas couler des une fois déposer sur celles-ci.

- **Shampooings et gels douche (fig.4) :** Un bon équilibre entre fluidité et viscosité permet une application facile et une répartition uniforme du produit. Ces produits présentent généralement un comportement newtonien à faible cisaillement (entre 0.1 et 10s-1 [fig.4](#)), et deviennent rhéofluidifiants à fort cisaillement. Cette transition est principalement due à la présence de tensioactifs comme la cocamidopropyl bétaine, qui contribue à épaissir la formule tout en favorisant la formation de mousse.

- **Maquillage :** La rhéologie influence la tenue et la facilité d'application des rouges à lèvres et fonds de teint. Il ne doit pas s'écouler du tube, doit s'étaler sur les lèvres et ne doit pas couler des une fois déposer sur celles-ci.

- **Shampooings et gels douche (fig.4) :** Un bon équilibre entre fluidité et viscosité permet une application facile et une répartition uniforme du produit. Ces produits présentent généralement un comportement newtonien à faible cisaillement (entre 0.1 et 10s-1 [fig.4](#)), et deviennent

rhéofluidifiants à fort cisaillement. Cette transition est principalement due à la présence de tensioactifs comme la cocamidopropyl bétaine, qui contribue à épaissir la formule tout en favorisant la formation de mousse.



↑ Figure 4 : Courbe de viscosité d'un shampooing

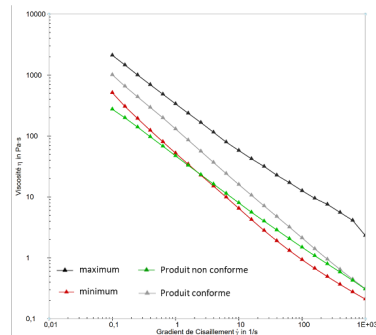
### 2. Pharmaceutique

- **Gels et pommades :** La consistance et l'adhésion sont essentielles pour une application efficace et un bon relargage des principes actifs.
- **Sirops et suspensions :** Une rhéologie adaptée évite la sédimentation des particules et garantit une bonne homogénéité du produit.
- **Injectables :** La fluidité des solutions influence la facilité d'administration et le confort du patient. Elle est en général proche de celui du sérum physiologique (10mPa.s à 37°C), lui permettant de passer à travers de fines aiguilles et de limiter la douleur d'injection au patient.

## Rôle de la rhéologie dans le développement de produits cosmétiques et pharmaceutiques

La rhéologie joue un rôle essentiel dans le développement de produits, de la recherche initiale à la mise sur le marché :

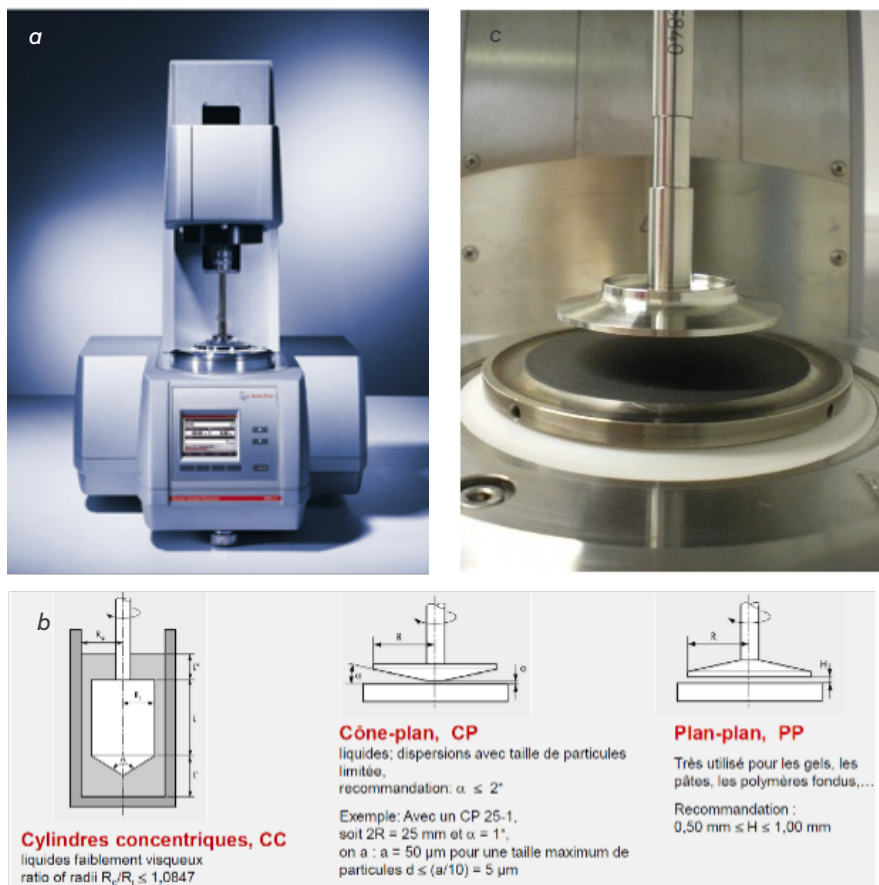
- **Contrôle de la qualité :** L'analyse rhéologique permet de surveiller la qualité des matières premières et des produits finis, assurant ainsi la cohérence et la conformité aux normes établies. La figure 5 présente une validation de produit grâce à 2 bornes maximum et minimum. Si le produit à un comportement entre les 2 références, il est validé, sinon, il est rejeté.



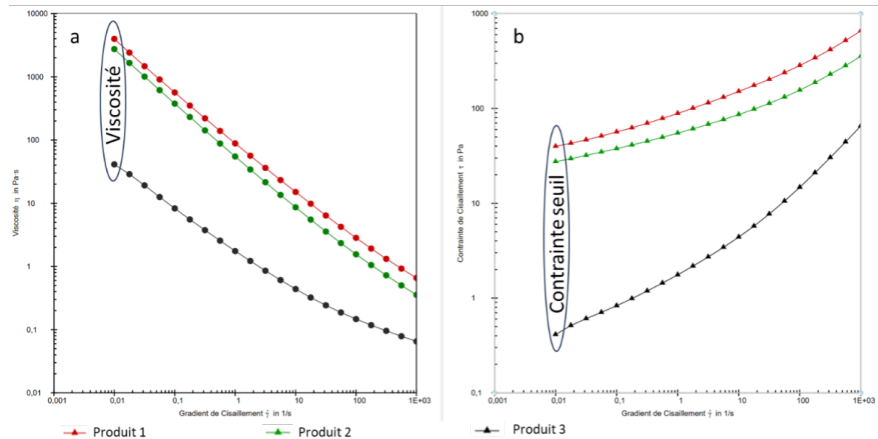
↑ Figure 5 : Contrôle de la conformité de 2 produits par une mesure de la viscosité

