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UNIVERSITY OF BIRMINGHAM
Precision Health Technologies Accelerator

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editorial

Dear Colleagues

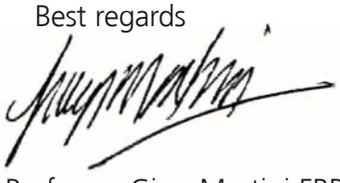
I write to you as the life sciences sector is undergoing radical changes and turbulent times with a number of organisations deciding to focus their investments in the United States for a number of reasons. It is also the exact time that the Precision Health Technologies Accelerator (PHTA, www.phta.co.uk) which is located on the new Birmingham Health Innovation Campus (BHIC) is opening its facility to Small/Medium innovative life science and med-tech/health tech companies across the United Kingdon (UK) and to potential International collaborators. The UK economy relies heavily on Small/Medium/Enterprises (SMEs) which account for 99.8% of the business population (5.5 million businesses) and accounts for three-fifths of the employment and around half of turnover in the UK private sector. I have always been struck by the amazing statistic referenced by David Cameron at the CBI conference of 2010, where he stated 'its astonishing to think that between 1980-2005, nearly all net job creation in the United States occurred in firms less than five years old'. That's right, new jobs were not being created by Ford, General Motors, Pfizer, Merck but the new 'kids on the block' such as Google, Amgen, Celltech, Gilead, Meta, Tesla to name but a few.

Hence, it is our ambition with the PHTA to help life science entrepreneurs scale their businesses from a 1- or 2- person operation to up to 30 persons by providing access to Category 2 laboratories, Makerspaces, Industrial Trials to help accelerate clinical studies, access to experts in Clinical Immunology or experts who can help companies/SMEs access the NHS. So it is with great pride and excitement that in this edition of the Industrial Pharmacy (IP) we are showcasing the opening of the PHTA and its capabilities, and highlighting the national importance of the work carried out at the Industrial Trials Hub anchored in the PHTA and which is coordinated by Becky Faville.

In addition, we are featuring an excellent article by Monica Di Mattia reviewing a methodology for conducting nitrosamine risk assessments. This has become an important and mandatory regulatory requirement for industry to conduct and assess. We are also including a timely article by Hasim Solmaz on the evolution of cleanroom operations – important capabilities if the UK is to compete on the global clinical trials stage. Most innovative medicines under development are biological in nature and will necessitate injection into the body and as such will require aseptic/sterile manufacture in a cleanroom. It is our ambition at the PHTA to deliver a 5,000 square foot cleanroom facility on the 5th floor thereby addressing a critical need to support clinical trials within the NHS in the UK and across the West Midlands.

Please enjoy this important edition and in the words of Corporal Jones from *Dad's Army* – 'Don't panic' – it may be turbulent times but cool heads and collaboration of great minds across the UK and globe will stimulate innovation and great science.

Best regards



Professor Gino Martini FRPharmS
Editor, *Industrial Pharmacy*

From heavy industry to health innovation: Birmingham's next industrial revolution

by Gino Martini

The Birmingham Health Innovation Campus (BHIC) is a new R&D hub that serves as a centre for healthcare innovation, providing state-of-the-art facilities and fostering collaboration between businesses and academic institutions. It supports research and development in genomics, diagnostics, medical technologies, and precision medicine, with the goal of developing new treatments for diseases, improving healthcare through data, and training future healthcare professionals.

Professor Gino Martini is the Chief Executive of Precision Health Technologies Accelerator (PHTA Ltd) based at Birmingham Health Innovation Campus. With over 25 years' experience as an academic and industrial pharmacist he has extensive expertise in oncology, rare and infectious diseases, drug development and medical engineering – as well as policy development and external advocacy.

As the Chief Executive of PHTA – the University of Birmingham's flagship life sciences research accelerator – Gino is responsible for helping growing businesses to succeed, through making connections to multidisciplinary opinion leaders and providing commercialisation support and expertise. Gino joined PHTA in 2021 from the Royal Pharmaceutical Society where, as Chief Scientist, he played a pivotal role in supporting pharmacists during the Covid-19 pandemic and in particular supporting the role of pharmacists as vaccinators. He was also instrumental in highlighting the dangers of Nitrous Oxide abuse in teenagers, the banning of Dinitrophenol, and the reclassification of Medicinal Cannabis. In 2023 Professor Martini was shortlisted as the Male Innovator of the Year by the Innovation Awards, with the PHTA itself shortlisted within the Manufacturing Innovation Champion and Technology Innovation Champion (Organisation Sector) categories.

Gino's career began with Senior Scientist roles at Scherer Drug Delivery Systems and SmithKline Beecham, before joining GSK – initially as Drug Delivery and Strategic Technologies Manager – rising to Senior Directorships across a 10-year stint. An experienced academic, Gino was formerly Professor of Pharmaceutical Innovation at King's College London, as well as undertaking visiting professorships and PhD supervision alongside his industry roles. Prior to his appointment at the RPS, he held a variety of commercial, innovative technology-based and medical affairs roles – directing groups in the US, Europe and emerging markets – for Shire Pharmaceuticals and Roche.

Professor Martini has an MBA specialising in SME success and business failure, awarded with distinction from the University of Liverpool. He is a past chair of the Industrial Pharmacists Group of the Royal Pharmaceutical Society, past president of the European Industrial Pharmacists Group and holds Fellowships from the Royal Pharmaceutical Society, Royal Society of Chemistry and European Industrial Pharmacists Group.

Background

The UK's second city has a long history of innovation, creativity and forward thinking. The birthplace of the Industrial Revolution, Birmingham was once hailed as 'the city of a thousand trades' – the world's first manufacturing city. Although dominated by the automotive industry in the 20th century, a new sector is emerging as the champion of the region – and it is one that may surprise.

With a unique concentration of prestigious education, research and clinical institutions, Birmingham is one of the few global cities truly equipped to become an international leader in health and life sciences.

The pedigree certainly exists – here, pacemakers and plastic heart valves were developed; the first artificial vitamin (Vitamin C) was synthesised; allergy vaccines were pioneered; the key components of artificial blood were synthesised; and the first clinical trials of the contraceptive pill outside the US were carried out.

Quietly, the region has been building one of the most dynamic data-driven healthcare and medtech economies in the UK. Home to an estimated 391 companies, the life sciences sector in the West Midlands employs around 34,000 people, turning over £16.4bn per year and contributing £3bn in GVA (Gross Value Added) annually. Small to medium enterprises (SMEs) make up 90% of the sector, including 111 micro-businesses, with an average annual growth rate of 3.8%. Of these companies, 59 are classified as high-growth firms – growing at over 20% annually.

This growth, and the huge potential in the city, were recognised in 2020 by the-then

Department for Business, Energy and Industrial Strategy (BEIS), who conferred 'Life Sciences Opportunity Zone (LSOZ)' status on Birmingham – one of only six sites to receive this designation.

Centred around the Birmingham Health Partners ecosystem – which brings together academics from the University of Birmingham, Aston University and six research-intensive and specialist NHS Trusts – the LSOZ ably demonstrated that the city has all the vital ingredients for health and medical innovation. But one element has, until recently, been in short supply – lab space.

With a lack of grow-on space for expanding companies, life sciences businesses have been forced to look outside Birmingham for larger lab and office accommodation – taking talent, jobs and ultimately money away from the local economy.

This trend, however, did not go unnoticed. The University of Birmingham and West Midlands Combined Authority recognised the growing demand for specialised grow-on facilities for spin-outs and SMEs (Small and Medium-sized Enterprises) scaling up from incubators. Importantly, they also acknowledged that supporting these businesses to succeed would mean going far beyond offering lab space – that Birmingham's expert clinical-academics were ideally placed to help industry partners to develop, validate and commercialise their health solutions.

Figure 1. The PHTA building

Birmingham Health Innovation Campus (BHIC)

A 10-acre former brownfield site in Selly Oak, Birmingham Health Innovation Campus (BHIC) is the University of Birmingham's answer to the question – how do we keep innovative life sciences companies in the region? Developed in collaboration with Bruntwood SciTech, and with the support of Birmingham City Council, the campus – which has just opened the doors to its first building, No.1 BHIC – will provide a total of 657,000 sq ft of state-of-the-art lab, office and incubation space. When the ten-year masterplan is complete, BHIC will be the largest science park of its kind to be co-located with a leading research-intensive University and major NHS Trusts, as well as being the only science park in the West Midlands dedicated to health and life sciences.

The focal point of this first phase of development is No.1 BHIC's anchor tenant – the Precision Health Technologies Accelerator (PHTA) – see **Figure 1**.