- **Optimisation des processus de fabrication :** La compréhension des propriétés rhéologiques des formulations est essentielle pour optimiser les étapes de mélange, de pompage, de remplissage et d'emballage. La [figure 6](#) présente les conditions de cisaillement auxquelles le produit est soumis tout au long de son cycle, incluant la fabrication, le transport et le stockage. Chaque étape peut être validée grâce à des mesures rhéologiques simples, permettant de garantir que ces processus s'effectuent dans des conditions optimales, en particulier lors de son acheminement à travers les canalisations. Si les mesures rhéologiques ne sont pas conformes aux contrôles ([même processus que sur la figure 6](#)), la formule est revue afin de pouvoir passer convenablement dans les tuyaux sans créer de blocage.

- **Amélioration de la stabilité et de la durée de conservation :** Les tests rhéologiques évaluent l'effet de divers paramètres, tels que la formulation, le temps de stockage et la température, sur la qualité et l'acceptabilité du produit final. La rhéologie en fréquence est un bon indicateur de stabilité de produits. Par exemple, sur la [figure 7](#), le produit TC est un solide viscoélastique ( $G' > G''$ ) et les 2 modules restent stables dans le temps, contrairement au produit TG, qui est un liquide viscoélastique ( $G'' > G'$ ) et dont les modules augmentent dans le temps, ce qui indique que le produit présentera une instabilité.

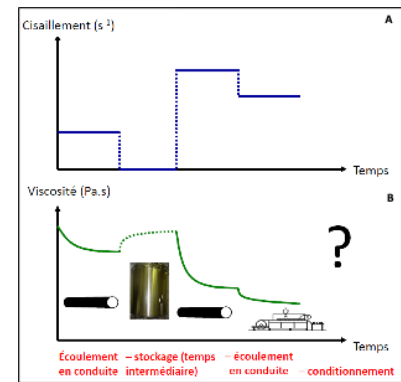


↑ Figure 2 : a-Rhéomètre MCR 302 (Anton Paar), b-Géométries, c-Zoom sur un système cône-plan (CP).

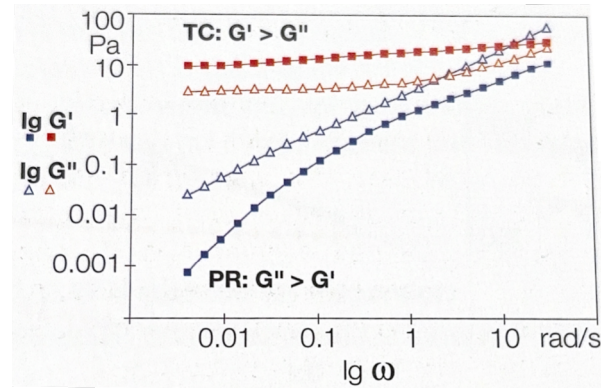


↑ Figure 3 : Courbe de viscosité(a) et d'écoulement(b) de 3 crèmes





↑ Figure 6 : Influence des contraintes de cisaillement sur la viscosité d'un produit : du stockage à l'application. A - cisaillement appliqué au produit, B - viscosité du produit.



↑ Figure 7 : Balayage en amplitude (oscillatoire) de 2 produits (TC et TG)

## Conclusion

Cet article souligne l'importance stratégique de la rhéologie pour la caractérisation des ingrédients, l'évaluation des formes galéniques et l'amélioration des procédés industriels. Toutefois, cette discipline exige une expertise poussée, ce qui constitue un frein majeur pour les entreprises, confrontées à deux défis : l'investissement élevé dans des équipements spécialisés (un rhéomètre haut de gamme coûtant au minimum 30 000 €) et la pénurie d'ingénieurs qualifiés en rhéologie appliquée.

Pour répondre à ce besoin sectoriel, l'École de Biologie Industrielle a intégré une mineure "Rhéologie et tribologie" dans son cursus ingénieur, combinant l'étude des propriétés d'écoulement avec l'analyse des frottements et de l'usure des matériaux – deux approches complémentaires pour optimiser les performances des produits formulés.

## Témoignages d'Experts

- **Dr. Marie Dupont**, Directrice de Recherche chez PharmaTech : *"La rhéologie est essentielle pour garantir la qualité et l'efficacité de nos produits. Grâce aux avancées dans ce domaine, nous pouvons développer des formulations plus stables et plus performantes."*

- **Prof. Jean-Luc Martin**, Université de Paris : *"L'intégration de la rhéologie dans nos programmes de recherche nous permet de mieux comprendre les propriétés des matériaux et d'optimiser les processus de fabrication."*

### - Développement de produits répondant aux attentes des consommateurs :

La rhéologie aide les développeurs à quantifier l'impact des modifications de formulation, à optimiser les propriétés pour correspondre aux préférences des consommateurs et à fabriquer à grande échelle des produits de qualité. Des méthodes rhéologiques ont montré qu'elles pouvaient prédire certains descripteurs sensoriels (Gilbert et al. 2013 ; Tranchant, Poulin, et Grossiord 2001)

- **Substitution d'ingrédients** : cette problématique occupe une place importante dans la formulation de produits car de nombreux ingrédients sont jugés nocifs, CMR ou irritant et apparaissent sur la liste rouge des industriels. Il est donc nécessaire de les substituer avant qu'une interdiction légale n'entre en vigueur. Cependant, remplacer un seul ingrédient dans une formule peut altérer les propriétés sensorielles du produit, ce qui risque de dérouter le consommateur et de le dissuader de renouveler son achat. L'étude de la rhéologie permet de mettre en évidence ces modifications comme l'illustre la figure 8. Ainsi, le formulateur peut adapter sa formule rapidement avant de réaliser l'analyse sensorielle qui est longue et coûteuse.

- **Sirops Médicamenteux** : Les sirops doivent avoir une viscosité suffisante pour éviter la sédimentation des particules, mais pas trop élevée pour être facilement administrés. Les tests rhéologiques garantissent cet équilibre.

- **Gels Transdermiques** : Les gels utilisés pour la libération de médicaments à travers la peau doivent avoir des propriétés viscoélastiques spécifiques pour assurer une libération contrôlée des principes actifs.