Occupying 65,000 sq ft over three floors of the building, PHTA is the University of Birmingham's flagship life science research hub. PHTA provides Category 2 lab and office space for up to 20 SMEs – as well as catalysing vital collaborations with key opinion leaders in an array of medical and scientific specialties. It is also home to the core capabilities for the campus that will support the commercial businesses based there: Clinical Immunology Services, PHTA Industry Trials Hub, and medtech Makerspace.

What's notable about PHTA is that it isn't a refurbishment or repurposing of existing facilities – it has been custom-designed by scientists, for scientists, and the scope for sustained growth is almost limitless: the wider

masterplan for BHIC will provide opportunities for bespoke facilities in forthcoming buildings, allowing successful PHTA residents to graduate to larger labs in subsequent BHIC phases. Overall, the development is set to create over 10,000 new jobs and contribute £400m GVA to the regional economy during the 2030s.

Businesses working with PHTA also benefit from comprehensive support from the earliest stages of innovation – including intellectual property protection and advice on investment and financing – as well as access to a talent pool of some 7,000 life sciences graduates per year. Ultimately, its aim is to make it as easy as possible for the region's entrepreneurs, spin-outs and growing businesses to find the talent, expertise and facilities they need to thrive – benefiting patients in the local community and far beyond.

PHTA will act as a catalyst and a home for collaborative interactions between academics, entrepreneurs and clinicians with complementary skillsets, who can come together to accelerate innovations in a way that just can't be done when the talent and experience isn't under one roof. The result will be innovative new treatments, diagnostic tools, health technologies and medical devices which can reach patients faster.

People and place

It's significant that this is taking place in Birmingham for another reason too – its people. With a large, stable and diverse community, we are a 'world within a city', representing the global population in terms of its ethnic profile and socioeconomic demographics. For example, 52% of Birmingham's residents are of a Black, Asian or minority ethnic background. It is also a young city, with 72% of the population aged under 45. When it comes to clinical trials of drugs and devices, this is invaluable – where trials have diverse, representative participants, their results are applicable to a greater number of people too.

Building health resilience

The strengths that Birmingham and the wider Midlands region can offer to life science businesses, are the strengths the sector is crying out for. Not just in basic science, but in clinical trials design and delivery, biomarker analysis and diagnostic development, medical technologies and devices, and regulatory support. While traditionally life sciences businesses have been clustered around the 'Golden Triangle' of London, Oxford and Cambridge, expanding lab provision in other areas builds resilience and futureproofs the entire UK life sciences sector. PHTA is therefore an inclusive facility open to any SME or entrepreneur – regardless of their origin or current location.

Ultimately, all this research and development is done for patients – to give them access to precision medicine, improved diagnostics and the latest life-enhancing technologies. Everyone should be able to benefit from world-class health innovation, not just those who are local to centres of excellence such as the Golden Triangle.

By keeping life science enterprises in the Midlands, and giving further opportunity to SMEs in the sector, PHTA is set to ensure patients in our region have easy access to life-changing innovations, and the whole region can benefit from sustainable economic growth.

UNIVERSITY OF BIRMINGHAM | Precision Health Technologies Accelerator

Premium lab space available now

Join us at the heart of Birmingham's life sciences ecosystem.
70,000 sq ft of **Category 2** wet and dry lab space available.

Be part of PHTA

Nitrosamine Risk Assessment: example approach

by Monica Di Mattia

Multiple pharmaceutical regulatory authorities globally, including the FDA and EMA, have undertaken initiatives to harmonize strategies for addressing nitrosamine contamination in existing pharmaceutical formulations and to minimize the risk of impurities in new drug developments. This article provides an example of a nitrosamine risk assessment to cover current regulation requirements. This includes identifying the source of the nitrosamines, risk ranking the potential source, and risk evaluation and implementation of actions.

Monica Di Mattia is the Quality Risk Manager at Kedrion BioPharma UK and data integrity lead. Prior to her roles in QA Compliance, Monica trained as a microbiology technician before transitioning to become a sterility assurance specialist. During her time in sterility assurance, Monica developed a series of HACCP risk assessments to enhance her facility's contamination control programme. (M.DiMattia@kedrion.com)

Introduction

In September 2019, a 'call for review' was issued for medicinal products containing chemically synthesized active pharmaceutical ingredients (APIs). Marketing Authorisation Holders (MAHs) were mandated to review their manufacturing processes to identify and, if necessary, mitigate the risk of nitrosamine impurities, and to report their findings to the relevant authorities.

A subsequent evaluation of sartans by the European Medicines Agency (EMA) concluded that the risk from N-nitrosamine impurities, which are classified as probable human carcinogens, was low. However, the risk cannot be entirely excluded, particularly in biological products containing chemically synthesized fragments, biologicals utilizing processes where nitrosating reagents are deliberately introduced, and biologicals packaged in primary packaging containing nitrocellulose.

The call for review comprises three steps

1. MAHs are required to perform a risk evaluation to ascertain if APIs and/or finished products (FPs) could be at risk of nitrosamine contamination.
2. If a risk is identified, MAHs must conduct confirmatory testing to verify or refute the presence of nitrosamines and report the outcomes expeditiously.
3. If the presence of nitrosamines is confirmed, MAHs must implement effective risk mitigation measures through the submission of a variation.

This review was to be completed by September 2022 for chemical medicines in Europe, July 2023 for biological medicines in Europe, and October 2023 in the United States.

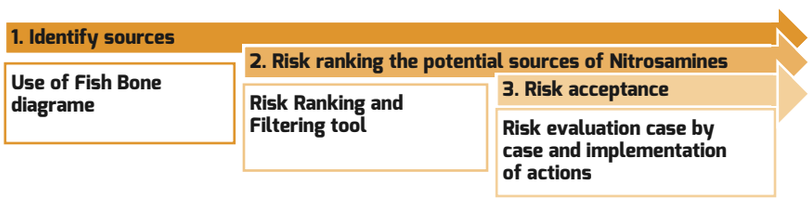
What is "nitrosamine"?

N-Nitrosamines are a group of compounds known for their strong carcinogenic properties and their widespread presence in the environment, including air, water, food, and pharmaceuticals.

These compounds have the general formula $R_2N–N = O$, where the R groups are usually alkyl chains. The defining feature of N-nitroso compounds is the N–N = O structure. The R_1 and R_2 groups attached to the nitrogen atom can vary from a simple hydrogen atom to more complex chemical groups, including ring structures that incorporate the nitrogen atom.

Risk assessment

The risk assessment structure is the following:



The potential contributions from each of the identified sources of nitrosamines needs to be considered to determine the overall contribution of nitrosamines to the drug product.

For a drug product the following sources must be considered as a minimum:

- Excipients
- API
- Utilities
- Manufacturing Process
- Primary Packaging

Excipients and API

I. Fish Bone Diagram

A fish bone diagram was performed with potential sources for nitrosamine contamination in reagents, excipients and APIs.

II. Risk Ranking and Filtering

As per the fish bone above, a risk matrix is created (**Table 1**). In order to provide the correct score, it is recommended to send a supplier questionnaire if necessary. Here is an example:

Based on the supplier questionnaire and fish bone information, risk scoring needs to be provided for each of the nitrosamine sources.

The scores listed in **Table 2** need to be detailed to derive a final score for each potential source of nitrosamines.

Each individual score for potential sources or risk factors (RF) should be calculated using the formula provided below:

RF1 + RF2 + RF3 + RF4 + RF5 + RF6 + RF7 + RF8 + RF9 = API/excipient overall risk score

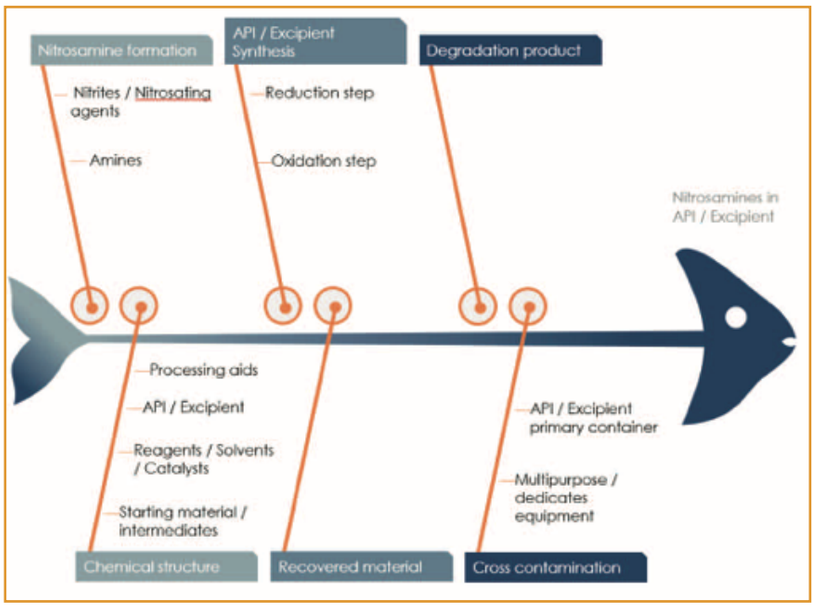


Figure 1. Fish bone for APIs and excipients

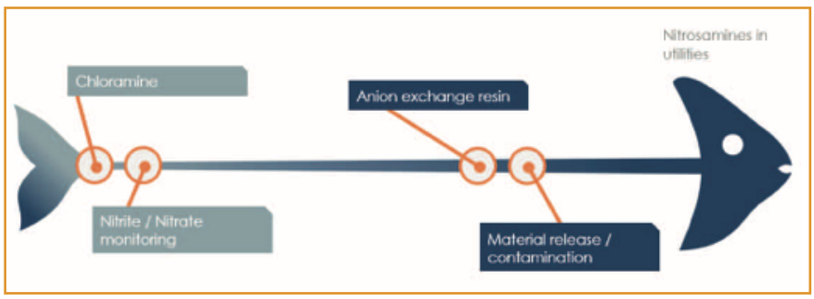


Figure 2. Fish bone for Utilities

The risk is classified as high, medium, or low, according to **Table 3**.

III. Risk Acceptance

The overall risk of nitrosamines should be assessed by considering the results from each individual potential risk source.

For low-risk components, no further assessment is necessary. However, if any component is identified as having a medium or high risk, a qualitative evaluation is required to determine if risk mitigation is feasible and to establish the final nitrosamine risk for the finished product.

Utilities

I. Fish Bone Diagram

The utilities used in the manufacturing process must be assessed for their risk of nitrosamine or nitrosamine precursors content.

II. Risk Ranking and Filtering

Based on the fish bone information, risk scoring needs to be provided for each of the nitrosamine sources.

The scores listed in **Table 4**

Table 1. Example of nitrosamine supplier questionnaire API/excipient/reagent/solvent

No.	Questions			
1	Does the product contain nitrosamines? If yes, ignore all other questions	Yes	No	I don't know
2	Is sodium nitrite ($NaNO_2$), or other nitrosating agents used in the production process?	Yes	No	I don't know
	If yes, is it used in acidic or slightly acid conditions?			
3	Are secondary, tertiary, or quaternary amines used in the production process?	Yes	No	I don't know
	If yes, please specify			
4	Are substances with a tetrazole group used in the production process?	Yes	No	I don't know
5	Are substances with an amide group used in the production process?	Yes	No	I don't know
6	In the manufacturing process, are you performing any step in the presence of secondary/ tertiary amines, and/or amides, and/or in any solvents that might decompose forming secondary or tertiary amine, such as – but not limited to- dimethylformamide (DMF), dimethylacetamide (DMAc) or N-methylpyrrolidone (NMP)?	Yes	No	I don't know
7	Is water used during the manufacturing process?	Yes	No	I don't know
	If yes of which grade (potable, PW, WFI), and is it tested for nitrates?			
8	Are any raw materials used in the production process contaminated with sodium nitrite ($NaNO_2$),or other nitrosating agents?	Yes	No	I don't know
9	Are any raw materials used in the production process contaminated with secondary, tertiary, or quaternary amines, or with solvents, reagents or catalysts susceptible to degradation to secondary or tertiary amines (e.g. DMF, NMP, TEA, DIPEA, N,N-dimethylaniline, TEA HCl and TBAB)?	Yes	No	I don't know
10	During manufacturing are there reduction steps in presence of inorganic Nitrates?	Yes	No	I don't know
11	During manufacturing are there Oxidation steps in presence of secondary/tertiary amines and/or in any solvents that might decompose forming secondary/tertiary amines	Yes	No	I don't know
12	Basing on your knowledge of the manufacturing process, is there any degradation product that contains nitrosating agents or Nitrosamine?	Yes	No	I don't know
	If yes, have you identified it/them?			
13	Basing on your knowledge of the manufacturing process, is there any degradation product that contains nitro/nitroso group or amines?	Yes	No	I don't know
	If yes, have you identified it/them?			
14	Are recovered materials (e.g. solvents, reagents and catalysts), including recovery outsourced to third parties, used in the production process?	Yes	No	I don't know
	If yes, please specify if recovering is performed in presence of nitrous acid, and if it is outsourced.			
15	Is the product subject to cross-contamination with a different product where nitrosamine, nitrosating agents, or solvents, reagents or catalysts susceptible to degradation to secondary or tertiary amines?	Yes	No	I don't know
16	Is the equipment used for production dedicated (not multipurpose)?	Yes	No	I don't know
17	If the equipment is multipurpose, are there validated cleaning procedures for the equipment?	Yes	No	I don't know
18	Is the primary container of the product supplied single use (container not re-used)?	Yes	No	I don't know

need to be detailed to derive a final score for each potential source of nitrosamines.

Each individual score for potential sources or risk factors (RF) should be calculated using the formula provided below:

RF1 + RF2 + RF3 + RF4 =

Utilities overall risk score

The risk is classified as high, medium, or low, according to the **Table 5**:

III. Risk Acceptance

The overall risk of nitrosamines should be assessed by considering the results from each individual potential risk source.

For low-risk components, no further assessment is necessary. However, if any component is identified as having a medium or high risk, a qualitative evaluation is required to determine if risk mitigation is feasible and to

Table 2. Risk matrix for API/excipients

	Potential source of nitrosamines	Criteria	Risk score
Chemical structure	Chemical structure (R1)	Presence of a secondary/tertiary/quaternary amino group/score group and a Nitrosating agents/ nitro group/ nitroso group	5
		Presence of a tetrazole group	5
		Presence of a secondary/ tertiary/quaternary amino group	3
		Presence of a Nitrosating agent	3
		Presence of nitro group/nitroso group or amide group	3
		No presence of a secondary/tertiary/quaternary amino group/ amide group and a Nitrosating agent/nitro group/nitroso group, nor tetrazole group	1
		Composite material (e.g. flavour) whose specific composition cannot be disclosed (industrial secrecy)	1
Nitrosamine formation	Nitrosating agent (R2)	Used in component manufacturing process in acid/slightly acid condition (considering also catalysts/adjuvants)	5
		Used in component manufacturing process (considering also catalysts/adjuvants)	3
		Used in starting material manufacturing process	3
		Used in the same component manufacturing line/equipment	2
		Potable/raw water used in the manufacturing process	3
		Not used	1
	Amines (R3)	Secondary/tertiary amines used in component manufacturing process	3
		Quaternary ammonium salt used in component manufacturing process	3
		Used in starting material manufacturing process	3
		Compound (Intermediates, solvents, processing aids) that might decompose forming secondary/tertiary amines used in manufacturing process	3
		Amide group used in component manufacturing process	3
		Not used	1
Synthesis step	Reduction step in presence of inorganic Nitrates (R4)	Performed during manufacturing process	3
	Oxidation step in presence of secondary/tertiary amines and/or in any solvents that might decompose forming secondary/tertiary amines (R5)	Not performed during manufacturing process	1
		Performed during manufacturing process	3
		Not performed during manufacturing process	1
Degradation product	Degradation product/Known Impurities (R6)	Presence of nitrosamine as degradation product	5
		Presence of degradation product containing nitrosating agents and amines	5
		Presence of degradation product containing nitrosating agents or amines	3
		Presence of degradation product containing nitro/nitroso group	2
		Absence of degradation product containing Nitrosamine, amine, nitrosating agents and nitro/nitroso group	1
Recovered material	Recovered Material (R7)	Recovery of solvent/catalyst/reagent externally performed	3
		Recovery of solvent/catalyst/reagent internally performed using nitrous acid	3
		Recovery of solvent/catalyst/reagent internally performed without the use of nitrous acid	2
		No recovered material is used	1
Cross contamination	Multipurpose/Dedicated equipment (R8)	Multipurpose equipment without cleaning procedures	3
		Multipurpose equipment with cleaning procedures	2
	API/Excipient primary container (R9)	Dedicated equipment	1
		API/Excipient primary container re-used	2
		API/Excipient primary container not re-used	1

establish the final nitrosamine risk for the finished product.

Manufacturing Process

I. Fish Bone Diagram

A fish bone diagram was performed with potential sources for nitrosamine contamination during the manufacturing process.

II. Risk Ranking and Filtering

Based on the fish bone information, risk scoring needs to be provided for each of the nitrosamine sources.

The scores listed in **Table 6** need to be detailed to derive a final score for each potential source of nitrosamines.