## Perspectives

La rhéologie continue d'évoluer avec les avancées technologiques et scientifiques :

### - Intégration de l'Intelligence Artificielle.

L'application de techniques d'apprentissage automatique en rhéologie permet d'améliorer la compréhension et la prédiction du comportement des fluides complexes.

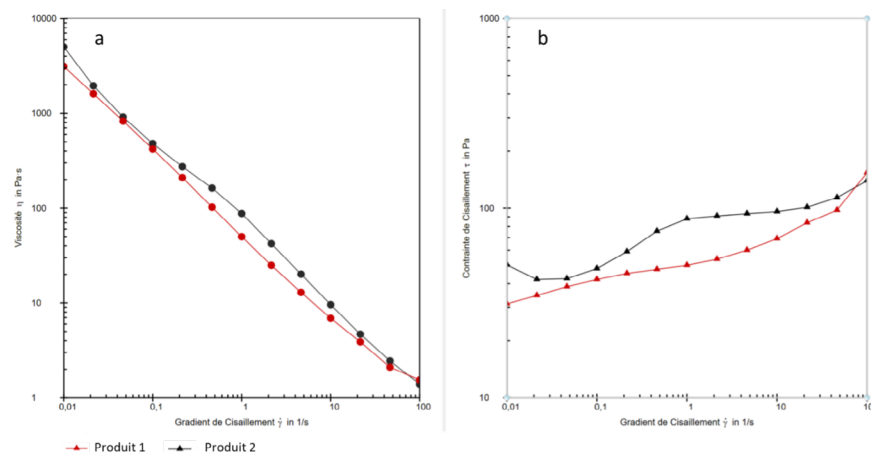
### - Développement de Matériaux Avancés.

Les recherches en rhéologie contribuent au développement de nouveaux matériaux aux propriétés viscoélastiques spécifiques, comme les gels biopolymères utilisés dans l'industrie médicale.

### - Corrélation sensorielle – instrumentale.

L'essor des outils numériques performants et des capacités de stockage massif de données ouvre la voie à la création de modèles mathématiques capables de corréler les propriétés

physiques des produits avec leur analyse sensorielle. La rhéologie se positionne comme une méthode clé pour ce type de modélisation, offrant un gain de temps significatif dans le développement de nouveaux produits en prédisant leurs caractéristiques sensorielles (Imbart et al. 2022).



↑ Figure 8 : Courbe de viscosité (a) et d'écoulement (b) d'un produit avec substitution d'un seul ingrédient



We're here for you.

Before supporting you with a unique portfolio of contamination control equipment, consumables and services, we ask about your objectives to help ensure **your success.**

**Comprehensive offerings.  
Integrated support.**

**STERIS**



# Technology.

## A Toolbox for an Effective Technology Transfer.

Rui ALMEIDA → ValGenesis

This article was originally published in the PDA Letter on May 1, 2025 and is republished with permission of PDA, Inc.



The pharmaceutical industry is undergoing a transformation driven by Pharma 4.0, the next phase of digital innovation. By integrating cutting-edge digital tools and methodologies with advanced technologies, pharmaceutical and biopharmaceutical companies are not only improving efficiency and competitiveness but also embracing a holistic, data-driven approach that is at the core of Pharma 4.0. This synergy underscores the transformative potential of digital innovation in driving the future of pharmaceutical manufacturing.

### The Pillars of the Pharma 4.0 Landscape

Pharma 4.0, introduced by the International Society for Pharmaceutical Engineering (ISPE) in 2017, builds on Industry 4.0 principles to modernize pharmaceutical manufacturing. This approach describes the integration of advanced digital technologies in the pharmaceutical industry, such as Artificial Intelligence (AI), the internet of things (IoT), and big data analytics using smart machines. It epitomizes the use of technology to optimize manufacturing processes through digitalization, leading to new levels of connectivity, flexibility, efficiency, and productivity. Pharma 4.0 simplifies compliance, achieves cost savings, reduces downtime and waste, and fosters innovation<sup>(1-5)</sup>.

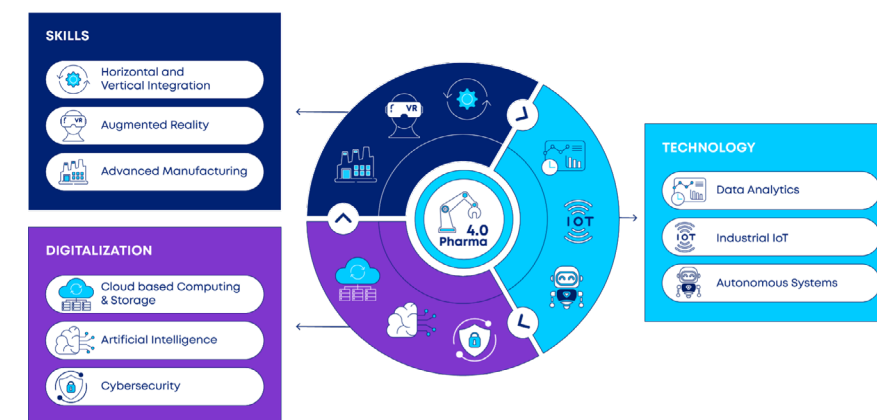
Pharma 4.0 consists of nine key pillars, encompassing three main areas: technology, digitalization and skills (see Figure 1)<sup>(16)</sup>.

#### Technology

- Big Data Analytics: Automation and digitalization generate vast amounts of data during manufacturing processes in Pharma 4.0. To handle this data influx, increased storage capacities are necessary. Big data analytics processes and analyzes these large amounts of data to extract insights that can optimize the manufacturing process.
- Industrial Internet of Things (IoT): The IoT refers to devices equipped with sensors, software, and other technologies that connect and exchange data with other devices. These IoT devices monitor and control various aspects of the manufacturing process, such as temperature, humidity, and pressure, among many others.
- Autonomous Systems: Robotics and automation enhance the manufacturing process by minimizing the need for human intervention. This leads to fewer errors and greater efficiency in production.

#### Digitalization

- Cloud-Based Computing and Storage: Cloud computing and storage allow pharmaceutical companies to store and manage various data types. It is the foundation of advanced technologies such as AI, machine learning (ML), and IoT. In Pharma 4.0, cloud storage is usually secured with cybersecurity measures to prevent unauthorized access or breaches.