Table 3. API/Excipient/Reagent risk levels

API/excipient/reagent Overall Risk Score	API/excipient/reagent Overall Risk Level
23-32	High
16-22	Medium
9-15	Low

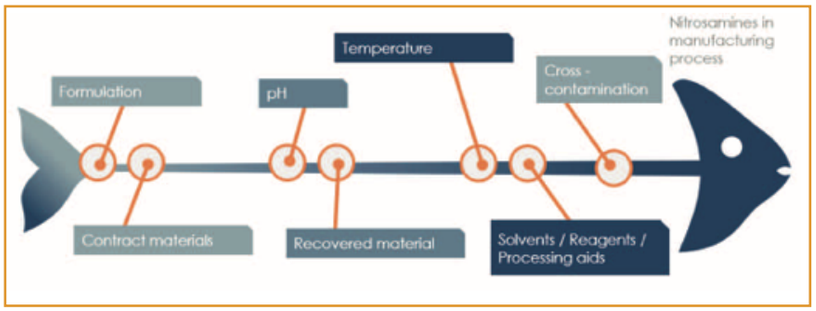


Figure 3. Fish bone for manufacturing process.

Table 4. Risk matrix for utilities

	Potential source of nitrosamines	Criteria	Risk score
Anion Exchange Resin & Chloramine	Anion-exchange resins as part of water treatment (R1)	Used	2
		Not used	1
	Chloramine as part of water treatment (R2)	Used	2
		Not used	1
Material Release/ Contamination	Materials (e.g. agents, pH modifier, etc) that could lead to the releasing/ contamination of nitro-group/ Nitrosamine/free amine (R3)	Material that could lead to the releasing/contamination of amine and nitro-group or nitrosamine	3
		Material that could lead to the releasing/contamination of amine and nitro-group	2
		Material that could lead to the releasing/contamination of amine or nitro group	2
		No material that could lead to the releasing/contamination of nitro group/ amines/Nitrosamine is used.	1
Nitrite/nitrate Monitoring	Nitrite/nitrate content monitoring on PW/WFI used in the relevant manufacturing process (R4)	Not performed	3
		Performed	1

Each individual score for potential sources or risk factors (RF) should be calculated using the formula provided below:

RF1 + RF2 + RF3 + RF4 + RF5 + RF6 + RF7 + RF8 = Manufacturing process overall risk score

Table 5. Utilities risk levels

Utilities Overall Risk Score	API/excipient/reagent Overall Risk Level
9-10	High
7-8	Medium
4-6	Low

Table 6. Risk matrix for manufacturing process

Source category	Potential source of nitrosamines	Criteria	Risk score
Drug product formulation	Drug product formulation (R1)	Presence (as formulation component) of Secondary/tertiary/quaternary amine and nitrosating agent	5
		Presence of secondary/tertiary/quaternary amines (as formulation component) and nitrocellulose in primary packaging material	5
		Presence of amide compound (as formulation component) and nitrocellulose in primary packaging material	5
		Presence (as formulation component) of amide compound and nitrosating agent	5
		Presence (as formulation component) of secondary/tertiary/quaternary amines or nitrosating agent	3
		Presence (as formulation component) of amide compounds	3
		Absence of secondary/tertiary/quaternary amines, amide compounds and nitrosating agent	1
Operational conditions	pH (R2)	One or more steps performed in acid/slightly acid conditions with nitrosating agents	3
		One or more steps performed in acid/slightly acid conditions without nitrosating agents	2
		No step performed in acid/slightly acid conditions	1
	Temperature (R3)	One or more steps performed at high temperatures with nitrosating agents	3
		One or more steps performed at high temperatures without nitrosating agents	1
		No step performed at high temperatures	1
Contact material	Contact material (equipment, auxiliary material, pipeline, etc.) (R4)	Nitrosamine potentially released from contact material	3
		Nitrosamine precursor (e.g. secondary/tertiary/quaternary amines and nitrosating agents) potentially released from contact material	3
		Nitrosamine precursor (e.g. secondary/tertiary/quaternary amines or nitrosating agents) potentially released from contact material	2
		Nor Nitrosamine nor nitrosamine precursor potentially released from contact material	1
	Contact time (R5)	Long contact time/high contact area and high temperature/acid pH	3
		Long contact time/high contact area or high temperature/acid pH	2
		Nor long contact time/high contact area nor high temperature/acid pH	1
Solvents, reagents and processing aids	Solvents, reagents and processing aids (R6)	Nitrosamine precursor (e.g. secondary/tertiary amines, nitrites, etc.) used as solvents, reagents and/or processing aids	5
		Material that might decompose forming Nitrosamine precursor used as solvents, reagents and/or processing aids	3
		No risk of nitrosamine contamination from solvents, reagents and/or processing aids	1
Recovered material	Recovered material (R7)	Recovery of solvent/catalyst/reagent externally performed	3
		Recovery of solvent/catalyst/reagent internally performed using nitrous acid	2
		Recovery of solvent/catalyst/reagent internally performed without the use of nitrous acid	1
		No recovered material is used	1
Cross contamination	Multipurpose/dedicated equipment (R8)	Multipurpose equipment without cleaning procedures	3
		Multipurpose equipment with cleaning procedures	2
		Dedicated equipment	1

The risk is classified as high, medium, or low, according to the **Table 7**:

III. Risk Acceptance

The overall risk of nitrosamines should be assessed by considering the results from each individual potential risk source.

For low-risk components, no further assessment is necessary. However, if any component is identified as having a medium or high risk, a qualitative evaluation is required to determine if risk mitigation is feasible and to establish the final nitrosamine risk for the finished product.

Table 7. Utilities risk levels

Process Overall Risk Score	Process Overall Risk Level
22-28	High
16-21	Medium
8-15	Low

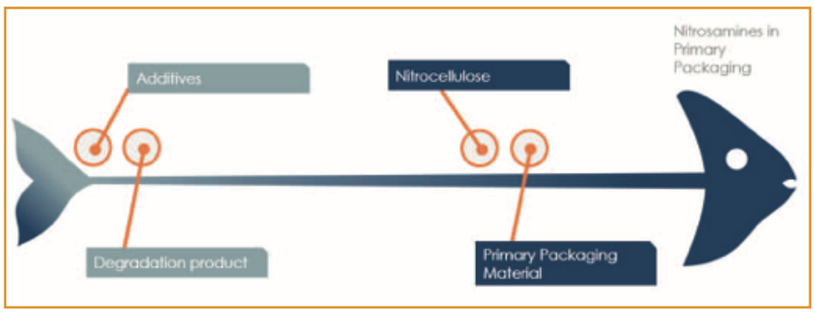


Figure 4. Fish Bone for primary packing.

Table 8. Risk matrix for sources of nitrosamines in primary packaging

Potential sources of nitrosamines	Criteria	Risk score
Nitrocellulose (R1)	Nitrocellulose contained in primary packaging material	3
	Nitrocellulose not contained in primary packaging material	1
Additives (R2)	Use of additives containing nitro/nitroso group and amine group	3
	Use of additives containing nitro/nitroso group or amine group	2
	Absence of additives containing nitro/nitroso group or amine group	1
Degradation product/Known Impurities (R3)	Presence of nitrosamine as degradation product	3
	Presence of degradation product containing nitrosating agents and amines	3
	Presence of degradation product containing nitrosating agents or amines	2
	Presence of degradation product containing nitro/nitroso group	2
	Absence of degradation product containing Nitrosamine, amine, nitrosating agents and nitro/nitroso group	1
Primary Packaging Material (R4)	Rubber, silicone	3
	Plastic	2
	Other materials (metal, glass, etc.)	1

Primary Packaging

I. Fish Bone Diagram

A fish bone diagram was performed with potential sources for nitrosamine contamination in the primary packing.

Table 9. Primary packaging risk levels

Primary Packaging Overall Risk Score	Primary Packaging Overall Risk Level
9-12	High
7-9	Medium
4-6	Low

II. Risk Ranking and Filtering

Based on **Figure 3** diagram provided above, **Table 8** outlines the criteria and corresponding risk scores to be utilized.

The scores listed in **Table 8** need to be detailed to derive a final score for each potential source of nitrosamines.

Each individual score for potential sources or risk factors (RF) should be calculated using the formula provided below:

RF1 + RF2 + RF3 + RF4 = primary packaging overall risk score

The risk is classified as high, medium, or low, according to **Table 9**.

III. Risk Acceptance

The overall risk of nitrosamines should be assessed by considering the results from each individual potential risk source.

For low-risk components, no further assessment is necessary. However, if any component is identified as having a medium or high risk, a qualitative evaluation is required to determine if risk mitigation is feasible and to establish the final nitrosamine risk for the finished product.

Conclusion

This document provided an example of a nitrosamine risk assessment to cover current regulation requirements.

Risk assessment has been based on three stages:

1. Identify sources of nitrosamines.
2. Risk ranking the potential sources.
3. Risk evaluation case by case and implementation of actions if required.

It is important to note the sources identified are just examples that may not apply to all pharmaceutical companies; however, the approach can be extrapolated to any company.

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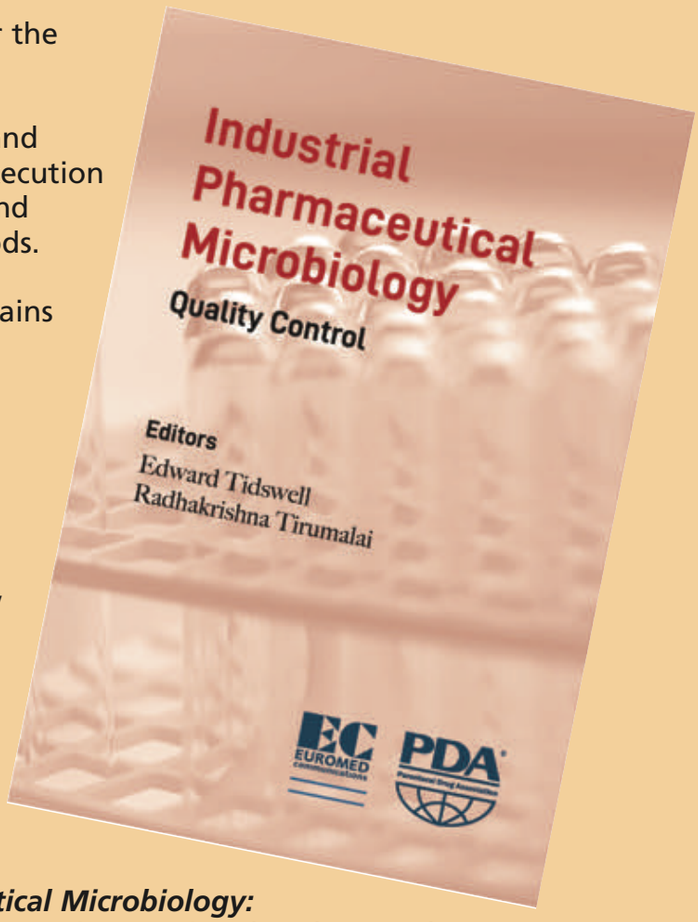
Industrial Pharmaceutical Microbiology: Quality Control

Edited by Edward Tidswell and Radhakrishna Tirumalai

Industrial Pharmaceutical Microbiology: Quality Control provides an in-depth comprehensive survey of QC pharma methods in the microbiology laboratory, to enable a better understanding of these methods, and to ensure better developed, more compliant, expedited procedures.

The reference text brings together the hitherto unavailable background, fundamental science, principles, development, intended purpose, and specific answers to questions of execution and qualification of compendial and related microbiological test methods. Key topics include the types of microbiological tests, reference strains and culture collections, and equivalence of reference strain.



Test methods and subject matter include bioburden, microbial enumeration, specified and objectionable microorganisms, antimicrobial effectiveness testing, endotoxins and sterility tests, microbial identification, biological indicators, water activity, disinfectant efficacy, and water. It also covers a critical, stimulating look into the topic of Environmental Monitoring.

In summary, ***Industrial Pharmaceutical Microbiology: Quality Control*** with its 20 chapters, 19 international authors and over 500 pages, enables the practitioner to have a complete understanding of these microbiological methods, and to ensure better developed, compliant, appropriate procedures and accurate meaningful data.

https://euromedcommunications.com/collections/pharmaceutical-sciences-manuals/products/industrial-pharmaceutical-microbiology-quality-control

UNIVERSITY OF BIRMINGHAM | Precision Health Technologies Accelerator

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Be part of PHTA

Driving innovation in clinical trials: how PHTA's Industry Trials Hub is transforming the pathway from bench to bedside

by Becky Faville

PHTA stands for the Precision Health Technologies Accelerator, which is the University of Birmingham's flagship life sciences research and innovation facility, located at the Birmingham Health Innovation Campus. It provides a 70,000 sq ft space with lab, incubation, and collaboration facilities for companies and researchers to accelerate the translation of research into patient benefit, particularly in the areas of precision medicine and diagnostics.

Becky Faville is a Clinical Trial Operations Leader with over a decade of experience delivering global and UK clinical trials across haematology, oncology, and rare diseases. Based at the University of Birmingham, she currently leads academic–industry collaborations through the Precision Healthcare Technologies Accelerator and the Haematology Trials Unit, overseeing registration and early- to late-phase studies.

Becky has a strong track record in vendor management, budget negotiation, regulatory submissions, and remote team leadership. She has successfully managed high-impact trials contributing to licensing submissions and is recognised for designing GCP-compliant systems, SOPs, and quality frameworks. Her collaborations span leading biopharma sponsors including Janssen, Regeneron, Moderna, and ADC Therapeutics.

An experienced public speaker and panellist at industry events such as Medidata NEXT and On Helix, Becky is passionate about digital transformation in clinical research and advancing innovation in paediatric and rare disease trials.

Introduction

At the Precision Health Technologies Accelerator (PHTA), our mission is clear: to accelerate the development of new treatments and technologies, and to deliver them to patients faster. As the University of Birmingham's flagship life sciences research facility, we provide companies with unrivalled access to both academic and clinical expertise – from multidisciplinary researchers across the University to clinicians within some of the UK's leading NHS hospitals, our ecosystem is designed to bring innovation from bench to bedside at pace.

Being co-located with the Queen Elizabeth Hospital Birmingham (part of University Hospitals Birmingham NHS Foundation Trust) and Birmingham Women's and Children's NHS Foundation Trust, allows us to build direct clinical connections. PHTA is also home to specialist services such as the Clinical Immunology Services, which delivers advanced diagnostics. Together, this environment creates a uniquely collaborative space that enables research, clinical trials, and industry partnerships to thrive in unison.

A cornerstone of this work is the PHTA Industry Trials Hub (ITH). The idea originated through the ACCELERATE platform, a collaborative initiative uniting academia, industry, and regulators to develop innovative therapies for children and adolescents with cancer. Within this forum, we recognised a key limitation: academic trials units like the University of Birmingham's Cancer Research UK Clinical Trials Unit (CRCTU) were predominantly running practice-changing academic trials, but these were not designed to registration standards and therefore not "fit for filing": in other words, they could not inform a licensing authority. As a result, while pharmaceutical companies valued the insights generated by our trials, they were often required to replicate these studies to regulatory standards themselves or through (Clinical Research Organisations) CROs – adding significant time to the already lengthy process of getting a drug approved for patients.

The Industry Trials Hub was established to bridge this gap. By setting up academic trials to registration standards from the outset, we ar in the process of creating the infrastructure and dedicated teams required to deliver industry-led trials at scale, while retaining the academic rigour and clinical excellence for

which CRCTU has been renowned for more than 30 years. This model significantly reduces duplication of effort and accelerates the trajectory from promising data to licensed treatment.

Delivering trials to registration level requires more than just intention – it requires a fundamental evolution of operating procedures. While our academic trials have always been robust and underpinned by strict processes, the regulatory requirements of industry studies are considerably more demanding, particularly regarding safety monitoring, risk-based monitoring, and data verification. To meet this challenge, we have expanded our capabilities, investing in growing our team of expert biostatisticians and partnering with specialists in areas such as database provision and management. Our teams have also upskilled in ICH-GCP compliance to ensure full regulatory alignment, and as a result we are now a much more agile operation capable of meeting the heightened expectations of industry and regulators.