↑ Figure 1 : Representation of the 9 pillars of Pharma 4.0 action plan into 3 main areas: Technology, Digitalization, and Skills

- Artificial Intelligence and Machine Learning: AI algorithms analyze data from IoT devices and other sources to detect patterns and trends. These findings are employed to enhance manufacturing processes and elevate the quality of the final product.
- Cybersecurity: The integration of standard communication protocols and enhanced connectivity with Industry 4.0 has increased the imperative to protect critical data from cybersecurity risks. Consequently, it has become indispensable to ensure reliable and secure communications and management channels.

#### Skills

- Horizontal and Vertical Integration: Currently, most IT systems lack full integration, causing limited connectivity between organizations, customers, and suppliers. However, Industry 4.0 allows for the development of cross-organization, universal data integration networks leading to automated value chains.
- Augmented Reality: Augmented-reality-based systems, still in their early stages, offer diverse functionalities, such as delivering repair instructions via mobile devices. In the future, these systems will provide real-time information, enhancing decision-making processes and optimizing work procedures.
- Advanced Manufacturing: With the implementation of Industry 4.0 technologies, advanced manufacturing techniques such as 3D printing are useful for manufacturing small batches of customized products, leading to enhanced performance or lightweight designs.

Each pillar represents a digital technology that manufacturers should adopt to improve their manufacturing processes. The combined application of these technologies enables companies to imple-

ment smart production and optimize their operations, thereby enhancing consistent product quality and faster time-to-market for new medicines<sup>(1,2)</sup>.

The move towards Pharma 4.0 can be seen in ISPE's GAMP 5 2<sup>nd</sup> edition, which was updated in 2022 to reflect the increased adoption of software and automation tools. The updated edition now includes a specific appendix on the use of AI and ML, offering a path for advanced process control to be used in pharmaceutical manufacturing<sup>(7,8)</sup>.

Ultimately, Pharma 4.0 enables the pharmaceutical industry to be more agile and adaptable to constantly evolving market demands, supporting companies in responding to changes in demand and manufacturing disruptions while improving patient safety<sup>(2-7)</sup>.

### Technology Transfer – Synergy with Digital Tools

The implementation of digital tools in the pharmaceutical industry presents opportunities to optimize manufacturing processes, including process design, control, smart monitoring, and maintenance, thereby ensuring the consistent and accurate execution of transferred processes. Moreover, AI-driven data integration, knowledge management, and risk assessment streamline the transfer process and accelerate learning at the receiving site, minimizing risks and ensuring compliance with regulatory requirements during technology transfer.

In successful Pharma 4.0 implementations, new techniques, platforms, and technologies are leveraged into digital toolboxes that enhance existing mathematical algorithms through AI and ML, process monitoring, and optimization tools. Among the many benefits of leveraging these toolboxes into a technology transfer process roadmap, let us consider the following. (see Figure 2)<sup>(9)</sup>



## 1. Process Design and Scale-up

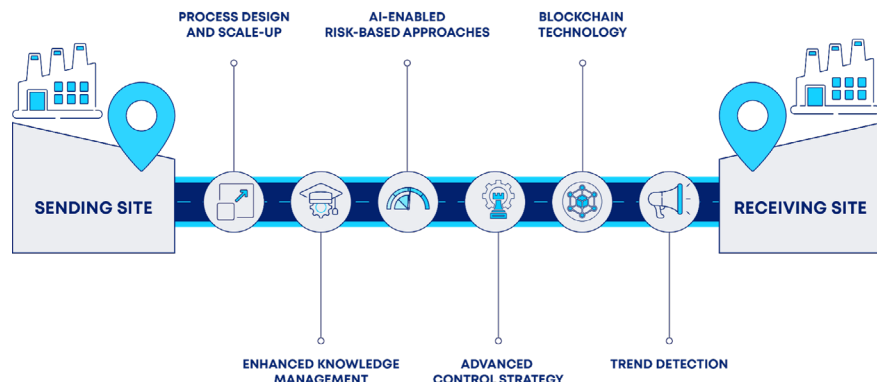
Digital tools, leveraging ML algorithms developed from process development data, swiftly uncover optimal processing parameters for scale-up processes, thereby reducing development time and minimizing waste<sup>(9)</sup>.

## 2. Enhanced Knowledge Management

A critical aspect of technology transfer involves data migration, which can present substantial challenges. While the concept of transferring data may seem straightforward, issues such as connection failures can result in data loss and retrieval difficulties. Moreover, existing data often remains unused and proves difficult to transfer due to a lack of structure, connectivity, and context, creating a bottleneck in the technology transfer process. To mitigate risks, it is advisable to migrate data incrementally<sup>(10)</sup>.

During technology transfer, several challenges arise<sup>(10)</sup>:

- **Data Collection Completion:** The initial stages of product development involve numerous trials and errors, generating a substantial influx of data. Stakeholders must meticulously record relevant data from these stages and employ proper methodologies and guidance to manage vast amounts of data effectively. Without adequate recording systems in place, data may remain underutilized, leading to statistically unsound analyses and missed insights.
- **Data Accuracy and Integrity:** Beyond data completeness, it is essential to ensure the accuracy and integrity of recorded data. This involves implementing robust recording methods, verifying data during the recording process, and selecting appropriate recording tools, whether digital or manual.
- **Structuring and Retrieving Data:** Organizing data into coherent structures is pivotal for enabling stakeholders to locate and access the required information accurately. In industries like pharmaceuticals and biotechnology, where data structures can be intricate, experts play a crucial role in planning data collection and organization strategies to ensure meaningful and logical arrangements.



↑ Figure 2 : Competitive advantages for technology transfer leveraged by a synergy with digital tools

In the era of big data, maintaining data integrity is paramount. Within a digital toolbox, AI algorithms are adept at detecting anomalies, ensuring data accuracy, and preventing tampering. Machine learning models can analyze vast datasets, identifying patterns that might elude human inspection. This strengthens data integrity throughout the pharmaceutical product lifecycle.

## 3. AI-Enabled Risk-Based Approaches

Digital tools have the potential to revolutionize quality risk management (QRM) within the ICH Q9(R1) framework.

The ability of AI to process complex data quickly and accurately makes it an ideal tool for real-time risk assessment, decision-making, and mitigation. By proactively identifying potential risks in large datasets, AI can detect patterns, identify correlations and relationships, and improve the accuracy of risk assessments<sup>(11)</sup>.

Automated risk assessments streamline risk assessment procedures and foster a systematic, proactive approach to risk management. Real-time monitoring continuously tracks critical quality parameters, with AI analyzing data to uncover risks that may be difficult to detect using traditional methods<sup>(11)</sup>.