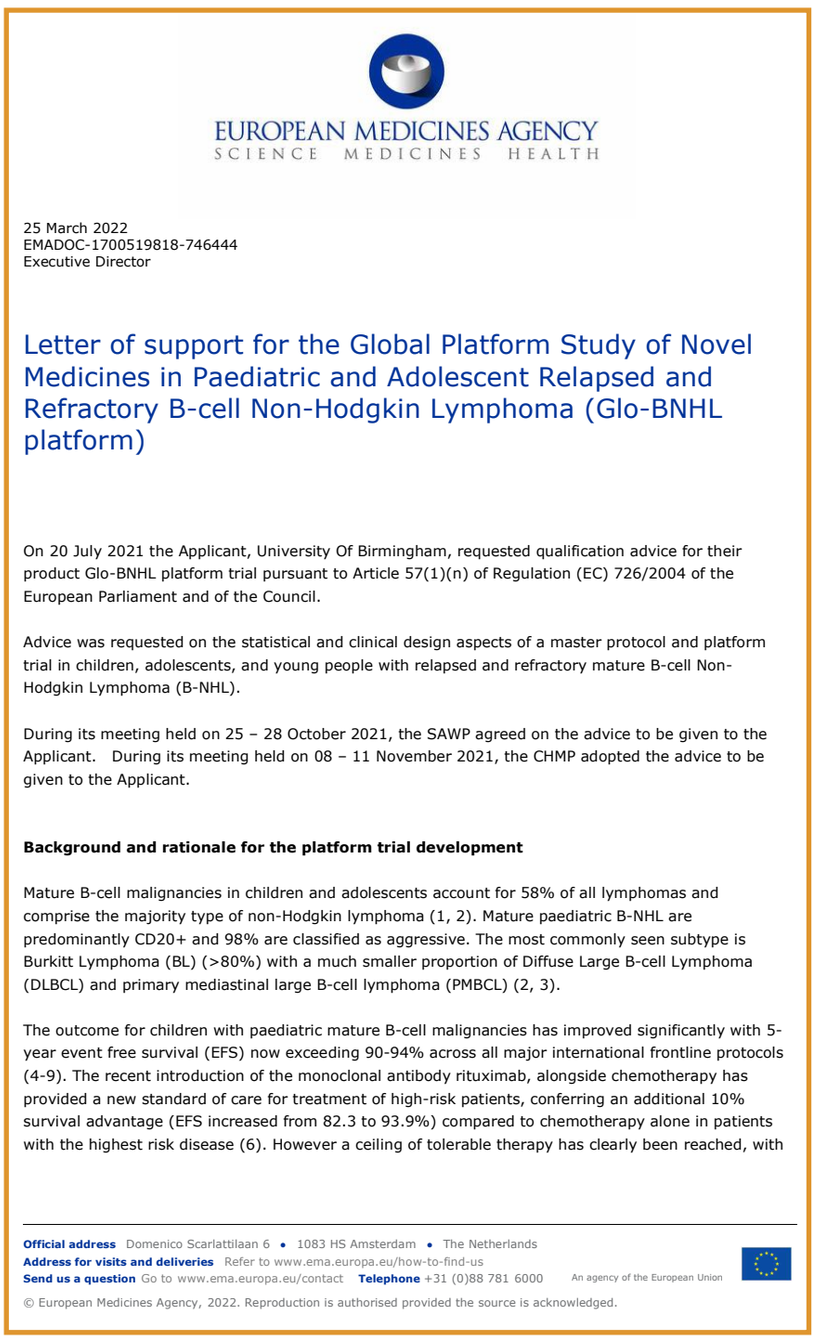
The Glo-BNHL Trial

The benefits of this "fit for filing" approach are already evident, with one example being Glo-BNHL, the world's largest platform trial in paediatric and adolescent B-cell non-Hodgkin lymphoma (B-NHL)

Clinical trials traditionally compare one new treatment to the standard treatment currently used by doctors. In the case of B-NHL that has not been cured (refractory) or has come back (relapsed), there are no adequate treatments anywhere in the world and most children will sadly die from the disease.

This international, early-phase platform study – developed in collaboration with a mix of transatlantic academic and industry partners – has received approvals from both the EMA and FDA, and regulators are now actively recommending Glo-BNHL to companies seeking solutions in this disease area.

Figure 1 shows the first page of the EMA letter supporting the Glo-BNHL platform. The letter highlighted the following points of the platform:



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 March 2022
EMADOC-1700519818-746444
Executive Director

Letter of support for the Global Platform Study of Novel Medicines in Paediatric and Adolescent Relapsed and Refractory B-cell Non-Hodgkin Lymphoma (Glo-BNHL platform)

On 20 July 2021 the Applicant, University Of Birmingham, requested qualification advice for their product Glo-BNHL platform trial pursuant to Article 57(1)(n) of Regulation (EC) 726/2004 of the European Parliament and of the Council.

Advice was requested on the statistical and clinical design aspects of a master protocol and platform trial in children, adolescents, and young people with relapsed and refractory mature B-cell Non-Hodgkin Lymphoma (B-NHL).

During its meeting held on 25 – 28 October 2021, the SAWP agreed on the advice to be given to the Applicant. During its meeting held on 08 – 11 November 2021, the CHMP adopted the advice to be given to the Applicant.

Background and rationale for the platform trial development

Mature B-cell malignancies in children and adolescents account for 58% of all lymphomas and comprise the majority type of non-Hodgkin lymphoma (1, 2). Mature paediatric B-NHL are predominantly CD20+ and 98% are classified as aggressive. The most commonly seen subtype is Burkitt Lymphoma (BL) (>80%) with a much smaller proportion of Diffuse Large B-cell Lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL) (2, 3).

The outcome for children with paediatric mature B-cell malignancies has improved significantly with 5-year event free survival (EFS) now exceeding 90-94% across all major international frontline protocols (4-9). The recent introduction of the monoclonal antibody rituximab, alongside chemotherapy has provided a new standard of care for treatment of high-risk patients, conferring an additional 10% survival advantage (EFS increased from 82.3 to 93.9%) compared to chemotherapy alone in patients with the highest risk disease (6). However a ceiling of tolerable therapy has clearly been reached, with

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Figure 1. Screenshot of the first page of the EMA letter supporting the Glo-BNHL platform.

- Critical clinical need: Current survival rates for relapsed/refractory paediatric B-NHL are less than 30%, with very poor outcomes after more than one line of therapy. There are no open trials worldwide for these patients, making this project urgently needed.
  - Innovation in trial design:
  - Uses a platform trial model that can test multiple novel medicines efficiently.
  - Applies adaptive Bayesian statistical design to allow medicines to be assessed quickly and replaced if ineffective.
  - Includes three initial treatment arms: bispecific antibodies, antibody-drug conjugates with chemotherapy, and CAR T-cells.
- PHTA relevance: Hosting and supporting such cutting-edge, global-impact research highlights the importance of Birmingham's Precision Healthcare Technologies Accelerator as a hub for next-generation clinical trials and translational medicine.

For industry, embedding investigational drugs into our platform trial is far more efficient than initiating standalone studies, as we already have eligible patients and the infrastructure to evaluate multiple drug candidates in parallel. For patients, the model allows seamless transition from one treatment to another within the same trial framework, minimising delays and improving access to potential therapies.

Advanced statistical methods will be used to evaluate if a treatment is working with a very small number of patients, very quickly. A treatment that is not working will be identified early and removed, to be replaced with another treatment. For treatments that do work, researchers believe there will be enough evidence to show regulators that the treatment should be adopted as standard care in the NHS and beyond. In this way, the usual lengthy process of trial and regulatory approval will be shortened significantly.

Crucially, the Industry Trials Hub maintains the highest standards of academic excellence while enabling industry-level trial delivery. Through establishing a dedicated team, we have empowered ourselves to take ownership of registration-level studies and to conduct them in collaboration with our industry partners. This approach removes unnecessary duplication of effort, reduces development timelines, and ensures patients gain access to life-changing therapies sooner.

Ultimately, the Industry Trials Hub exemplifies what PHTA was designed to achieve: to accelerate innovation by uniting academia, industry, and healthcare in a single, collaborative ecosystem. By redefining how industry trials are conducted within an academic setting, we are not only enhancing the UK's clinical research capacity but also ensuring that patients – who are at the heart of everything we do – benefit from scientific advances without unnecessary delay.

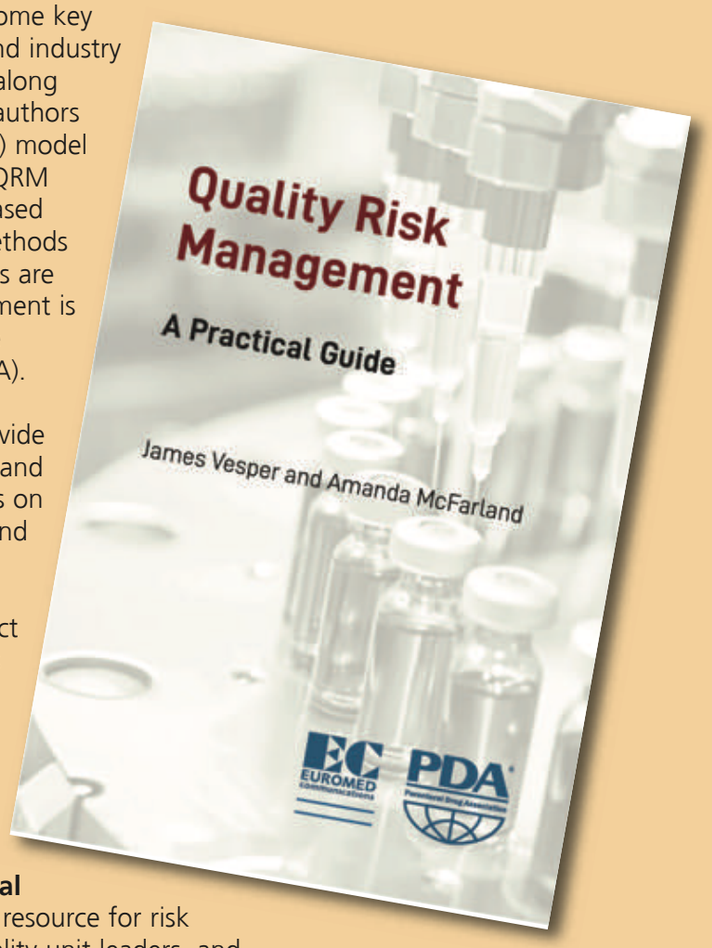
phta.co.uk/industry-trials-hub/

Risk Management – A Practical Guide

By James Vesper and Amanda McFarland

Since the publication of the first Quality Risk Management (ICH Q9) guideline in 2005 and *Risk Assessment and Risk Management in the Pharmaceutical Industry* by James Vesper in 2006, the pharmaceutical industry has made considerable strides in its understanding and application of QRM and risk-based decision making. This evolution is captured in a revised and expanded volume, **Quality Risk Management: A Practical Guide.**

Beginning with a historical context of some key events that have shaped how society and industry think about risks and controlling them along with defining concepts and terms, the authors provide an overview of the QRM Q9(R1) model and do a deeper dive into each of the QRM phases. An emphasis is made on risk-based thinking and bias reduction. Various methods and tools used in doing risk assessments are described, illustrating that risk management is more than just using a singular tool like Failure Mode and Effects Analysis (FMEA).