## 4. Advanced Control Strategy

Digital tools can also be employed to develop advanced process controls that predict manufacturing process trajectories using real-time sensor data combined with AI methods. These controls, known as soft sensors, offer an effective alternative to traditional hardware sensors for gathering, monitoring, and regulating crucial process variables.

This data-driven, AI-enabled approach offers a novel and more efficient way to obtain accurate readings throughout the entire processing chain without requiring costly hardware installations. By optimizing process control, it enhances efficiency and reduces waste.

Several pharmaceutical manufacturers have already implemented these methods, integrating an understanding of the underlying chemical, physical, and biological transformations occurring in the manufacturing process with AI-driven techniques<sup>(9)</sup>.

## 5. Blockchain Technology

Blockchain is seen as a key driver in improving drug safety, reducing counterfeiting and fraud, enhancing supply chain efficiency, and ensuring regulatory compliance. It relies on veracity, transparency, independence, and security to ensure certified, publicly accessible, and cryptographically protected transactions<sup>(2)</sup>.

Employing blockchain to store data collected from sensors on IoT devices serves multiple purposes, such as facilitating more efficient real-time decision-making and enabling the creation of predictive models based on environmental hazards encountered throughout the cold chain cycle. These models reinforce the pharmaceutical cold chain by assessing and mitigating potential risks even before they arise<sup>(12)</sup>.

## 6. Trend detection

As part of the digital toolbox, AI plays a crucial role in identifying and analyzing clusters of problem areas, facilitating their prioritization for continuous improvement<sup>(9)</sup>.

One of AI's significant advantages lies in its ability to pinpoint trends associated with manufacturing deviations, fostering a comprehensive understanding of the underlying root causes. For instance, AI models and expert systems can predict optimal values for complex variables under investigation to optimize formulations or processes<sup>(9)</sup>.

Digital tools are key players in scrutinizing deviation reports, enabling more accurate and efficient data analysis,

even when extensive textual content is involved. Consequently, digital tools allow businesses to proactively adapt their strategies and stay ahead of the competition<sup>(13,14)</sup>.

## Key Considerations for Application of Digital Tools in the Technology Transfer Process

Major players in the life sciences and pharmaceutical industries have begun investing in and dedicating resources to incorporating digital tools, AI, and ML algorithms into their initiatives. However, reaching the highest levels of manufacturing performance and quality requires a paradigm shift in mindset, significant investment in new technologies and infrastructure, in-demand skills within the organization, adoption of specialized IT frameworks integrated with legacy systems, and the development of innovative corporate strategies<sup>(2,15)</sup>.

With the potential to reduce costs, drive innovation in treatments, and enhance patient outcomes, digital tools represent the future of the pharmaceutical industry, and their implementation is already feasible.

Those who initiate their digital transformation journey now will gain a competitive edge, as standards, strategies, use cases, and ecosystems are still evolving. However, while new technologies offer promising prospects, prioritizing user experience during implementation is crucial.

In regulated sectors, such as drug development, manufacturing, and distribution, every digital data point undergoes auditing by various regulatory bodies, presenting a significant challenge. Therefore, use cases must be meticulously defined, verified, validated, and completely transparent<sup>(2)</sup>.

Here are three initial steps to embark on digital transformation:

The shift to a Pharma 4.0 operating model within your organization's digital strategy is paramount. Moving forward, every business opportunity should be evaluated through an analytics-driven lens. Embracing this cultural and mindset shift will cultivate a data-driven organization capable of swiftly recognizing, validating, and capitalizing on opportunities<sup>(15)</sup>.

## Main Takeaways and Final Remarks

The integration of digital toolboxes in technology transfer processes within the Pharma 4.0 initiative enables automated digitalization and validation, ensuring compliance with ICH Q10 PQS guidelines. This comprehensive approach leverages knowledge and quality risk management to reduce risk levels and time to market while improving quality standards. By promoting interconnectivity and breaking down silos, it allows for better management of complex supply chain challenges.

Pharma 4.0 optimizes manufacturing by eliminating inefficient production loops through streamlined digital workflows. Additionally, the Pharma 4.0 paradigm ensures data integrity and high-level production quality while reducing manufacturing costs. Furthermore, digital toolbox functionalities increase GMP application through predictive analytics, bottleneck elimination, and smarter maintenance strategies.

Finally, digitally centered initiatives lead to better decision-making and improved overall performance. By closely monitoring the manufacturing process, these initiatives reduce everyday stress and uncertainty, increasing stakeholder engagement and ultimately fostering innovative thinking<sup>(15)</sup>.



Champions for Digital Transformation



Cultivate Partnerships



Small-Scale Proof of Value (POV)

Identify and empower advocates within your organization for digital transformation to explore potential applications and foster enthusiasm across teams.

Cultivate relationships within the emerging digital toolbox ecosystem by establishing partnerships with like-minded research labs, academic institutions, technology providers, application developers, and startups.

Prioritize use cases for small-scale Proof of Value (PoV) investments based on their potential to deliver value through business and process insights. When prioritizing, consider therapeutic focus areas, business strategy, customer value propositions, and future growth plans. Continuously monitor the performance of these PoV initiatives and scale up those that demonstrate effectiveness.

## References

1. Innopharma technology [Internet]. [cited 2024 May 23]. To Industry 4.0 and Beyond. Available from: <https://www.innopharmatechnology.com/news/to-industry-4-0-and-beyond>
2. Boel J. DBL Group. 2023 [cited 2024 May 23]. Pharma 4.0: The Future of Pharmaceutical Manufacturing. Available from: <https://qbdgroup.com/en/blog/pharma-4-0-the-future-of-pharmaceutical-manufacturing/>
3. Bridge Automation [Internet]. 2023 [cited 2024 May 23]. Pharma 4.0: How AI and ML are changing the landscape of the biopharmaceutical industry. Available from: <https://www.linkedin.com/pulse/pharma-40-how-ai-ml-changing-landscape-biopharmaceutical/>
4. Heesakkers H, Schmitz S, Kuchenbrod U, Wölbeling C, Zimmer T. ISPE . [cited 2024 May 23]. The ISPE Pharma 4.0 Operating Model's - Pharma-Specific Maturity Index. Available from: <https://ispe.org/pharmaceutical-engineering/may-june-2019/ispe-pharma-40tm-operating-models-pharma-specific-maturity>
5. The History Of Pharmaceutical Manufacturing: Industry 1.0 to Pharma 4.0 [Internet]. [cited 2024 May 23]. Available from: [golighthouse.com/en/knowledge-center/industry-1-pharma-4](https://golighthouse.com/en/knowledge-center/industry-1-pharma-4)
6. Kidwai A. Polestar. 2021 [cited 2024 May 24]. The Nine Pillars Of Industry 4.0: Technological Advancements. Available from: <https://www.polestarllp.com/blog/what-is-industry-40-and-its-nine-technology-pillars>
7. Mack J, Lovett D, Mercer E, McEwan M. Pharma 4.0-A Vendor's Perspective.
8. ISPE GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems (Second Edition). 2022.
9. Dashpute S V, Pansare JJ, Deore YK, Pansare MJ, Sonawane PJ, Jadhav SP, et al. Artificial Intelligence and Machine Learning in the Pharmaceutical Industry INTRODUCTION. IJPPR [Internet]. 2023 [cited 2024 May 27];28(2):111–31. Available from: [https://www.researchgate.net/publication/374914821\\_Artificial\\_Intelligence\\_and\\_Machine\\_Learning\\_in\\_the\\_Pharmaceutical\\_Industry\\_INTRODUCTION](https://www.researchgate.net/publication/374914821_Artificial_Intelligence_and_Machine_Learning_in_the_Pharmaceutical_Industry_INTRODUCTION)
10. Korber [Internet]. [cited 2024 May 27]. How data management and analytics ensure a successful tech transfer. Available from: <https://www.koerber-pharma.com/en/blog/how-data-management-and-analytics-ensure-a-successful-tech-transfer>
11. Haddad G. Revolutionizing QRM: The Impact of AI and ML. 2024.
12. Misra S. LinkedIn. 2021 [cited 2024 May 27]. AI in Pharma: Emerging Use Cases Across the Value Chain. Available from: [linkedin.com/pulse/ai-pharma-emerging-use-cases-across-value-chain-sachin-misra](https://www.linkedin.com/pulse/ai-pharma-emerging-use-cases-across-value-chain-sachin-misra)
13. Silvertown A. LinkedIn. 2023 [cited 2024 May 27]. Artificial Intelligence in Retail Pharmacy: The Impact and Potential of AI. Available from: [linkedin.com/pulse/artificial-intelligence-retail-pharmacy-impact-ai-adam-silvertown-6vqic](https://www.linkedin.com/pulse/artificial-intelligence-retail-pharmacy-impact-ai-adam-silvertown-6vqic)
14. Akmal A, Binti Y, Jayus M. LinkedIn. 2023 [cited 2024 May 27]. The Role of Artificial Intelligence (AI) in Tech Commercialization: Powering the Future of Innovation. Available from: <https://www.linkedin.com/pulse/role-artificial-intelligence-ai-tech-powering-future-innovation/>
15. VimaChem [Internet]. [cited 2024 May 23]. Pharma 4.0 - A practical guide for a successful digital transition. Available from: <https://www.vimachem.com/resources/pharma-4-0/>



# Environnemental.

## Excess heat in pharmaceutical industry.

Rodolphe HENRIETTE → GIC Performance environnementale



The greater the number of waste heat recovery systems, the greater the efficiency of the total energy consumed. The best way to implement this recovery is to apply this cascade:

- start by limiting waste heat,
- implement reuse through the same process,
- reuse elsewhere on the site,
- end with reuse on another site.

In the following, I expand on different solutions for illustrating this approach.

### Definition of waste heat

In industry, a small share of the total heat produced (in red on the graph) is used for production (in green on the image).

Waste heat is all the energy produced that is not used for direct production (orange part). There are different categories of waste heat.

Final waste heat (purple). The amount of this waste energy can be limited.

All other parts of the excess heat (light blue and yellow) can be reused in different systems in different ways:

- Recoverable by the same equipment
- Recoverable by a neighboring process
- Recoverable on other sites or in other industries.

### Pharmaceutical industry process

Thermal energy is used at various stages of production:

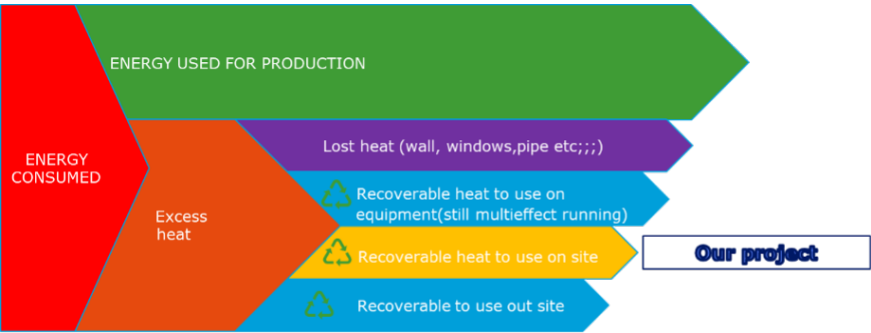
- To generate clean steam, used in manufacturing:
  - for Sterilization,
  - to clean in place/sterilize in place,
  - for autoclaving.
- To produce water for injection, and to control temperature on the water distribution loop.
- To control temperature in production areas, whether classified or not.
- Control humidity in the production area.

### Heat lost

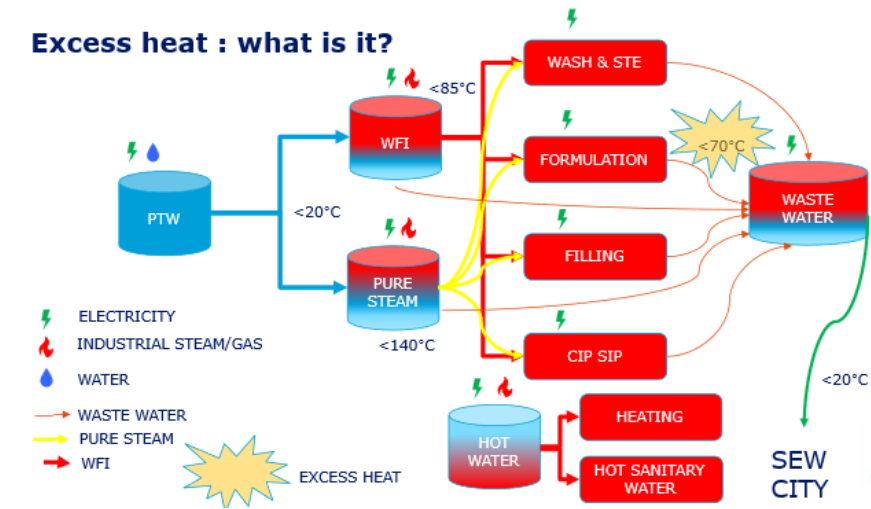
The breakdown of these losses is as follows:

- **Production rooms** : To reduce losses, exterior walls must be insulated, and dedicated pharmaceutical walls and floors installed. Depending on exposure, windows and doors should be at least double-glazed, if not triple-glazed; the higher the Uw thermal efficiency, the better the insulation; for windows and external doors, we consider the airtightness index, known as AEV.