In twenty-two chapters the authors provide all the information you need to understand the concept of QRM, including chapters on facilitating risk management activities and the connection between risk management and knowledge management. QRM is an essential aspect of the pharmaceutical industry, and this volume is based on the authors' experience as facilitators, risk-tool developers, and instructors to pharma and biopharma risk teams around the world.

Quality Risk Management: A Practical Guide will prove an important and key resource for risk owners, risk assessment facilitators, quality unit leaders, and those who make risk-based decisions.

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The Evolution of Cleanroom Operations: ISO 14644-5:2025 and its impact on industry

by Haşim Solmaz

ISO 14644-5:2025 marks a significant revision of the operational requirements for cleanrooms and associated controlled environments, replacing the 2004 edition after nearly two decades. This technical paper outlines the major updates in the standard, highlights their relevance to industry, and provides guidance for cleanroom managers and quality professionals on transitioning from the 2004 version.

Hasim Solmaz is the VP of Innovation at Lighthouse Worldwide Solutions and General Manager of Lighthouse Worldwide Solutions EMEA Operations. Hasim focuses on cleanroom design and management concepts, environmental monitoring systems, pharmaceutical manufacturing, and regulatory concerns.

Hasim is a founding chair of the Cleanroom Technologies Society of Turkey (CTS), head of delegates in ISO TC209 "Cleanrooms and associated controlled environments", chair of Turkish Standardization Institute (TSE) Mirror Technical Committee 165 "Cleanroom Technologies" and an expert in various ISO TC209 Working Groups. He is the chair of the International Confederation of Contamination Control Societies (ICCCS), a multi-national community, with over 20 member countries' societies of cleanrooms and contamination control.

As a faculty member of the Institute of Environmental Sciences and Technology (IEST) Contamination Control Institute (CCI), he lectures in the CCI about Cleanroom Classification, Monitoring, Testing and Certification. For the 2024-2026 terms, Hasim will serve as a VP of Planning in the IEST Executive Board. He is an active member of the IEST, CTS, the International Society for Pharmaceutical Engineering (ISPE), and the Parenteral Drug Association (PDA).

Introduction

Cleanroom operations play a critical role in safeguarding contamination-sensitive processes in industries such as pharmaceuticals, biotechnology, microelectronics, optics, aerospace, and healthcare. With evolving technologies, heightened regulatory expectations, and greater emphasis on sustainability, ISO 14644-5:2025 was introduced to modernize the framework for cleanroom operations. This revision not only aligns operational practices with other ISO 14644 parts (such as ISO 14644-9, -10, -16, and -18) but also establishes a more systematic and risk-based approach to contamination control.

Key Changes in ISO 14644-5:2025

Introduction of the Operations Control Programme (OCP)

A major innovation in the 2025 edition is the requirement to establish and document an Operations Control Programme (OCP). The OCP ensures the cleanroom operates within its specified cleanliness levels across all states (operation, reduced operation, maintenance, shutdown). It integrates:

- Material and personnel flow diagrams
- SOPs for operation, maintenance, and shutdown
- Cleaning and monitoring programmes
- Maintenance schedules

The OCP formalizes how cleanrooms are managed, transforming operational practices from reactive to proactive.

Mandatory Impact Assessment

Before designing the OCP, an impact assessment is now required. This structured evaluation identifies factors that could prevent the cleanroom from attaining or maintaining specified cleanliness levels. The assessment covers operations, personnel behavior and hygiene, material flows, maintenance, and equipment. It forms the foundation of contamination control by linking operations directly to risk identification.

Clearer Risk Management Structure

Unlike the 2004 version where risk assessments were general and implicit, ISO 14644-5:2025 explicitly separates impact assessments (performed at the outset) and risk assessments

(targeted, event-specific analyses after the OCP is established). This encourages a tiered, data-driven approach to managing contamination risks.

Alignment with Sustainability Goals

For the first time, the standard encourages efficient use of resources, linking the OCP to sustainability (referencing ISO 14644-16 and 14644-18). This includes responsible selection of consumables, minimizing waste, and promoting energy-efficient operations.

Transitioning from ISO 14644-5:2004

The Shift from Flexible Guidance to Structured Compliance

ISO 14644-5:2004 offered broad, flexible guidance for cleanroom operations, allowing facilities significant freedom in how they defined and applied operational controls. Many practices were informal or locally adapted, with limited documentation and varying degrees of consistency. The 2025 revision, however, requires a more formal, structured, and evidence-based approach that demands clear documentation, accountability, and traceability.

Building the Operations Control Programme (OCP)

One of the most significant shifts is the introduction of a mandatory impact assessment, which forms the foundation of the new Operations Control Programme (OCP). This assessment requires facilities to systematically analyze operational factors that affect cleanliness—such as material and personnel flows, gowning, cleaning, equipment handling, maintenance, and shutdown procedures—and document the risks and controls for each. Unlike the general risk assessments encouraged by the 2004 edition, the impact assessment in 2025 is a formal, required step tied directly to operational planning.

The OCP itself must integrate these findings into detailed procedures covering all states of operation: normal, reduced, shutdown, and restart. Facilities will need to replace or update informal practices and un-documented routines with clear SOPs, validated flow diagrams, and defined monitoring and maintenance programmes.

Embedding Sustainability and Resource Efficiency

The 2025 revision also introduces sustainability and resource efficiency considerations, requiring organizations to evaluate their use of consumables, energy, and waste management practices—areas not addressed in the 2004 edition. This encourages more responsible, efficient cleanroom operations that align with modern environmental expectations.

Transitioning to ISO 14644-5:2025 will involve not just technical updates, but cultural change. Facilities must build a proactive contamination control mindset, enhance training and cross-departmental collaboration, and invest in systems that ensure compliance and continuous improvement.

Pathway to Adoption

To successfully adopt ISO 14644-5:2025, cleanroom managers and quality professionals should follow a structured process:

First, conduct a comprehensive gap analysis. This involves systematically comparing current operational procedures, documentation, and practices against the detailed requirements of the OCP and associated programmes in the new standard. The goal is to identify specific areas where updates or new processes are needed to align with ISO 14644-5:2025.

Next, perform a formal impact assessment. This is the foundation of the OCP and requires evaluating all factors that could affect the cleanroom's ability to meet specified cleanliness levels. This includes examining material and personnel flows, equipment placement, maintenance practices, and potential contamination sources.

ISO14644-5 2025 vs 2004 — Key differences at a Glance

	2004	2025
Approach	General operational guidance	Structured OCP based on formal impact assessment
Risk Management	Risk factors identified; encouraged monitoring	Mandatory impact assessment + event-specific risk assessments
Cleaning	General requirements	Enhanced cleaning programme with validation
Material flow	Basic guidance	Documented flow, approvals, controls
Sustainability	Not addressed	Integrated into OCP

Develop or revise the Operations Control Programme based on the impact assessment findings. This should include documented SOPs for all states of operation (start-up, full operation, reduced operation, shutdown), flow diagrams, cleaning and maintenance schedules, and monitoring plans. The OCP must reflect current operations while incorporating improvements identified during the gap analysis.

Implement a training programme to ensure all staff understand the revised procedures and their role within the OCP. Training should cover new SOPs, changes to material and personnel flow, contamination control practices, and monitoring requirements. Certification and periodic retraining should be part of this programme to ensure ongoing compliance.

Engage with stakeholders and external partners including suppliers, contractors, and service providers to align external activities with the new operational requirements. This ensures that all parties contributing to cleanroom operations support compliance with the revised standard.

Finally, update documentation and audit readiness. All procedures, records, diagrams, and supporting documents must be traceable, verifiable, and ready for internal and external audit. Facilities should establish internal audit schedules to verify adherence to the new OCP and identify opportunities for continuous improvement.