Thermal bridges must be avoided in construction design. It is paramount to pay attention to this when temperatures across adjacent rooms differ, e.g. cooling storage room with ambient storage room, or aseptic production room with technical room (e.g. HVAC technical room).



↑ Figure 1 : Energy and excess heat repartition diagram



↑ Figure 2 : Pharmaceutical process and excess heat flow diagram

- **The respective pipes of water network**, cooling water, heat water, water for injection, industrial steam, clean steam, etc. Must be insulated, it is overall performed for fixed part but not for removable equipment parts that require to be accessible for maintenance : valve, steam trap, probes etc. These specific sections can be equipped with removable insulating cushion to limit lost heat.



| Chaudière N°1 | ECS N°1 | Chaudière N°2 | ECS N°2 | Chaudière N°3 | Récupération des Chaudières N°1/2/3 |
|---------------|---------|---------------|---------|---------------|-------------------------------------|
|               |         |               |         |               |                                     |
| Nombre        | Nombre  | Nombre        | Nombre  | Nombre        | Nombre                              |
| DN 25         | 3       | /             | /       | 5             | /                                   |
| DN 40         | 0       | 17            | 7       | 9             | /                                   |
| DN 65         | 0       | 8             | 12      | 18            | /                                   |
| DN 80         | 2       | 7             | 10      | 2             | 5                                   |
| DN 100        | 12      | /             | /       | 15            | /                                   |
| DN 125        | 5       | /             | /       | /             | /                                   |
| DN 150        | 8       | /             | /       | /             | /                                   |

Voici le gain engendré par cette préconisation :

| Mise en place de calorifuge sur les points singuliers |           |        |        |
|-------------------------------------------------------|-----------|--------|--------|
| Economies en énergie                                  |           |        |        |
| énergie combustible économisée                        | 392,3 kWh | par an |        |
| tonnes de CO <sub>2</sub> économisées                 | 21,5 t    | par an |        |
| investissement                                        | 91,8 k€   |        |        |
| temps de retour                                       | 28 k€     |        | 1,8 an |

↑ Figure 3 : Below an illustration of removable insulated cushion, together with an assessment of the related energy saving.

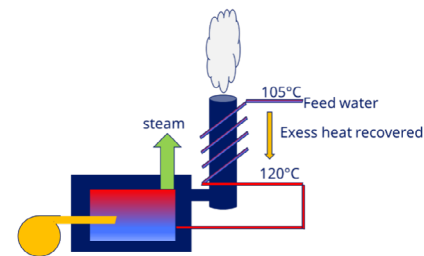


## Loop back heat recovery (same process)

Once the first step has been taken, the next is to determine the possibilities for cold or heat recovery. This applies to air, water, smoke, etc.

Then it's time to identify the various opportunities for reuse. Here are a few examples of industrial processes used in pharmaceutical plants.

For fossil fuel-fired boilers producing process steam, we can use the heat from the exhaust smoke to raise the temperature of the incoming water.

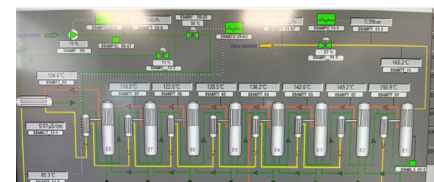


Another option is to use hot air, accumulated in the upper part of the room, to supply the air burner, thus improving boiler efficiency.

Where multi effect distiller is used to produce WFI, the same principle applies to a double flow system:

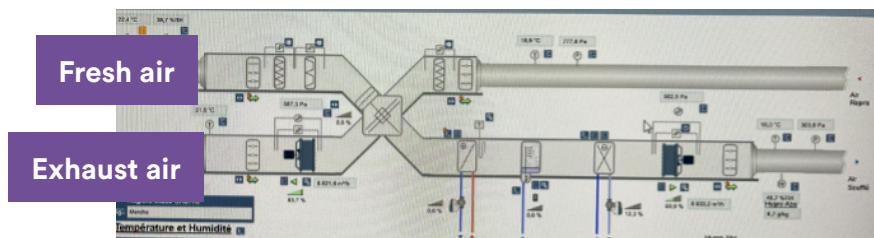
The last column is then supplied with cold pretreated water and the first column with industrial steam.

Next, cooling energy from the supplied water is used to condensate the clean steam created in the first column and simultaneously heat from condensated water is used to increase temperature of pretreated water across the cascade columns.

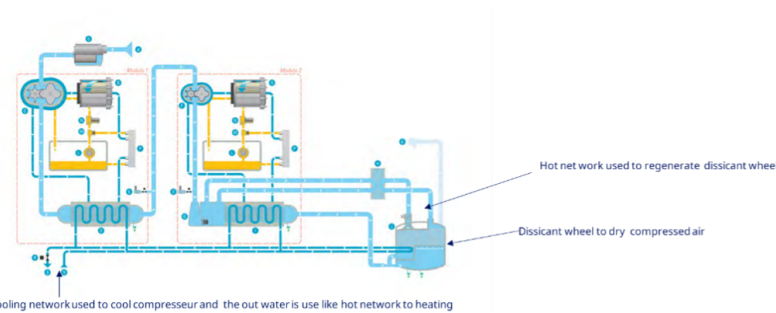


↑ Figure 5 : Green circuit cold feed water to preheat before evaporation it use steam water calories to heat. Orange circuit steam to colt hot water it use feed water to condensate steam in reverse flow of feed water

In production area a part of the air energy is recovered in recovery. On average 90% of supplied air is recovered, the remaining 10% being fresh air, but where it comes to laboratories where chemical substances are in use, air recovery is banned, due to chemical risk for people, but we can then recover energy via an air exchanger plugged on the air exhaust, and next to transfer this energy towards the fresh air inlet.



↑ Figure 6: Heat air exchange without mix air



↑ Figure 7: Heat air exchange

Such recovery process allows for saving around 70% energy (heat or cold). Double flow HVAC system exists to exchange directly energy between fresh and exhaust air with the same efficiency (Figure 6).