Conclusion

ISO 14644-5:2025 represents a significant advancement in cleanroom operational standards. By adopting this revision, organizations can enhance their contamination control strategies, improve regulatory readiness, and support sustainable operations. Early adoption will provide a competitive advantage as cleanroom compliance expectations evolve globally.

For more details, professionals should consult the full ISO 14644-5:2025 standard and related ISO 14644 series documents.

This article was first published in CACR, Issue 54, July 2025.

bottled brown

Industrial Pharmacy: Humanity's Hope

Dr Malcolm E. Brown has degrees in natural and social science research and elected a Fellow of the Royal Pharmaceutical Society (FRPharmS) for distinction in the profession of pharmacy. He has worked in senior positions as a production manager (big Pharma) and in the British NHS including at director level — and as a community pharmacist. He has tutored many future pharmacists and trained the "entire" sales force of a major international company on selling medicines to the NHS. He was the keynote speaker at an international multidisciplinary conference at the Hague. Dr Brown is an award-winning writer with over 170 publications.

The pharmaceutical industry stands at a cusp, facing both the challenges of evolving healthcare needs and the existential threat of human decline. All species become extinct, eventually, but the palaeontologist Henry Gee, in his remarkably cheerful book, "The Decline and Fall of the Human Empire", suggests that humanity could face extinction within 10,000 years. This article examines the interconnection between the microbiome, pharmaceutical innovation, and the pressing need to address our species' genetic vulnerability to secure a future for humankind.

Our health co-workers: our Microbiome

Our bodies are intricate ecosystems, comprising mammalian cells and a non-mammalian community known as the microbiome; which includes bacteria, archaea, fungi and viruses. The microbial world acquired during or shortly after birth is fundamental to our health, influencing everything from digestion to immunity.

The pharmaceutical and food industries have historically focused on excluding or meticulously controlling microorganisms in their products, as exemplified by the sterile production of vaccines and the specific fungal inoculation that is crucial to certain types of cheese. Anthropologist Heather Paxson reports that cheesemakers view microbes as essential, respected and revered partners. We now understand that antibiotics, while life-saving, can profoundly disrupt the delicate balance of our microbiome.

This understanding has led to a fascinating "rediscovery" of ancient remedies. Faecal microbiota transplantation (FMT), for instance, is licensed for the treatment of recurrent and refractory *Clostridioides difficile* infection. While seemingly novel, the therapeutic use of faeces dates back centuries, with dung from cattle, chicken, dogs, lizards, mice, pigeons, sheep and even humans being employed as remedies. Today, FMT involves rigorous donor screening, standardised manufacturing processes, and careful recipient monitoring. The development of lyophilised faecal microbiota capsules is like a palimpsest. Its modern text proclaims quality assurance standards. There is even a suggestion that individuals could bank their own microbiome samples when young and healthy, for future recolonisation if their immune system becomes compromised later in life.

Humanity's Precarious Future

Gee's unsettling premise is that humanity is on a trajectory toward extinction. Several factors contribute to this grim forecast: climate change, depletion of easily extractable resources, our reliance on a narrow diet, decreasing sperm counts and the role of Western biomedicine in allowing the "unfit" to survive, potentially weakening our gene pool.

Remarkably, humans have endured at least one evolutionary bottleneck, leaving us genetically astonishingly similar. In 1989, mitochondrial DNA studies suggested that our matrilineal bloodline traces back to one woman in Africa around 200,000 years ago. In 2001, nuclear DNA studies mapped the

complete human genome, corroborating the African origin. A single chimpanzee troop boasts more genetic diversity than the entire human population. We are inbred. That is thought to be connected to our susceptibility to many infectious diseases. They include worms, protists, bacteria, fungi, viruses and prions, including transmissible spongiform encephalopathy.

Adding to the concern is our declining total fertility rate (TFR), which is projected to fall below the replacement level (2.1 births per woman) by 2034. While the global population continues to grow, we are approaching a tipping point, after which a decline is expected to begin. Remember that outside Africa, *Homo sapiens* has traces of interbreeding with Neanderthals, Devisovans and others. Unlike previous eras, where *Homo sapiens* coexisted and interbred with other such *Homo* species, we are now the last ones standing. There's no genetic hiding place within more fecund relatives.

Historically, prophets of doom, such as Thomas Malthus, who predicted human decline in 1798, have been proved wrong by technological innovations like the Green Revolution and genetic engineering. However, future solutions depend on the rarest of resources: super-geniuses—individuals crucial for inventing the breakthroughs that could save us. Such rare individuals, presumably, are connected with the random genetic shuffling that evolved two billion years ago: sexual reproduction. An African proverb states that it takes a village to raise a child. But Gee emphasises that, "It takes … a civilization of hundreds of millions, even billions, to produce a Darwin or a Pasteur, a Gates or a Jobs, a Bezos or a Musk, a Newton or an Einstein".

His chilling conclusion: we may only have a sufficiently large population to produce such luminaries for another *two centuries*.

The threat of a really severe pandemic looms. COVID-19 was merely a rehearsal, a warning. Imagine an Ebola-like virus with the transmissibility of measles, impacting a genetically limited population.

The Pharmaceutical Industry's Pivotal Role

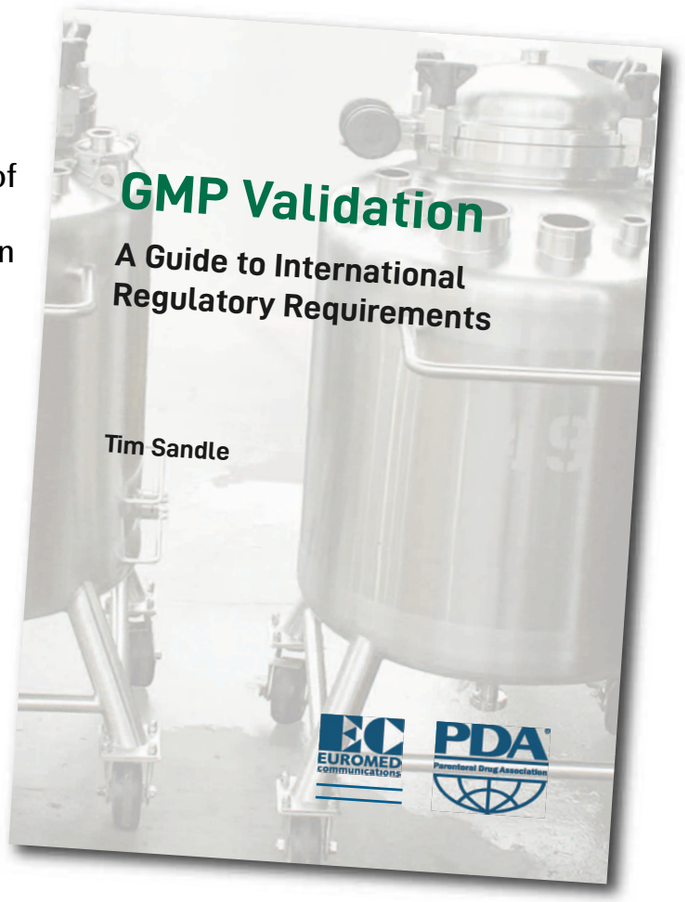
From Gees's perspective, the pharmaceutical industry (and, in fairness, many health professionals, including pharmacists) do help the "unfit" survive: they could be perceived to weaken the gene pool. However, the pharmaceutical industry also helps to foster public health. This includes the development of life-saving vaccines and advanced diagnostics, such as DNA-based infection identification and genetically targeted therapies. That may include to an ancestor of a crucial supergenius or the individual supergenius.

Malcolm E Brown

GMP Validation

A guide to international regulatory requirements

Tim Sandle



Within the pharmaceutical and healthcare sector, validation and qualification form an important part of the quality system. However, understanding the differences between different regulatory agencies and the recommendations of different standards can be a bewildering project. This new book seeks to provide a map and a compass for navigating the choppy waters of international regulations.

GMP Validation **provides a text for those who need to assess validation and ensure that validation is conducted according to current GMP. These include the validation manager and personnel engaged in validation activities; quality assurance; quality control; R&D; and production personnel. Some of the scientific aspects will also appeal to students, especially those working within or aspiring to enter the pharmaceutical sector. The book also serves as a good starting point for those who are tasked with auditing validation systems or items of equipment or processes.**

This comprehensive handbook of 650 pages is comprised of 30 chapters which are divided into two parts. The first part is dedicated to the management process, with an emphasis upon appropriate formality and risk-based approaches. The second part focuses on case studies, providing an overview of different GMPs and standards for different areas of validation and qualification. The book concludes with four useful appendices providing templates to aid the reader.

Further information and ordering details can be found at:

https://euromedcommunications.com/collections/pharmaceutical-sciences-manuals/products/gmp-validation-a-guide-to-international-regulatory-requirements-1