On the compressed air generator, the manufacturer uses the heat generated during the compression phase to preheat a water network used to dehumidify a desiccation wheel. The dehumidification wheel is one of the technologies available to treat the dew point of compressed air.

Many other solutions are available, to evaluate the possibilities, an energy flow diagram can be used while discussions with the equipment supplier(s) should be initiated to explore all the possibilities. (Figure 7)

## Recovery by another process

To evaluate the possibilities, a flow diagram such as a Sankey chart can be used, this chart identifies the fluid inputs and outputs along with their enthalpic characteristics, resulting in highlighting possible heat recovery opportunities.

Regarding injectable production, water for injection is used at large to wash, rinse and for-mulate, the estimated final usage of water dedicated to the product itself ranges from 1 to 2 %, the remaining 98% being a low heat energy effluent, expected to be cooled before rejected to a public sewer network.

A first possibility, depending on the quality of low energy effluent, is to use it directly to feed a boiler, then both saving water and heat energy.

Where this is not possible, low specific enthalpy effluent cooling can be achieved using a heat pump, for example, to supply energy to a hot water network, which is more effective when relative humidity control in aseptic environments is required, necessitating a year-round heating source. (Figure 8)

Other principles are applicable, previously we considered air compressor immediate reuse, however another recovery possibility is to use it to preheat a heat network. Notice that both energy recovery ways can be combined.

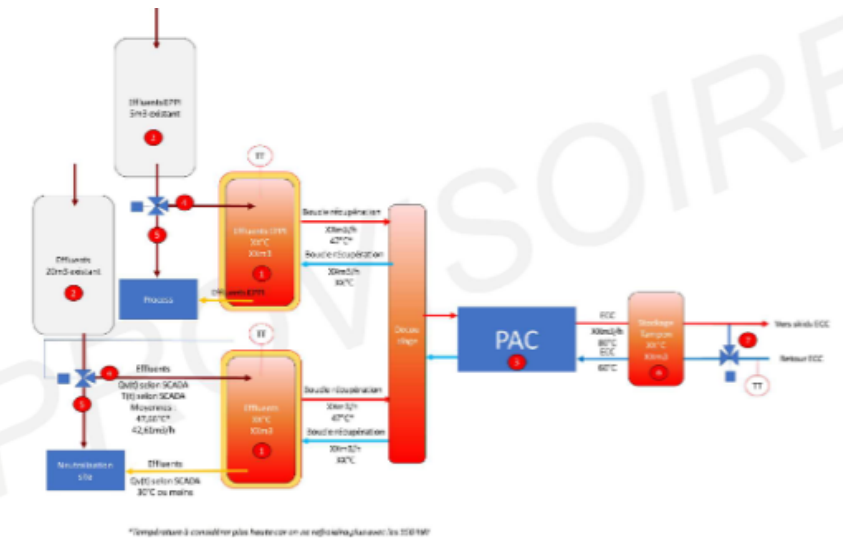
Yet we first considered the recovery possibilities associated with heat-generating equipment, in the pharmaceutical industry the chiller system is widely used, both for air conditioning and for the process. A chiller, which is itself a heat pump, generates a lot of by-product energy. With the help of equipment suppliers, we can use this generated energy to supply various heat networks.

## Recovery reused on other sites

After exhausting all heat recovery options on site, often a part of the waste energy still re-mains. Then, based on the same assessment principle, it can be used by other companies, one possibility is to supply it to a public heat network to convey this heat to another site. Depending on on season and usage this allows for saving energy.

All these recovery initiatives generate a decrease of energy usage and CO<sub>2</sub> emissions, it is the first step of improvement, it enables a practical way to decarbonate energy, like using energy from wind farm, solar farm does.

The best energy is that which is not used, but as for the inevitable part that you do use, don't waste it - that's the mindset of lost energy recovering.

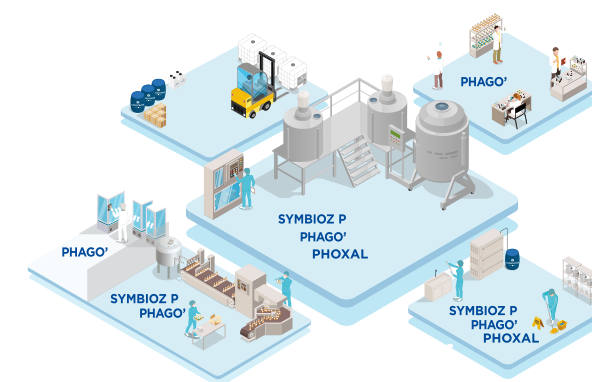


↑ Figure 8: Principe sytème actif PAC



# DÉTERGENCE ET DÉSINFECTION

- 1 DÉFINIR
- 2 OPTIMISER
- 3 CONSEILLER
- 4 PROPOSER
- 5 SOUTENIR



**NOTRE EXPERTISE**  
POUR CHACUNE  
DE VOS ZONES

### NOS GAMMES

- **SYMBIOZ P**  
DÉTERGENTS/DÉSINFECTANTS
- **PHAGO'**  
DÉTERGENTS/DÉSINFECTANTS  
POUR ENVIRONNEMENTS CONTRÔLÉS
- **PHOXAL**  
TRAITEMENT PRÉVENTIF/CURATIF DU ROUGING



FEEL SAFE WITH US

CHRISTEYNS FRANCE • 31 rue de la Maladrerie • 44120 Vertou • T +33 (0)2 40 80 27 27 • www.christeyns.com





# DÉVELOPPEMENT ET FABRICATION DE MÉDICAMENTS STÉRILES INJECTABLES

## **CERTIFICATION BPF (GMP) INSPECTÉ PAR L'ANSM JANVIER 2025**



- • INFRASTRUCTURE À LA POINTE DE LA TECHNOLOGIE
- • PROJETS COMPLEXES EN MILIEU STÉRILE
- • LOTS CLINIQUES ET COMMERCIAUX
- • PRODUITS HAUTEMENT ACTIFS
- • CONFORMITÉ À L'ANNEXE 1



[www.carbogen-amcis.com/sterile-drug-product-cdmo](http://www.carbogen-amcis.com/sterile-drug-product-cdmo) | [drugproduct@carbogen-amcis.com](mailto:drugproduct@carbogen-amcis.com)



**CARBOGEN AMCIS: BRINGING YOUR SCIENCE TO LIFE**